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FACULTAD DE HUMANIDADES Y CIENCIAS DE LA EDUCACIÓN
DEPARTAMENTO DE PSICOLOGÍA

TESIS DOCTORAL

APLICACIÓN DE LA MEDIDA DE FLUJO SANGUÍNEO CEREBRAL, MEDIANTE TÉCNICAS DE ULTRASONOGRAFÍA DOPPLER TRANSCRANEAL FUNCIONAL (FTCD), AL ESTUDIO DE LA SENSIBILIZACIÓN CENTRAL AL DOLOR Y LOS DÉFICITS COGNITIVOS EN LA FIBROMIALGIA

PRESENTADA POR:
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"La irracionalidad de una cosa no es un argumento en contra de su existencia, sino más bien una condición de la misma."

(Friedrich Nietzsche)

“Que este candil ilumine el camino hacia el crecimiento profesional y cultural para que nos permita mitigar el dolor y llevar la esperanza a todos aquellos que lo necesiten.”

(Florence Nightingale)

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Garantiza que:

La Tesis Doctoral titulada: “Aplicación de la medida del flujo sanguíneo cerebral, mediante técnicas de ultrasonografía Doppler Transcraneal funcional (fTCD), al estudio de la Sensibilización Central al Dolor y los déficits cognitivos en la fibromialgia”, realizada por la doctoranda Casandra Isabel Montoro Aguilar, ha sido elaborada bajo mi dirección y reúne las condiciones de calidad, originalidad y rigor científico necesarias para que se proceda a su defensa pública de acuerdo con la legislación vigente.

Fdo.: Gustavo Adolfo Reyes del Paso.:

Jaén, a 19 de Noviembre de 2015.

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"Todos los cambios, incluso los más deseados, acarrean cierta melancolía, porque lo que dejamos atrás es parte de nosotros mismos; Hay que morir en una vida antes de poder entrar en otra (Anatole France; Premio Nobel de Literatura, 1921)". No hay forma mejor de comenzar esta sección de agradecimientos que expresando con esta frase mi sentimiento al escribir estos párrafos tras la finalización de mi Tesis Doctoral. Y reconociendo que la magnitud de este aporte no hubiese sido posible sin la participación de personas e instituciones que han facilitado este proceso desde un primer momento. Por ello, para mí es un verdadero placer tener la oportunidad de expresar mis agradecimientos y que estos queden sólidamente grabados en tinta y papel.

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RESUMEN

El Síndrome de Fibromialgia o fibromialgia es un trastorno de dolor crónico caracterizado por dolor musculo-esquelético persistente y generalizado que afecta del 2 al 4% de la población general y se produce predominantemente en mujeres. Además de dolor, la fibromialgia incluye una gama heterogénea de síntomas como fatiga, insomnio, rigidez matutina, deterioro cognitivo leve, trastornos emocionales, migraña y síndrome del intestino irritable, entre otros; lo que pone de manifiesto que la fibromialgia no es una entidad discreta, sino una superposición de síndromes y síntomas. La fibromialgia es uno de los problemas de dolor crónico más importantes en los países industrializados dadas su alta prevalencia y morbilidad, siendo una de las enfermedades que más recursos sanitarios consume. Aunque existe un gran volumen de literatura científica centrada en la fibromialgia, su etiología y fisiopatología actualmente se desconocen y hasta ahora no se han encontrado signos somáticos específicos para esta enfermedad. La naturaleza subjetiva de los síntomas que engloba la fibromialgia ha dado lugar a un gran debate acerca del mecanismo involucrado en la etiología de la misma y los factores intervinientes, siendo los resultados hallados hasta el momento muy heterogéneos. La opinión actual más generalizada es que el dolor en la fibromialgia tiene que ver con procesos de Sensibilización Central. Por ello, una de las hipótesis más plausible y que está recibiendo mayor apoyo empírico en la actualidad implicaría la existencia de un procesamiento central anormal del dolor y deficiencias en los mecanismos centrales inhibitorios del dolor, que daría lugar a una elevada hiperalgesia (aumento de la sensibilidad a estímulos dolorosos) y la presencia de alodinia (sensibilidad a estímulos inocuos o no dolorosos). En este sentido, las técnicas de Neuroimagen Funcional han demostrado ser una herramienta valiosa en el análisis de los mecanismos implicados en el procesamiento del dolor en la fibromialgia. Sin embargo, aunque los estudios realizados mediante estas técnicas han aportado importantes resultados, carecen de una buena resolución temporal. Sería aconsejable analizar la dinámica temporal de los patrones de reactividad cerebral al dolor (como posibles indicadores de Sensibilización Central), mediante metodologías más resolutivas temporalmente como la *ultrasonografía Doppler transcraneal funcional* (fTCD). Por otra parte, uno de los síntomas más frecuentes en la fibromialgia son las disfunciones cognitivas, presentándose distintos tipos de déficits neuropsicológicos. Entre otros factores, la existencia de Sensibilización Central se podría relacionar con los déficits cognitivos

encontrados en la fibromialgia, ya que el procesamiento del dolor puede interferir claramente con la cognición al requerir recursos neurales y reclutar las mismas áreas cerebrales. Se podría considerar así una hipótesis que relacionaría el nivel de Sensibilización Central al Dolor de forma negativa con el rendimiento neuropsicológico. En este sentido un número muy extenso de estudios han aportado evidencia de que la fTCD también constituye una excelente herramienta para la cuantificación de los cambios rápidos en flujo sanguíneo cerebral que acompañan a la actividad cognitiva y otros procesos cognitivos.

Partiendo de estas premisas, la presente Tesis Doctoral pretende evaluar mediante fTCD: 1) La existencia de alteraciones en los mecanismos subyacentes mediadores del procesamiento del dolor, que pongan de manifiesto la existencia de un fenómeno de Sensibilidad Central o procesamiento aumentado del dolor en la fibromialgia. 2) Evaluar la posible existencia de patrones aberrantes de respuesta del flujo sanguíneo cerebral durante el procesamiento cognitivo, y el posible efecto intrusivo del dolor como mediador de estas alteraciones. 3) Los factores afectivos y cognitivos pueden tener una gran relevancia en la transición de dolor agudo al crónico y en el desarrollo de la Sensibilización Central en la fibromialgia. Por ello, se evaluará el efecto de modulación de los factores clínicos, emocionales, cognitivos, funcionales y de personalidad en las respuestas de flujo sanguíneo cerebral al dolor en la fibromialgia. 4) Con el propósito de esclarecer el rol de los factores de personalidad en la manifestación de los síntomas de la fibromialgia, se analizará la presencia de posibles perfiles de personalidad en la fibromialgia y su asociación con la sintomatología y calidad de vida en la fibromialgia.

En esta Tesis Doctoral se llevaron a cabo cinco estudios secuenciales, el primero de ellos tuvo por objetivo el análisis de las modulaciones de la dinámica temporal del flujo sanguíneo cerebral durante estimulación dolorosa en pacientes con fibromialgia y controles sanos, utilizando la ya citada técnica de *ultrasonografía Doppler transcraneal funcional (fTCD).* Los resultados de este primer estudio demostraron que el procesamiento del dolor agudo se asocia con un complejo patrón de modulaciones del flujo sanguíneo cerebral (FSC), donde las pacientes con fibromialgia exhiben alteraciones en todas las fases de la respuesta.

El segundo estudio tuvo por objetivo el análisis de las respuestas de flujo sanguíneo cerebral durante el procesamiento aritmético en fibromialgia y su relación con el rendimiento cognitivo. También se analizó la influencia de factores clínicos sobre el rendimiento y las respuestas de flujo sanguíneo cerebral. Los resultados muestran según lo esperado que el deterioro cognitivo en la fibromialgia se asocia con alteraciones en las respuestas de flujo sanguíneo cerebral durante el procesamiento cognitivo. La severidad del dolor clínico en pacientes con fibromialgia se asoció con el rendimiento cognitivo y las respuestas de flujo sanguíneo cerebral, sugiriendo así la existencia de una potencial vía fisiológica a través de la cual los factores psicosociales y clínicos pueden afectar a la cognición en la fibromialgia.

El tercer estudio tuvo por objetivo el análisis de las respuestas de flujo sanguíneo cerebral y frecuencia cardíaca durante una tarea de tiempo de reacción con estímulo de aviso en pacientes con fibromialgia. Los resultados muestran según lo esperado y de acuerdo con el estudio anterior, la interferencia de los factores clínicos en la cognición. Además, se encontró un déficit en el componente de alerta de la atención en pacientes con fibromialgia, tanto a nivel comportamental, como de respuesta autonómica y de flujo sanguíneo cerebral.

Tras los resultados hallados en el primer estudio, se llevó a cabo un reanálisis del mismo cuyo fin fue la evaluación de las posibles modulaciones de las respuestas de flujo sanguíneo cerebral por parte de factores emocionales (depresión), funcionales (insomnio), cognitivos (catastrofización) y de personalidad (neuroticismo, extraversión, psicoticismo y alexitimia) más relacionados con los síntomas de la fibromialgia. La evidencia de este estudio sugiere que, contrariamente a lo que hasta ahora se ha propuesto, los factores psicológicos y emocionales en la fibromialgia pueden afectar la percepción del dolor a través de la modulación del procesamiento sensorial y no sólo por la modulación de los aspectos emocionales y cognitivos de éste.

Posteriormente se realizaron dos estudios para analizar la relación entre algunos factores de personalidad y la manifestación de los síntomas de la fibromialgia, dada la discrepancia existente en la literatura sobre este tema y la evidencia que apoya su implicación en la cronificación del dolor. En el estudio quinto se evaluaron las tres dimensiones de la Personalidad identificadas por J.H. Eysenck en la fibromialgia. Los

resultados encontrados sugieren una menor implicación del neuroticismo en las manifestaciones clínicas de la fibromialgia, mientras que la extroversión parece tener una influencia protectora, dada su asociación con mejores resultados en salud en los diferentes dominios evaluados.

Los resultados del sexto y último estudio corroboraron la alta prevalencia de alexitimia en la fibromialgia, especialmente en la dimensión de dificultad para identificar sentimientos, que a su vez fue la más relacionada con los síntomas afectivos, la discapacidad funcional y las estrategias de afrontamiento no adaptativas en pacientes con fibromialgia. Además, se observó una importante interacción entre alexitimia, ansiedad y depresión, que apoya la existencia de una asociación entre los déficits en el procesamiento afectivo y el estatus funcional en la fibromialgia.

En resumen, los resultados encontrados en la presente Tesis Doctoral añaden evidencia a la idea de que existen alteraciones en el procesamiento del dolor a nivel del Sistema Nervioso Central en la fibromialgia. Estas alteraciones se encuentran moduladas por los factores psicológicos y clínicos presentes en esta enfermedad. Además de ello, los resultados ponen de manifiesto la existencia de deterioro cognitivo en la fibromialgia, el cual se asocia con alteraciones en las respuestas de flujo sanguíneo cerebral durante el procesamiento cognitivo. Estas alteraciones vendrían moduladas a su vez por algunas características clínicas de la fibromialgia como el dolor, apoyando la idea de que el dolor en la fibromialgia podría estar restando recursos a la cognición, lo que explicaría la alta prevalencia de problemas cognitivos en las pacientes con fibromialgia.

1. INTRODUCCIÓN

1.1 DESCRIPCIÓN DE LA FIBROMIALGIA

1.1.1 Definición

El Síndrome de Fibromialgia o fibromialgia es un trastorno complejo de dolor crónico, de etiología actualmente desconocida, consistente en dolor músculo-esquelético persistente y generalizado. El dolor, que no puede ser debido a una dolencia diagnosticada ni daño o inflamación del tejido, suele ser de intensidad variable según los días, pero de moderado a intenso. Otros síntomas de la fibromialgia incluyen fatiga, rigidez matutina, trastornos del sueño, rendimiento mental reducido, ansiedad y depresión (Reyes del Paso, Pulgar, Duschek y Garrido, 2012; Van Middendorp y cols., 2008; Wolfe, 2010; Wolfe y cols., 1990; Wolfe, Ross, Anderson, Russell y Hebert, 1995; Yunus, 2007).

A lo largo de la historia los médicos han informado de enfermedades con síntomas muy similares a la fibromialgia. Se considera que el primer caso documentado de fibromialgia es el referente a Florence Nightingale, enfermera del ejército Inglés y pionera en la medicina moderna. Florence Nightingale mostró síntomas similares a la fibromialgia durante la Guerra de Crimea (1854-1856). Estuvo postrada en la cama gran parte de su vida, con dolor y fatiga hasta su muerte en 1910 (Lee, 2006). No obstante, aunque este caso podría considerarse el primer caso documentado de fibromialgia, la primera descripción médica de la fibromialgia probablemente se remonte al siglo XVI y más concretamente al año 1592, bajo el término reumatismo muscular, usado en un trabajo de Guillaume de Baillou, incluido posteriormente en su libro “Liber de Rheumatismo” (1736), donde se detalla un caso de dolor muscular con algunos descriptores muy similares o consistentes con la fibromialgia (Baillou, 1736).

Conviene, sin embargo, advertir que el término “fibromialgia” (del latín *“fibro”*, que significa tejido fibroso, del griego *“mios”*, músculo y *“algia”*, dolor) no fue acuñado hasta 1976 por Kahler Hench, como una forma de reumatismo no articular

(Hench, 1976), siendo aceptado por la comunidad médica en 1981 bajo otro término, “fibrositis” (Yunus, Masi, Calabro, Miller y Feigenbaum, 1981).

El término “fibrositis” fue acuñado por William R. Gowers en 1904, como un nombre específico para el dolor a punta de dedo localizado en regiones musculares endurecidas por inflamación del tejido fibroso. Este autor apuntaba ya en su momento hacia un dolor espontáneo y una hipersensibilidad a la presión mecánica, fatiga y trastornos del sueño, además de una agravación de los síntomas por frío y sobreesfuerzo muscular. En el mismo año Ralph Stockman establecería los fundamentos patológicos para la teoría de la inflamación del tejido fibroso de William R. Gowers. Este autor planteaba la existencia de nódulos dolorosos, en los que se observaba una hiperplasia inflamatoria del tejido conectivo (Stockman, 1904). Esta teoría terminó siendo rebatida debido a que las biopsias realizadas en los tejidos musculares no aportaban indicios de inflamación. Boland (1947) en ausencia de hallazgos que justificasen la sintomatología dio un giro al concepto y propuso el término “reumatismo psicógeno”, definiéndolo como la expresión musculoesquelética de desórdenes funcionales, estados de tensión, o psiconeurosis.

Posteriormente, entre otros diversos apuntes relevantes para el conocimiento de esta enfermedad, Graham (1952, 1953) introduciría la “fibrositis” como un síndrome de dolor en ausencia de una enfermedad orgánica específica. Traut (1968) de acuerdo con el concepto que hoy entendemos de fibromialgia, describió la “fibrositis muscular” o “reumatismo no articular” como un síndrome constituido por dolor generalizado, cansancio, trastornos del sueño y dolor a la palpación en áreas gatillo, que incluían los tejidos blandos del cuello, hombro, codo, túnel carpiano, palmas (contractura de Dupuytren) y zona baja de la espalda.

En vista de la inexistencia de un daño inflamatorio específico Kahler Hench (1976) reemplazó el término “fibrositis” por el de “fibromialgia”. Tras lo cual, Smythe y Moldofsky (1977) contribuyeron a la comprensión de la fibromialgia con la publicación de la primera descripción clínica detallada de la misma. Propusieron los primeros criterios diagnósticos, los cuales requerían la presencia de dolor generalizado y la identificación de un número mínimo de regiones de sensibilidad extrema o puntos dolorosos, además de la existencia de alteraciones del sueño, fatiga y rigidez matutina.

Por añadidura, era frecuente la distinción entre fibromialgia primaria y secundaria en ausencia o presencia, respectivamente, de otras condiciones médicas que podrían causar o contribuir a sus síntomas. No obstante, esta distinción fue abandonada.

A pesar de las referencias históricas existentes sobre la fibromialgia, su reconocimiento como enfermedad es relativamente reciente. No es hasta el año 1981 cuando el término "fibromialgia" ("fibrositis") es aceptado universalmente (Yunus y cols., 1981), reconociendo la Asociación Médica Americana en 1987 la fibromialgia como una condición médica real. Tras este reconocimiento el Colegio Americano de Reumatología constituyó un comité para establecer los criterios diagnósticos para la misma, refiriéndose a ella en principio como síndrome, y posteriormente únicamente mediante el término fibromialgia (Wolfe y cols., 1990). Durante un tiempo se discutió si era una enfermedad por sí misma o un síndrome que englobaba un conjunto de enfermedades y trastornos (Millea y Halloway, 2000). Actualmente la fibromialgia se reconoce como síndrome, dada la heterogeneidad de síntomas que engloba (Wolfe, 2010; Wolfe y cols., 2010).

1.1.2 Sintomatología, criterios diagnósticos y comorbilidad

Los síntomas que engloba la fibromialgia han sido estudiados desde la década de 1800, identificándolos con una amplia variedad de términos, incluyendo, entre otros, paroxismo histérico, reumatismo muscular, dolor idiopático, miositis, myofibrositis, psychalgia, neurastenia y la ya citada "fibrositis" (Beard, 1869; Boland, 1947; Helleday, 1986; Gowers, 1904; Murray, 1929). Ya en 1980 autores como Moldofsky y Lue observaron la presencia de alteraciones del sueño en pacientes con fibromialgia (Moldofsky y Lue, 1980). Yunus y colaboradores (1981) serían los primeros autores en advertir de la alta prevalencia de síndromes asociados a esta enfermedad, como el síndrome del intestino irritable y los dolores de cabeza. Hudson y colaboradores fueron posiblemente los primeros investigadores en tener en cuenta la fuerte prevalencia familiar de la fibromialgia, proponiendo que esta enfermedad podría ser una variante de

la depresión, conceptualizándola como un trastorno del espectro afectivo (Hudson, Hudson, Pliner, Goldenberg y Pope, 1985; Hudson y Pope, 1989).

Gracias a trabajos como los citados, en la actualidad se reconoce que la fibromialgia, además de presentar dolor músculo-esquelético generalizado, se caracteriza por una heterogénea gama de síntomas como fatiga crónica no ligada a esfuerzo (influida por el dolor, la calidad del sueño y los síntomas depresivos), alteraciones neuroendocrinas y del sueño (insomnio y sueño poco profundo), bruxismo, rigidez muscular matutina, tensión mandibular, deterioro cognitivo leve (atencional y de memoria), alta prevalencia de trastornos de ansiedad y del estado de ánimo, dolor de cabeza, mareos, mala coordinación motora, alteraciones genitourinarias (urgencia urinaria, inflamación en la pared de la vejiga, dolores en la vulva), endometriosis (aparición y crecimiento del tejido endometrial fuera del útero), dismenorrea (o menstruación dolorosa), síndrome de piernas inquietas, dolor torácico, parestesias (percepción de quemazón o pérdida de sensibilidad en las extremidades), cambios auditivos y visuales, alteraciones gastrointestinales (irritación vesicular y biliar), fenómeno de Raynaud (extrema sensibilidad al frío, sobre todo en los dedos), fluctuaciones de peso, alergias, congestión sinusal y nasal, inusual sensibilidad a los medicamentos, problemas de la piel como sequedad o manchas y sensación de hinchazón en las manos, entre otros (Epstein y cols., 1999; Fietta, Fietta y Manganelli, 2007; Hudson, Goldenberg, Pope, Keck y Schlesinger, 1992; Reyes del Paso y cols., 2012; Van Middendorp y cols., 2008; Wolfe y cols., 2010; Yunus 2007).

Se ha demostrado que tales síntomas empeoran, entre otros factores, con el esfuerzo, el estrés (incluyendo el estrés emocional), cambios de clima, el frío, el clima húmedo, la falta de sueño (insomnio), la menstruación (siendo los periodos menstruales más dolorosos), la mala alimentación y consumo de ciertos fármacos (Bennett, Jones, Turk, Russell y Matallana, 2007; Boulware, Schmid y Baron, 1990; Hagglund, Deuser, Buckelew, Hewett y Kay, 1994; Strusberg, Mendelberg, Serra y Strusberg, 2002).

En lo que respecta al diagnóstico, en 1990 el Colegio Americano de Reumatología (*American College of Reumatology*, ACR) desarrolló unos criterios diagnósticos para facilitar su estudio. Estos criterios son los siguientes (Wolfe y cols., 1990):

1. Presencia de dolor generalizado al menos durante 3 meses. Se considera generalizado cuando afecta a cada uno de los cuatro cuadrantes del cuerpo (lado derecho e izquierdo, por encima y por debajo de la cintura). Debe existir dolor en el esqueleto axial (columna cervical, dorsal, lumbar y pared torácica anterior).

2. Dolor a la presión digital (algometría), que implique una fuerza de unos 4 kg, en 11 de los 18 puntos anatómicos clave (palpación dolorosa), llamados puntos gatillo o sensibles. Los puntos gatillo son bilaterales y están situados de la siguiente forma (Boulware y cols., 1990) *(véase Figura 1)*:

- Occipucio: en la intersección del músculo suboccipital (1-2).
- Cervical inferior: en la cara anterior de los espacios intertransversos entre las vértebras C5-C7 (3-4).
- Trapecio: en el punto medio del borde superior (5-6).
- Supraespinoso: en el punto de origen supraescapular del borde medio (7-8).
- Segunda costilla: en las segundas articulaciones osteocondrales (9-10).
- Epicóndilo lateral: 2 cm distal a los epicóndilos (el relieve óseo de húmero donde se originan los músculos extensores del antebrazo) (11-12).
- Glúteo: en los cuadrantes superiores externos de las nalgas y pliegues anterior del músculo (13-14).
- Trocánter mayor: posterior a la protuberancia troncantérica (15-16).
- Rodilla: en la almohadilla medial de grasa cerca de la articulación (músculos en la cara interna de la tibia) (17-18).

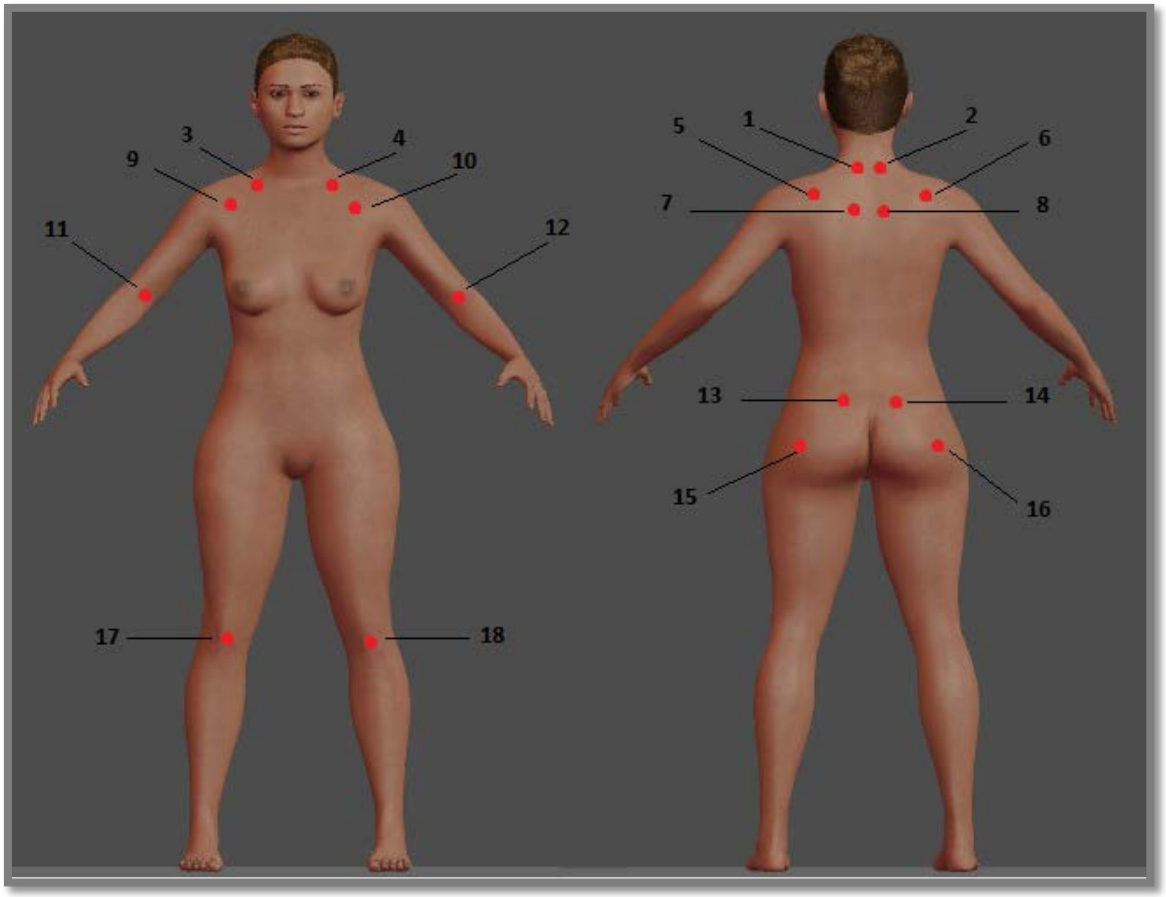

Figura 1. Localización de los puntos dolorosos en la fibromialgia.

En 1992 el II Congreso Mundial del Dolor Miofascial y de la Fibromialgia (Copenhague) acuerda un documento sobre la fibromialgia donde se aceptan los criterios diagnósticos del ACR, añadiéndose otros síntomas como fatiga persistente, rigidez matutina generalizada y sueño no reparador. También se aceptó que las personas afectadas pueden presentar menos de 11 puntos de dolor ("posible fibromialgia"), reconociéndose la complejidad de la enfermedad, que entre otras manifestaciones, puede incluir síntomas de dolor de cabeza, intestino irritable, sensibilidad extrema al frío, dismenorrea, síndrome de piernas inquietas, parestesias, hormigueo y entumecimiento.

De acuerdo con los criterios anteriormente expuestos, la evaluación de la presencia de puntos sensibles tradicionalmente se ha llevado a cabo tanto en contextos clínicos como experimentales. En la práctica clínica se ha procedido de forma manual

siguiendo el criterio del ACR sobre la presencia de un mínimo de 11 puntos de dolor, de los 18 existentes, ante una presión de 4 kg. Si un individuo informa de dolor cuando una de las regiones en las que están presentes estos puntos es estimulada con 4 kg de presión, se considera un punto positivo. En entornos de investigación la sensibilidad se ha evaluado mediante diversos dolorímetros mecánicos (algómetros de presión). Sin embargo, ambos métodos han mostrado que la sensibilidad a la presión en la fibromialgia no se restringe sólo a estos puntos, sino que se extiende por todo el cuerpo (Mikkelsson, Latikka, Kautiainen, Isomeri y Isomaki, 1992; Petzke y cols., 2001; Quimby, Block y Gratwick, 1988; Scudds, Rollman, Harth y McCain, 1987; Sorensen, Graven-Nielsen, Henriksson, Bengtsson y Arendt-Nielsen, 1998; Wolfe y cols., 1995).

Debido a ello y a la baja asociación entre el dolor evocado mediante presión y el dolor clínico, la dificultad en el uso de la algometría de presión en la clínica cotidiana, la alta falsabilidad de los puntos dolorosos en los servicios médicos primarios (donde con mayor frecuencia se diagnostica la fibromialgia), y la alta correlación entre los puntos sensibles y las medidas de malestar psicológico, la utilidad de los puntos gatillo como criterio diagnóstico ha sido cuestionada (Buskila, Neumann, Sibirski y Shvartzman, 1997; Fitzcharles y Boulos, 2003; Petzke, Clauw, Ambrose, Khine y Gracely, 2003; Wolfe, 1997). Por ello, se ha propuesto recientemente un método alternativo para el diagnóstico de la fibromialgia, basado en el uso de dos escalas de auto-informe que comprenden la medida tanto del dolor generalizado (Widespread Pain Index Scale, WPI), como de la severidad de los síntomas (Symptom Severity Scale, SS), incluyendo ésta última la evaluación de problemas cognitivos, sueño no reparador, fatiga, deterioro emocional y síntomas somáticos (Wolfe, 2010, 2011). Este nuevo método detecta el 88,1% de los casos de fibromialgia diagnosticados mediante los criterios del ACR desarrollados en 1990 (Wolfe y cols., 2010). Cabe señalar que la escala de severidad sintomática ha mostrado una alta asociación con el dolor clínico ($r = .733$) (Wolfe y cols., 2010).

Esta enfermedad afecta a las esferas biológica, psicológica y social de la persona que la padece (Amaro, Martín, Soler y Granados, 2006; Collado, 2006; García y Pascual, 2006), su evolución es compleja y variable y en algunos casos puede llegar a ser invalidante (Cathey, Wolfe, Kleinheksel, Millner y Petteti, 1988; Wolfe y Potter, 1996). La evolución, severidad e impacto de los síntomas de la fibromialgia dependerá

de variables individuales tales como el manejo de los síntomas, el nivel de depresión, las creencias, expectativas, tiempo trascurrido hasta su diagnóstico, nivel social, económico, laboral y educativo, nivel de estrés y forma de afrontar éste, etc. (Goldenberg, 2003).

En cuanto a la comorbilidad, la fibromialgia puede ir asociada a otras enfermedades, entre las que destacan el síndrome de dolor miosfacial, el síndrome de intestino irritable, el síndrome articular temporomandibular, síndrome de vejiga dolorosa (o cistitis intersticial) y el síndrome de fatiga crónica. El Síndrome de Fatiga Crónica consiste en fatiga prolongada y debilitante, además de múltiples síntomas inespecíficos como dolor de cabeza, dolor de garganta recurrente, quejas neurocognitivas y dolor muscular y articular (Fukuda y cols., 1994; Holmes y cols., 1988), incluyendo dolor generalizado y persistente (Buchwald, 1996; Goldenberg, Simms, Geiger y Komaroff, 1990). Esta condición ha sido el síndrome más relacionado con la fibromialgia. La evolución de este síndrome conlleva en muchos casos su asociación con otros síndromes y enfermedades relacionadas, entre los cuales se encontraría la fibromialgia (Fernández-Solà, 2004). No obstante, a pesar de las similitudes entre los dos síndromes, los estudios disponibles ponen de manifiesto que las estructuras cerebrales activadas durante el procesamiento del dolor difieren entre ambos (Costa, Tannock y Brostoff, 1995; Mountz y cols., 1995; Tirelli y cols., 1998). Además, mientras que en la fibromialgia se ha observado una elevación del nivel de la sustancia P en el fluido cerebroespinal, ésta elevación no ha sido observada en el Síndrome de Fatiga Crónica (Evengard y cols., 1998; Russell y cols., 1994;). Por el contrario, las disrregulaciones inmunológicas observadas en el Síndrome de Fatiga Crónica en cuanto a la vía inmunológica 2-5A Sintetasa/RNasa L no han sido detectadas en pacientes con fibromialgia (Nijs y De Meirleir, 2005).

A parte de su asociación con las enfermedades citadas de tipo reumático, la fibromialgia también puede asociarse a otras patologías, siendo las más comunes las siguientes: Lupus sistémico eritematoso, artritis reumatoide, espondiloartropatías, esclerosis múltiple, hipotiroidismo, neuropatías periféricas, alteraciones estructurales mecánicas o degenerativas del raquis, miopatía (metabólica o inflamatoria), polimialgia reumática, trastornos somatomorfos, trastorno depresivo mayor, trastornos facticios y simulación (Alfonso, Álvarez y Alegre, 2000).

1.1.3 Epidemiología.

La fibromialgia afecta del 2 al 4% de la población general (Wolfe y cols., 1990; Wolfe y cols., 1995) y aproximadamente el 15% de los pacientes en muestras reumatológicas entre los diferentes Países (Neumann y Buskila, 2003). La fibromialgia tiene un claro predominio femenino, afectando aproximadamente al 3,4% de las mujeres y el 0,5% de los hombres (Wolfe y cols., 1990). La mayor prevalencia se sitúa entre los 40 y los 49 años, presentando un curso crónico (Cathebras, Lauwers y Rousset, 1998; Collado, 2008; Mas, Carmona, Valverde y Ribas, 2008). No obstante, se han encontrado casos en adolescentes e incluso en niños pequeños (Conte, Walco y Kimura, 2003; Yunus y Masi, 1985). Debido a su alta prevalencia en la población adulta, el todavía insuficiente conocimiento de los mecanismos implicados en la misma y la ausencia de un tratamiento de mediana eficacia, en la actualidad constituye uno de los problemas sanitarios más importantes de dolor crónico en los países industrializados y en vías de desarrollo, variando la prevalencia a nivel internacional de forma significativa, desde el 0,4% en Grecia (Guermazi y cols., 2008) al 9,3% en Túnez (África) (Andrianakos y cols., 2003) (*Ver Queiroz, 2013*). Datos referentes a España en el año 2008 cifran la prevalencia de la fibromialgia en un 2,4% de la población general, dándose de forma casi exclusiva en mujeres (4,2% con respecto al 0.2% en hombres) (Mas y cols., 2008). Además de su alta prevalencia, entre las distintas enfermedades de dolor crónico, la fibromialgia conlleva un mayor impacto en la salud de los pacientes (Hoffman y Dukes, 2008) y unos costes socio-sanitarios superiores en comparación con otras enfermedades de forma general (Lachaine, Beauchemin y Landry, 2010; Wolfe y cols., 1997).

1.1.4 Etiopatogénesis.

A pesar de las extensas investigaciones realizadas, en la actualidad la etiología y fisiopatología de la fibromialgia se desconocen, no hay signos somáticos específicos del trastorno, y no se ha encontrado una causa que justifique los síntomas que engloba la misma. La fibromialgia se consideraría por lo tanto dentro del espectro de síndromes sin explicación médica (Jackson y Kroenke, 2008).

No obstante, existen varias hipótesis acerca de la etiopatogenia de la fibromialgia, detallándose a continuación las más relevantes:

La principal de ellas implicaría un procesamiento central anormal del dolor y deficiencias en los mecanismos centrales inhibitorios del dolor (Jensen y cols., 2009). De esta forma, se produciría una alteración en el sistema nociceptivo, dando lugar a que las vías dolorosas ascendentes que trasmiten el dolor no se desconecten, produciéndose un aumento en la respuesta de dolor y activándose vías nerviosas que normalmente no trasmiten sensaciones de dolor (Price & Staud., 2005). En presencia de un daño tisular mínimo e indetectable, se produciría una amplificación de la señal nociceptiva debido a la hiperexcitabilidad neuronal (Banic y cols., 2004). En otras palabras, se observaría un fenómeno de sensibilidad central al dolor, lo que resultaría en hiperalgesia (disminución del umbral de dolor con una mayor respuesta a estímulos dolorosos) y alodinia difusa (respuestas dolorosas ante estímulos inocuos o no dolorosos, como por ejemplo el tacto) (Loggia y cols, 2014; Price y Staud, 2005; Sumpton y Moulin, 2013). Dada su mayor relevancia y por ser objeto de la presente Tesis Doctoral, se profundizará de forma detalla en esta hipótesis en los siguientes apartados.

Alternativamente, otra posibilidad consiste en un mal funcionamiento de los sistemas inhibitorios periféricos del dolor, como el constituido por el Sistema Cardiovascular (Furlan y cols., 2005; Martínez-Lavín, 2004; Thieme y col., 2006). En este sentido, los estudios disponibles muestran diversas alteraciones en la regulación autonómica cardiovascular, así como un funcionamiento aberrante del reflejo barorreceptor (el mecanismo implicado en el efecto anti-noceptivo mediado por el sistema cardiovascular), que predicen tanto el dolor clínico (Reyes del Paso, Garrido,

Pulgar, Martin y Duschek, 2010) como el dolor evocado experimentalmente en la fibromialgia (Reyes del Paso, Garrido, Pulgar y Duschek, 2011). Además de la rama cardiovascular del reflejo barorreceptor que amortigua las oscilaciones de la presión arterial, existe una rama central que consta de una vía de retroalimentación negativa al cerebro por la cual la función cardiovascular modula la actividad del Sistema Nervioso Central (SNC), y produce un efecto inhibidor generalizado en estructuras cerebrales (Rau y Elbert, 2001). Esta inhibición generalizada del SNC en la que interviene el sistema barorreceptor es uno de los mecanismos que median la conocida asociación entre presión sanguínea y la sensibilidad al dolor (France, 1999). De esta forma se produciría una relación inversa entre la experiencia subjetiva de dolor y los niveles de presión arterial (Bruehl y Chung, 2004; Duschek, Dietel, Schandry y Reyes del Paso, 2009; Duscheck, Schwarzkopf y Schandry, 2008; France, 1999; Ghione, 1996; Reyes del Paso y Perales, 2011). En pacientes con fibromialgia se ha observado una sensibilidad del reflejo barorreceptor muy disminuida, además de una presión sanguínea menor en comparación con participantes sanos (Reyes del Paso y cols., 2010, 2011).

Siguiendo esta línea, la fibromialgia y otros trastornos relacionados parecen reflejar deficiencias en la transmisión serotoninérgica y noradrenérgica, fallando así los mecanismos de inhibición del dolor y produciéndose un aumento del procesamiento del dolor a nivel del Sistema Nervioso Central. Ello también podría ser debido a un aumento de neurotransmisores como el glutamato y la sustancia P (Clauw, 2009). De esta forma, podríamos distinguir entre los sistemas relacionados con la amplificación del dolor en los que intervienen los receptores NMDA, sustancia P, factor de crecimiento nervioso, dinorfinas y aminoácidos excitatorios, que parecen estar hiperactivados, y los relacionados con la inhibición del dolor en los que intervienen sustancias químicas como noreprinefrina, serotonina, dopamina, y endorfinas, que parecen estar hipoactivados (Neeck y Riedel, 1994; Russell, 1994; Rusell y cols., 1994). Más recientemente se ha observado que la actividad endógena opioide está alterada (Baraniuk, Whalen, Cunningham y Clauw, 2004; Harris, Clauw, Scott, McLean, Gracely & Zubieta, 2007), evidencia acorde con la menor eficacia de los opiáceos exógenos en el tratamiento de la fibromialgia (Ngian, Guymer y Littlejohn, 2011; Peng y cols., 2015). Existen pruebas de que los opioides pueden empeorar la hiperalgesia relacionada con la fibromialgia y otros estados de dolor de origen central, por medio de hiperalgesia inducida por opioides (Brummett y cols., 2013).

También se ha planteado una cierta contribución genética, ya que se ha observado una cierta agregación familiar en la fibromialgia (Arnold y cols., 2004; Buskila y Sarzi-Puttini, 2006), aunque actualmente no existen datos concluyentes. Se ha encontrado en estos pacientes una mayor frecuencia de ciertos polimorfismos del gen trasportador de la serotonina 5-HTT (concretamente el genotipo corto 5-HTTLPR) en comparación con controles sanos (Cohen, Buskila, Neumann y Ebstein, 2002; Offenbaecher y cols., 1999), el cual también se asocia con el trastorno depresivo mayor y la ansiedad (Graeff, 1997). Por otra parte, algunos estudios, han encontrado que el genotipo homocigoto Met/Met es significativamente más frecuente en enfermos con fibromialgia que en controles sanos. El polimorfismo homocigoto Met/Met (que condiciona una baja actividad enzimática de la Catecol O-metiltransferasa), se ha relacionado con mayores puntuaciones en el FIQ (Cuestionario de Impacto de la Fibromialgia, que mide el grado de gravedad e interferencia de la enfermedad) (García, Lao-Villadóniga, Beyer y Santos, 2006). La Catecol O-metiltransferasa (COMT), la principal enzima que degrada las catecolaminas (norepinefrina, epinefrina y dopamina), a su vez ha sido implicada en la modulación del dolor (Diatchenko y cols., 2005) y en la fibromialgia de forma específica (Gursoy y cols., 2003; Vargas-Alarcon y cols., 2007). Se ha llegado a sugerir que la baja actividad enzimática de la COMT podría producirse mediante la interacción ambiente-genética (Martínez-Lavín y Hermosillo, 2000; Martínez-Lavin y cols., 2002). No obstante, es importante añadir que estos estudios hoy en día no han podido ser replicados.

Igualmente se ha planteado la existencia de alteraciones autoinmunes, pero las investigaciones no han revelado ninguna alteración concreta (Buskila y Sarzi-Puttini, 2008; Caro, 1989; Caro y Winter, 2014; Caro, Winter y Dumas, 2008). Como ejemplo de ello, se ha observado una asociación significativa entre la fibromialgia y la presencia de polineuropatía desmielinizante mediada inmunológicamente (Caro y cols., 2008), siendo esta idea reforzada por la presencia de neuropatía de fibras pequeñas (o neuropatía periférica) (Caro y Winter, 2014).

Además, la fibromialgia se ha asociado repetidamente con estresores vitales en la infancia/adolescencia (eventos traumáticos tales como abusos sexuales/malos tratos y/o negligencia emocional) y con una mayor prevalencia de problemática social, laboral y familiar grave. Se ha observado que los pacientes muestran una vulnerabilidad

psicológica que comprende una historia vital traumática, perseverancia sobre-compensatoria (obstinación), percepción pesimista de la vida y situación laboral insatisfactoria (Hallberg y Carlsson, 1998). También se ha informado de una mayor frecuencia de accidentes (como accidentes de tráfico) que involucran pequeños traumatismos físicos con anterioridad al inicio del trastorno (Al-Allaf y cols., 2002; Buskila, Neumann, Vaisgerg, Alkalay y Wolfe, 1997). No obstante, se ha demostrado que estos eventos traumáticos físicos tendrían poco impacto en la aparición de dolor generalizado, explicándose en mayor medida en parte por el malestar psicológico (Wynne-Jones, Macfarlane, Silman y Jones, 2006). Se podría considerar que todos estos factores podrían actuar como predisponentes para el trastorno o al menos para el inicio de una respuesta desadaptativa al estrés futuro (McLean, Williams y Clauw, 2005).

En esta línea diferencias interindividuales en las respuestas emocionales al estrés también pueden ser relevantes en la modulación de los resultados de adaptación y de salud psicosocial en la fibromialgia (Crofford y Demitrack, 1996; Goldenberg, 1996), donde la vulnerabilidad puede ir asociada en parte a formas no adaptativas de regular las emociones y responder a los estímulos aversivos (Bartley, Rhudy y Williams, 2009; Duschek, Werner, Limbert, Winkelmann y Montoya, 2014). Se ha sugerido que las respuestas anormales ante el estrés serían un importante mecanismo fisiopatológico que contribuiría a la predisposición a la fibromialgia (Crofford y cols., 2004). De esta forma se han relacionado patrones psicofisiológicos específicos de respuesta con el afrontamiento psicológico y los desórdenes mentales en la fibromialgia (Thieme, Turk, Gracely, Maixner y Flor, 2015). Los factores psicológicos han demostrado su influencia en la intensidad del dolor y modulación de la gravedad del malestar percibido en la fibromialgia (Hassett, Cone, Patella y Sigal, 2000). La menor educación y otros indicadores de bajo estatus social también han sido consistentemente identificados como factores de riesgo en el desarrollo de la fibromialgia (Bergman, 2005; Macfarlane, Norrie, Atherton, Power y Jones, 2009).

1.2 FENÓMENO DE SENSIBILIZACIÓN CENTRAL AL DOLOR EN LA FIBROMIALGIA.

Si bien se ha apuntado en el apartado anterior la existencia de varias teorías que pretenden esclarecer la etiología de la fibromialgia, en la actualidad entre éstas la que está recibiendo mayor apoyo empírico es la concerniente a la implicación de un fenómeno de Sensibilización Central al Dolor y deficiencias en los mecanismos inhibitorios del dolor en la fibromialgia (Clauw, 2014; Gracely y Ambrose, 2011; Jensen et al., 2009).

En circunstancias anormales las personas pueden experimentar dolor sin estimulación nociva como consecuencia de un daño neural concreto, lo que comúnmente llamaríamos dolor neuropático (Baron, Binder y Wasner, 2010; Costigan, Scholz y Woolf, 2009). Sin embargo, el dolor también puede aparecer de forma espontánea sin lesión neural aparente, como sería el caso de la fibromialgia, donde se podría producir un fenómeno de Sensibilización Central al Dolor por cambios neuroplásticos que pueden ocurrir en el SNC, conduciendo así a una transmisión del dolor aumentada. Estos cambios neuroplásticos vendrían determinados por un aumento en la actividad espontánea, la mejora de la capacidad de respuesta ante los estímulos tanto nociceptivos como no nociceptivos y una ampliación de los campos receptivos de las fibras C de las neuronas del asta dorsal de la médula espinal, estando estos cambios mediados por la proteína Kinasa C, óxido nítrico, diversos neurotransmisores y prostaglandinas (Coderre, Katz, Vaccarino y Melzack, 1993; Dougherty, Palecek, Paleckova, Sorkin y Willis, 1992; Staud y Smitherman, 2002). Las consecuencias incluirían dolor espontáneo, así como hiperalgesia y alodinia (Loggia y cols., 2014; Price y Staud, 2005; Sumpton y Moulin, 2013). De esta forma, los síntomas de la fibromialgia podrían ser mantenidos por amplificación de las respuestas neuronales aferentes ante estímulos sensoriales (Cook y cols., 2004).

Esta noción ha sido apoyada mediante diversos estudios en los que se ha examinado la sensibilidad al dolor experimental en la fibromialgia. Se ha encontrado que las pacientes con fibromialgia presentan bajos umbrales de dolor, menor tolerancia

al dolor, una mayor experiencia sensorial y afectiva en cuanto al dolor, y la presencia de alodinia ante diferentes estímulos de dolor (Desmeules y cols., 2003; Duschek y cols., 2012; Granges y Littlejohn, 1993; Jensen y cols., 2009; Petzke y cols., 2003; Price y Staud., 2005; Reyes y cols., 2011).

Asimismo, las técnicas de neuroimagen, como la resonancia magnética funcional (fMRI) han sido de especial utilidad para analizar las respuestas de flujo sanguíneo cerebral (FSC) ante estimulación dolorosa moderada y conocer las bases neuronales del dolor aumentado en la fibromialgia. Esta estimulación dolorosa se ha llevado a cabo mediante diversos métodos que incluyen presión mecánica y estimulación cutánea eléctrica y térmica (mediante frio y calor). En estos estudios se ha observado que, aunque las áreas cerebrales activadas tanto en condiciones de dolor experimental (Gracely y cols., 2004) como durante reposo (Cook y cols., 2004) no difieren entre controles sanos y pacientes con fibromialgia, si se observa una mayor activación de estas áreas en pacientes con fibromialgia, con mayores diferencias en las regiones implicadas en el procesamiento de aspectos sensoriales, cognitivos y emocionales del dolor (Cook y cols., 2004). Se observa una actividad exagerada en la neuromatriz del dolor, o lo que es lo mismo, un claro aumento de la respuesta al dolor a nivel central (Cook y cols., 2004; Gracely, Petzke, Wolf y Clauw, 2002; Pujol y cols, 2009). Asimismo, se ha evidenciado un debilitamiento de las conexiones entre estructuras cerebrales relacionadas con la inhibición del dolor y una exagerada conexión entre las estructuras cerebrales facilitadoras del dolor (Cifre y cols., 2012; Napadow y cols., 2010; Pujol y cols., 2014). En este contexto, Jensen y colaboradores (2009) han encontrado una disminución de la capacidad para activar áreas del cerebro implicadas en la modulación endógena del dolor, como sería el caso de la corteza cingulada anterior rostral y regiones del tronco cerebral. Recientemente, Pujol y colaboradores (2014) han observado la existencia de un patrón de conectividad anormal que implicaría a la sustancia gris periacueductal, apoyando la existencia de alteraciones en las vías ascendentes implicadas en la modulación sensorial del dolor.

De esta forma, se observaría una mayor activación específica en áreas como la corteza prefrontal (que implica un aumento del dolor de origen periférico), la corteza motora suplementaria, la ínsula (implicada en la codificación de la intensidad sensorial del estímulo), la corteza cingulada anterior (anticipación, atención y recuerdos de

dolor), la corteza sensorio-motora (posible inhibición motora para evitar la retirada de la mano estimulada), el tálamo derecho (función de relé para la transmisión de los componentes sensoriales y discriminativos del dolor al sistema lateral del dolor) y los ganglios basales, en pacientes con fibromialgia (Burgmer y cols., 2009; Cook y cols., 2004; Gracely y cols., 2002; Pujol y cols., 2009; Qiu y col., 2006). Algunos autores han llegado a sugerir una activación especifica de áreas cerebrales relacionadas con la elaboración emocional y cognitiva del dolor en pacientes con fibromialgia, en contraste con el procesamiento del dolor predominantemente sensorial en individuos sanos (Burgmer y cols., 2009; Pujol y cols., 2009), dado que la respuesta en estos últimos se encuentra más restringida a la corteza somatosensorial (Pujol y cols., 2009). Esta conclusión se ha basado en la mayor activación de estructuras que constituyen el sistema medial del dolor y por tanto implicadas en la elaboración cognitiva y emocional del dolor, en pacientes con fibromialgia.

Los estudios que han examinado los sistemas regulatorios del dolor han sido de especial ayuda para entender los procesos patológicos involucrados en la aberrante nocicepción y apoyar la implicación de un fenómeno de Sensibilización Central al Dolor. En este sentido, los trabajos que indagan en el efecto de “sumación temporal” (windup) son de especial relevancia. Estos estudios se basan en la presentación repetida de estímulos cutáneos mecánicos o térmicos, los cuales provocan la activación específica de nociceptores C no mielinizados (Vierck, Cannon, Fry, Maixner y Whitsel, 1997). Estos receptores están situados en la dermis y son propensos a una prolongada descarga en respuesta a estímulos químicos, mecánicos, térmicos y sustancias liberadas tras daño tisular (Holzer, 1991; Torebjork y Hallin, 1974). Los inputs procedentes de los nociceptores C no mielinizados activan receptores de segundo orden en las neuronas, por ejemplo para el N-metil-D-aspartato (NMDA), induciendo a la entrada de calcio en las neuronas del asta dorsal (Bennet, 2000), lo que origina a su vez la liberación de la enzima óxido nítrico sintetasa, responsable de la síntesis de óxido nítrico (Meller y Gebhart, 1993). La liberación de óxido nítrico afectaría a la liberación de neuropéptidos sensoriales como la sustancia P (Luo y Cizkova, 2000), un neurotrasmisor nociceptivo que reduce el umbral de excitabilidad sináptica, sensibilizando a las neuronas del asta dorsal y expandiendo sus campos receptivos, dado su poder de extensión a lo largo de la médula espinal (Liu y cols., 1994; Staud, 2002).

Mediante esta metodología, las pacientes con fibromialgia han mostrado una exagerada respuesta de sumación temporal del segundo dolor ante estímulos de dolor repetitivos (Staud, Vierck, Cannon, Mauderli y Price, 2001), así como una prolongación temporal en el intervalo de decadencia de este segundo dolor en comparación con personas sanas sin dolor. Este aumento en el periodo de decadencia del segundo dolor se produciría debido a que una vez que ha ocurrido el efecto de "sumación temporal", las frecuencias bajas de estimulación provocarían el mantenimiento de las respuestas de las fibras C de las neuronas del asta dorsal, aumentando la sensibilidad al dolor (mantenimiento de la "sumación temporal" del segundo dolor) (Liu y cols., 1994; Staud, Price, Robinson, Mauderli y Vierck., 2004; Staud, Robinson y Price, 2007). Se observa así que el último estímulo de dolor mecánico o térmico de cada serie produce mayores percepciones de dolor, además de una mayor duración y frecuencia de éstas, en pacientes con fibromialgia (Staud y cols., 2001).

Se ha planteado que el efecto de "sumación temporal" refleja en pacientes con fibromialgia alteraciones a nivel central y no a nivel periférico (Staud, Courtney, Robinson y Price, 2008). Aunque los estudios disponibles con esta metodología muestran que la activación y conexión entre las distintas regiones cerebrales no difiere sustancialmente entre participantes sanos y pacientes con fibromialgia (Craggs y cols., 2012), se destaca la necesidad de una mayor magnitud en la intensidad del estímulo doloroso necesaria para producir el efecto de "sumación temporal" y activar las zonas cerebrales relacionadas con el dolor en participantes sanos frente a pacientes con fibromialgia (Staud, Craggs, Perlstein, Robinson y Price., 2008). Por añadidura, se pueden observar patrones únicos de activación al dolor en el hemisferio izquierdo en pacientes con fibromialgia: S1 (corteza somatosensorial primaria), S2 (corteza somatosensorial secundaria) e ínsula posterior (Craggs y cols., 2012), áreas relacionadas con aspectos sensoriales y discriminativos del dolor (Peyron, Laurent y Garcia-Larrea, 2000).

No obstante, hay que precisar que los datos disponibles a este respecto no son del todo concluyentes. Existen estudios cuyo planteamiento parte de la posibilidad de manipulación del efecto de sumación temporal, dado su carácter central, en pacientes con fibromialgia mediante la administración de analgésicos, siendo los resultados poco satisfactorios, ya que los efectos producidos por los analgésicos son similares entre

participantes sanos y pacientes con fibromialgia (Price y cols., 2002). Por ejemplo, dosis orales del antagonista DEX del receptor NMDA producen la atenuación de la "sumación temporal" del segundo dolor ante estimulación mecánica de forma semejante en pacientes con fibromialgia y participantes sanos (Staud, Vierck, Robinson y Price, 2005).

Análogamente, se ha planteado la existencia de deficiencias en el control difuso inhibitorio medular (DNIC), sistema modulador del dolor que se basa en mecanismos espinales y supraespinales (Kosek y Hansson, 1997; Lautenbacher y Rollman, 1997). Experimentalmente, el control difuso inhibitorio se ha estudiado en relación con el efecto de "sumación temporal". Para ello se provoca la activación del mismo incluyendo un estímulo distractor (aplicación de un estímulo nocivo intenso en una parte del cuerpo distal a la estimulada mediante un segundo estímulo nocivo) que provoque la inhibición del segundo dolor. Aunque se ha demostrado que las pacientes con fibromialgia exhiben déficits en el control difuso inhibitorio medular, los resultados apuntan a que los efectos del control difuso inhibitorio en la sumación temporal del segundo dolor son específicos del género, careciendo las mujeres en general de este mecanismo (Staud, Robinson, Vierck y Price, 2003).

También se ha destacado la ausencia de respuesta analgésica inducida por el ejercicio aeróbico (Kosek, Ekholm y Hansson, 1996; Mengshoel, Saugen, Forre y Vøllestad, 1995). Durante la realización de contracciones isométricas se ha observado una disminución en el umbral de dolor en pacientes con fibromialgia, lo que indicaría la presencia de sensibilización de los mecanonociceptores y/o una disfunción en la modulación del dolor durante contracción muscular (Kosek y cols., 1996). Además de ello, se ha observado también un menor aumento de las concentraciones de catecolaminas en plasma durante el ejercicio en estos pacientes (Mengshoel y cols., 1995).

Los estudios expuestos anteriormente, que han analizado las respuestas de FSC como indicadores se Sensibilización Central al Dolor, han utilizado en su mayoría técnicas de imagen cerebral como la resonancia magnética funcional (fMRI), la cual posee una alta resolución espacial, pero está limitada en cuanto a la detección de los

cambios temporales rápidos, y por tanto, no es óptima para el análisis de la dinámica temporal del flujo sanguíneo cerebral (Stroobant y Vingerhoets, 2000).

El análisis de los patrones temporales de reactividad cerebral al dolor podría ser de utilidad como posible indicador de Sensibilización Central al Dolor y puede aportar información complementaria a la aportada por las técnicas clásicas de imagen cerebral. Este análisis se puede realizar mediante metodologías más resolutivas temporalmente como el análisis del flujo sanguíneo cerebral con técnicas de *ultrasonografía Doppler transcraneal funcional* (fTCD) (Deppe, Ringelstein y Knecht, 2004; Duschek y Schandry, 2003). Estas técnicas permiten evaluar los cambios rápidos hemodinámicos en la circulación intracraneal, obteniendo una medida del FSC en las grandes arterias cerebrales.

1.3 TÉCNICA DE ULTRASONOGRAFÍA DOPPLER TRANSCRANEAL FUNCIONAL (fTCD)

La utilización de la técnica de *ultrasonografía Doppler transcraneal funcional* (fTCD) (*Ver imagen 1*) se remonta a los primeros trabajos de Aaslid (Aaslid, Markwalder y Nornes., 1982), y se basa en el principio desarrollado por el físico y matemático austriaco Christian Doppler en 1842 (“efecto doppler” o cambio de frecuencia de una onda producido por el movimiento relativo de la fuente respecto a su observador) (Roguin, 2002). De forma general, esta técnica permite el registro continuo no invasivo de los cambios en la velocidad del flujo sanguíneo cerebral (asociados a la activación neuronal) en las arterias cerebrales basales (*Ver imagen 2*). Las arterias cerebrales basales conformarían la arteria cerebral anterior, cuyas ramas corticales irrigan la cara medial y superior de los lóbulos frontal y parietal, la arteria cerebral media, cuyas ramas corticales irrigan la superficie lateral de los hemisferios cerebrales, incluyendo el polo anterior del lóbulo temporal (o área de asociación límbica), y la arteria cerebral posterior cuyas ramas corticales irrigan la superficie medial e inferior de los lóbulos temporal y occipital y continúan hasta parte de la superficie lateral de estos lóbulos (*Ver figura 2*). No obstante, las fronteras de los territorios vasculares pueden

variar entre los individuos (Van der Zwan y Hillen, 1991; Van der Zwan, Hillen, Tulleken, Dujovny y Dragovic, 1992, 1993). A diferencia de las arterias que poseen vasos sanguíneos de diámetro pequeño, los de las arterias basales insonadas mediante fTCD permanecen prácticamente sin cambios en diversas condiciones de estimulación, por lo que los cambios en flujo sanguíneo cerebral en estas arterias no resultarían de su propia actividad vasomotora, sino que reflejan cambios en las tasas metabólicas en sus territorios de perfusión (Giller, Bowman, Dyer, Mootz y Krippner, 1993; Kontos, 1989). Dado el acoplamiento metabólico que se produce entre activación neuronal y riego sanguíneo, se pueden registrar los cambios en la actividad neural regional transformados en cambios en velocidad de flujo sanguíneo en las arterias cerebrales basales (Deetjen y Speckmann, 1994; Jueptner y Weiller, 1995).

Imagen 1. Técnica de ultrasonografia Doppler transcraneal funcional

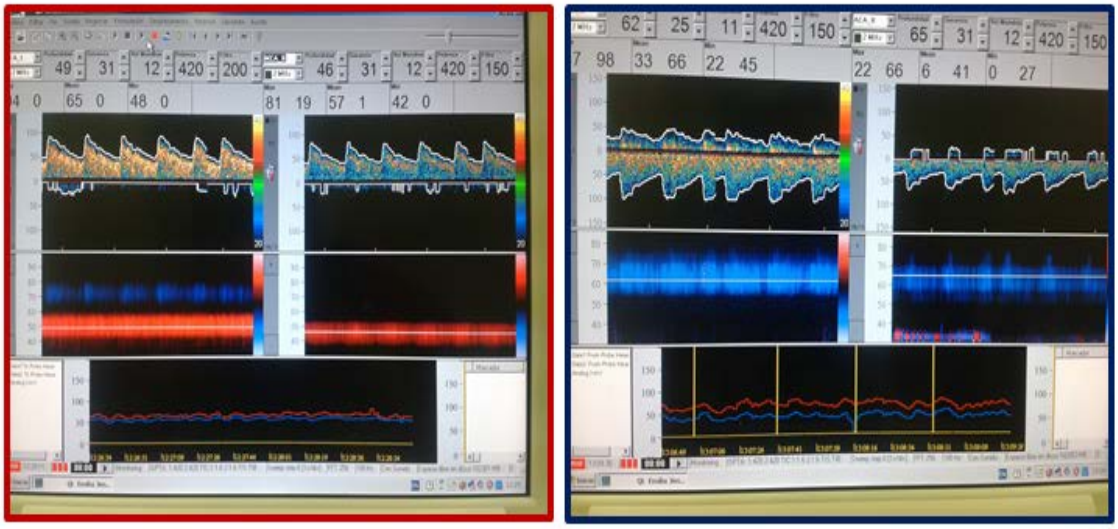

Imagen 2. Registro continuo en las arterias cerebrales media y anterior

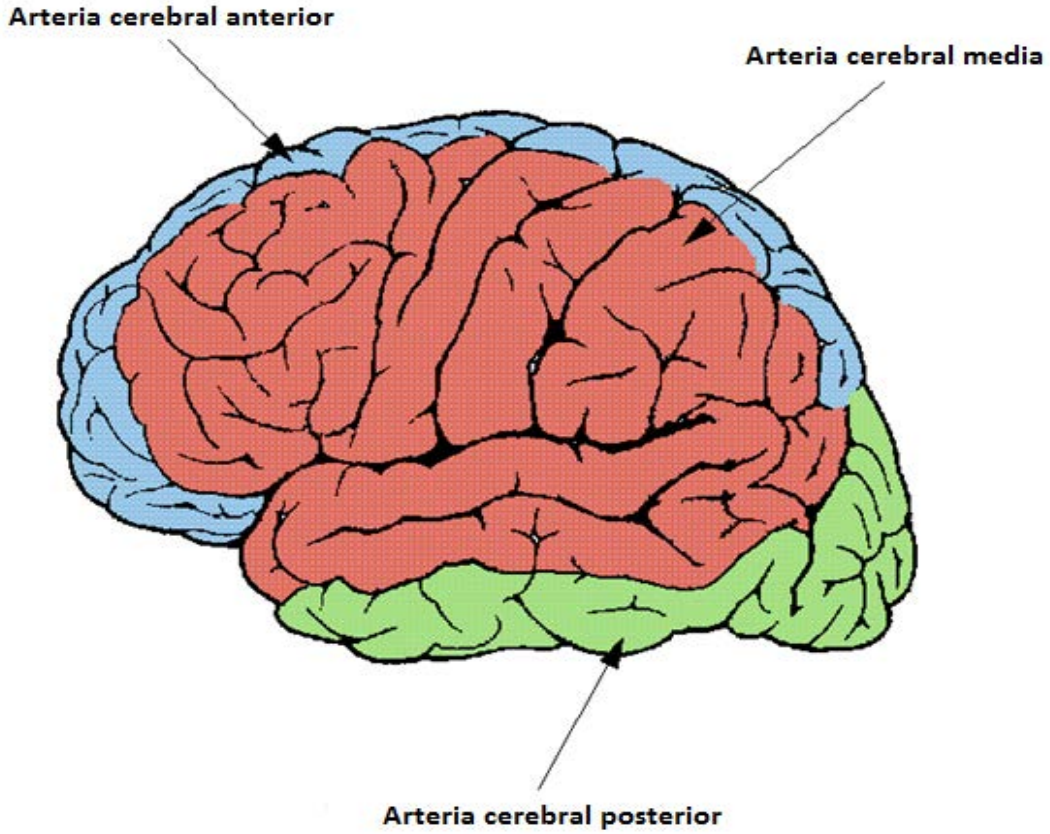

Figura 2. Zonas de vascularización de las arterias cerebrales basales.

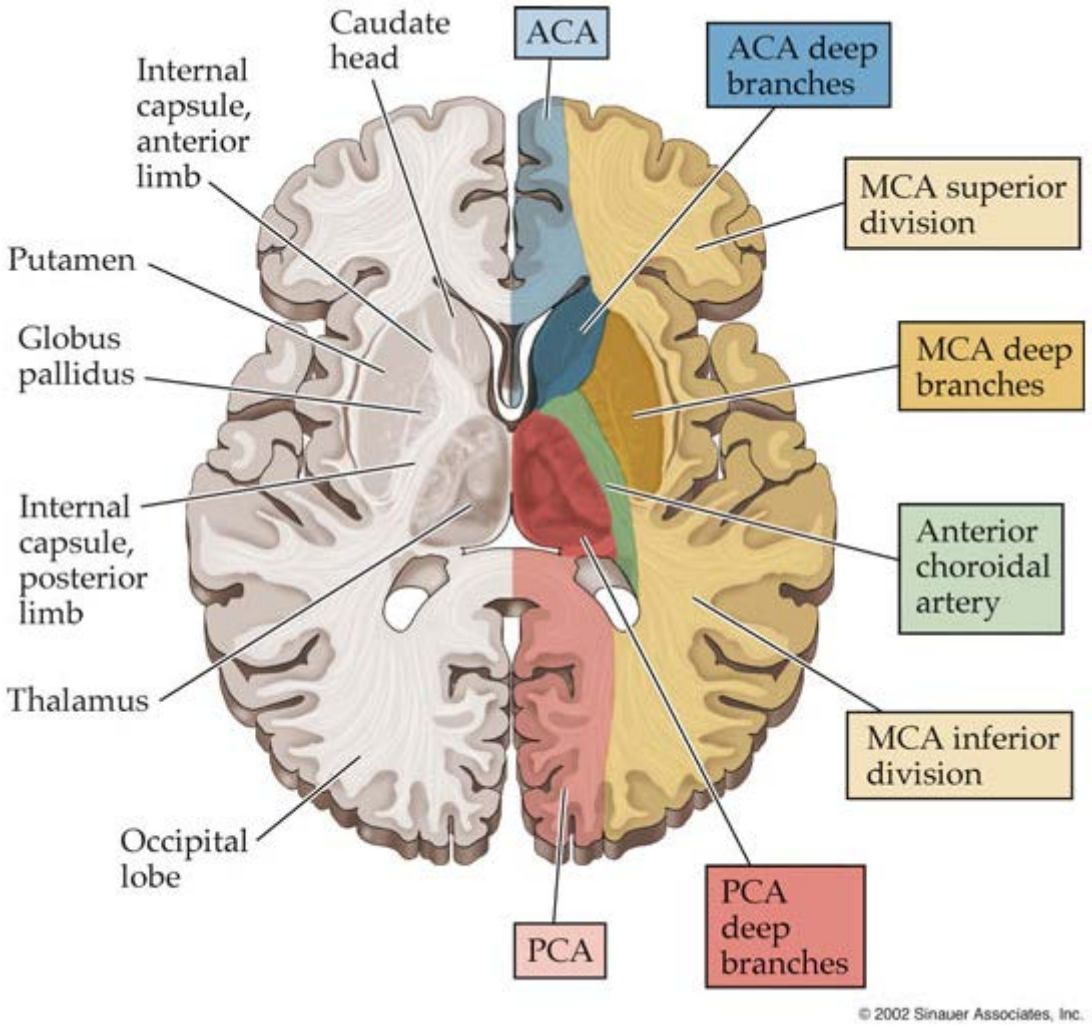

Figure 2. Sección transversal zonas de vascularización de las arterias cerebrales basales.

La técnica de fTCD ha demostrado su utilidad en el estudio de la modulación hemodinámica cerebral en pacientes con fibromialgia. Aunque hay que subrayar que hasta ahora los datos disponibles mediante este tipo de metodología son escasos, se ha observado mediante esta técnica y usando estimulación térmica, la existencia de un componente temprano de aumento (presente tras los 2-3 segundos posteriores al inicio del estímulo doloroso) en flujo sanguíneo cerebral en la arteria cerebral anterior (ACA), de mayor magnitud para las pacientes con fibromialgia que para los controles sanos. Este componente sería indicativo de la presencia de hiperactividad en las estructuras mediales implicadas en la nocicepción, en concreto las estructuras relacionadas con los

aspectos afectivos y cognitivos del dolor, cuya activación, además, se relacionó con la severidad del dolor clínico presente en los pacientes (Duschek y cols, 2012). Por el contrario, no se hallaron diferencias en las respuestas de flujo sanguíneo cerebral en la arteria cerebral media (ACM), la cual suministra a las áreas cerebrales laterales, incluyendo las cortezas somatosensoriales, implicadas en los aspectos sensoriales y discriminativos del dolor. Estos datos serían congruentes con la sugerencia previa de Burgmer y colaboradores (2009), en cuanto a la activación específica de áreas cerebrales relacionadas con la elaboración emocional y cognitiva del dolor en fibromialgia.

1.4 FACTORES COGNITIVOS Y EMOCIONALES: SU INFLUENCIA EN LA SENSIBILIZACIÓN CENTRAL AL DOLOR EN LA FIBROMIALGIA.

De acuerdo con la sugerencia de la activación específica de áreas cerebrales relacionadas con la elaboración emocional y cognitiva del dolor en la fibromialgia (Burgmer y cols., 2009; Duschek y cols., 2012), se ha sugerido el posible papel clave mediador de los factores cognitivos y emocionales en el fenómeno de Sensibilización Central al Dolor en esta enfermedad (Clauw y Crofford, 2003; Cook y cols., 2004; Duschek y cols., 2012; Giesecke y cols., 2003, 2005; Gracely y cols., 2002, 2004; Montoya, Pauli, Batra y Wiedemann, 2005; Thieme, Spies, Sinha, Turk y Flor, 2005).

El dolor es una percepción compleja que está influenciada por la experiencia previa y por el contexto en el que el estímulo nociceptivo se produce (Winkelstein, 2004). Un modelo muy usado para entender el dolor es el de la teoría de la compuerta de Melzack y Wall (1965), en el que el dolor se entiende como un fenómeno multidimensional con tres dimensiones: Sensorial-discriminativa (intensidad, magnitud y localización del dolor), cognitiva-evaluativa (actitudes, creencias, expectativas y pensamientos) y motivacional-afectiva (desagradable o nocivo, escape, ansiedad). Por ello, es fácil de entender que el dolor como experiencia multidimensional se vea afectado por factores atencionales, emocionales y cognitivos, además de la experiencia previa (Bantick y cols., 2002; McMahon, y Wall, 2006; Wager y cols., 2004), jugando

estos factores un papel clave en la transición del dolor de agudo a crónico (Cook y cols., 2004; Giesecke y cols., 2003, 2005; Gracely y cols., 2004; Montoya y cols., 2005; Thieme y cols., 2005). Se ha observado que las regiones cerebrales activadas ante condiciones de dolor agudo y de dolor crónico fundamentalmente difieren en áreas relacionadas con la evaluación cognitiva y emocional del dolor (por ejemplo, la amígdala) (Apkarian, Bushnell, Treede y Zubieta, 2005). Factores afectivos y cognitivos, como la anticipación, la atención, los estados de ansiedad o depresivos, podrían modular la percepción del dolor al influir en la activación de áreas cerebrales como la corteza dorsolateral y prefrontal (córtex prefrontal dorsolateral) (Lorenz, Minoshima y Casey, 2003).

Los factores psicológicos (depresión, ansiedad, autoeficacia, apoyo social, etc.) pueden jugar un papel importante en el desarrollo y mantenimiento del dolor crónico, así como en la severidad de los síntomas y quejas informadas (Martínez, Sánchez, Miró, Medina, y Lami, 2011; McMahon y Wall, 2006). El dolor aumenta los estados negativos emocionales y los trastornos psicológicos, los cuales a su vez pueden dar lugar a incrementos posteriores en dolor (Loggia, Mogil y Bushnell, 2008; Martínez et al, 2011). En este sentido, las medidas afectivas se han asociado con los informes de dolor clínico en pacientes con fibromialgia (Petzke, Gracely, Parque, Ambrose y Clauw, 2003).

En los siguientes apartados se expondrán los factores emocionales y cognitivos más estudiados en relación con la fibromialgia.

1.4.1 DEPRESIÓN

La fibromialgia se ha asociado a una prevalencia muy alta de trastornos de ansiedad y trastornos del estado de ánimo (incluyendo niveles bajos en autoestima que influirían en el uso de estrategias de afrontamiento desadaptativas, Dysvik, Natvig y Eikeland, 2005), con una prevalencia significativamente mayor en cuanto a la depresión (Epstein y cols., 1999; Fietta, Fietta y Manganelli, 2007; Reyes del Paso y cols., 2012; Van Middendorp y cols., 2008). El 30% de pacientes con fibromialgia presentan depresión en el momento que acuden a consulta y un 60% en algún momento de su historia clínica (Bennett, 2002). Varios estudios subrayan a la depresión como el principal predictor de la disminución en calidad de vida y la discapacidad física asociada a la fibromialgia (Rojas, Zapata, Anaya y Pineda, 2005).

La depresión es una de las mayores causas de discapacidad en el mundo (Murray, Vos, Lozano, AlMazroa, Memish, 2013). Entre los pacientes con depresión es frecuente la existencia de condiciones comórbidas de dolor (Arnow y cols., 2006*;* Bair, Robinson, Katon, Kroenke, 2003; Kroenke, Shen, Oxman, Williams Jr y Dietrich, 2008). Siendo la depresión también un trastorno emocional frecuente en enfermedades de dolor (Catona y cols., 2005). La depresión se ha relacionado con un mayor dolor, peor pronóstico e incapacidad funcional en pacientes con dolor crónico (Borsbo, Peolsson y Gerdle, 2009). En la actualidad, el debate se centra en si la depresión es causa o consecuencia del dolor. Los datos disponibles sobre este debate no son del todo claros. Existen estudios que apoyan que la depresión podría producir cambios cognitivos, comportamentales e incluso a nivel neurobiológico, que incrementarían la vulnerabilidad al dolor (Gupta y cols., 2007). Mientras que otros estudios apoyan los síntomas de dolor como factores de riesgo para el desarrollo de la depresión (Gerrits, Oppen, van Marwijk, Penninx y van der Horst, 2014).

Algunos datos apuntan a que los estilos cognitivos relacionados con la personalidad depresiva no forman parte necesariamente de la fibromialgia (Nordahl y Stiles, 2007). Mientras que desde otra perspectiva, la depresión en mujeres con fibromialgia se ha considerado como el vínculo afectivo entre una historia de infortunio

(abuso sexual, maltrato, estresores vitales) y el dolor crónico, dada la prevalencia de sucesos vitales graves en estas pacientes (De Civita, Bernatsky, y Dobkin, 2004).

Hasta la fecha, existen muy pocos estudios que hayan intentado dilucidar si la depresión en la fibromialgia influiría en la mayor activación de áreas cerebrales relacionadas con los aspectos motivacionales y emocionales del dolor. A nivel neurobiológico, la vía nociceptiva que envuelve el dolor psicológico compartiría la activación de estructuras relacionadas con el procesamiento de los aspectos motivacionales y afectivos del dolor físico (Eisenberger, 2012; Eisenberger y Lieberman, 2004; Meerwijk, Ford y Weiss, 2013). Entre estas estructuras se encontrarían la ínsula anterior, la corteza prefrontal, la corteza cingulada anterior y el tálamo (Meerwijk, Ford y Weiss, 2013), estructuras relacionadas con el fenómeno de Sensibilización Central en la fibromialgia (Burgmer y cols, 2009; Cook y cols., 2004; Gracely y cols., 2002; Pujol y cols., 2009; Qiu y cols., 2006). De esta forma, el procesamiento del dolor a nivel central podría ser alterado a través de cambios en el estado emocional (Edwards, Bingham III, Bathon y Haythornthwaite, 2006; De Souza, Potvin, Goffaux, Charest y Marchand, 2009; Godinho, Magnin, Frot, Perchet y Garcia-Larrea, 2006; Ploghaus y cols., 2005).

En este sentido, Giesecke y colaboradores (2005) encontraron un aumento en la actividad de la ínsula y de la amígdala durante estimulación dolorosa sostenida en asociación con el aumento de los síntomas depresivos en la fibromialgia, regiones relacionadas con el procesamiento motivacional y afectivo del dolor. Estos autores además observaron que los síntomas depresivos no tenían ninguna influencia sobre la intensidad del dolor clínico o el procesamiento sensorial, sugiriendo una mayor participación del procesamiento emocional en respuesta a la estimulación dolorosa en pacientes con fibromialgia deprimidos. Por el contrario, Jensen y colaboradores (2010) señalan que existen aberraciones en el procesamiento del dolor en pacientes con fibromialgia independientemente de los factores psicológicos tales como los síntomas depresivos, ansiedad y catastrofismo.

1.4.2 CATASTROFIZACIÓN Y ANTICIPACIÓN AL DOLOR

Las estrategias de afrontamiento se han relacionado ampliamente con la personalidad y su influencia en la manera de afrontar el dolor y adaptarse a la enfermedad. Las diferencias de género en las estrategias de afrontamiento han sido esgrimidas en cuanto a la mayor prevalencia de la fibromialgia en mujeres. Las mujeres, a diferencia de los hombres, utilizan en mayor medida estrategias de afrontamiento basadas en la búsqueda de apoyo social, el catastrofismo y estrategias centradas en la emoción para afrontar el dolor (Affleck, Tennen, Urrows y Higgins, 1992; Buckelem y cols., 1990; Jensen, Turner, Romano y Lawler, 1994; Reid, Gilbert y McGrath, 1994). Estas estrategias de afrontamiento suelen asociarse a mayores niveles de neuroticismo, y éste, a su vez, con mayores niveles de dolor. La evidencia muestra que los hombres toleran más el dolor que las mujeres (éstas evalúan el estímulo doloroso como más intenso y discriminan mejor entre las diferentes intensidades), lo que puede ser debido a variaciones hormonales (Rollman y Harris, 1987) y a diferencias en las estrategias de afrontamiento utilizadas (Feine, Bushnell, Miren y Duncan 1991; Ruda, 1993). No obstante, también habría que tener en cuenta la resistencia de los hombres al dolor en asociación a la deseabilidad social, las diferencias educativas y el sexo del experimentador.

La fibromialgia se ha asociado repetidamente con el uso de estrategias de afrontamiento al dolor poco adaptativas, y en mayor medida con el uso específico de una de ellas, la catastrofización (Gracely y cols., 2004). Variables cognitivas, tales como el catastrofismo, son relevantes para el desarrollo y mantenimiento del círculo vicioso del dolor crónico (Keefe, Rumble, Scipio, Giordano y Perri, 2004). Las pacientes con fibromialgia presentan un elevado nivel de catastrofismo y ello afecta de manera importante al nivel de dolor que refieren, los estados depresivos, el sentimiento de inutilidad, fracaso y la aversión e ideación hacia la muerte (Montoya, Pauli, Batra y Wiederman, 2005). Una mayor catastrofización se ha asociado a un mayor aumento del dolor y la discapacidad relacionada con el dolor en fibromialgia (Geisser y Roth, 1998; Geisser y cols., 2003; Keefe, Brown, Wallston y Caldwell, 1989), así como con el aumento de la activación de áreas cerebrales asociadas con el procesamiento del dolor (Gracely y cols., 2004). Además, se ha sugerido una estrecha interrelación entre el

catastrofismo, la anticipación del dolor y el desarrollo de la Sensibilización Central al Dolor en fibromialgia (Gracely y cols., 2004). Este punto de vista ha sido respaldado mediante estudios de neuroimagen cerebral que demuestran mayor aumento en la actividad de la corteza cingulada anterior (ACC), la ínsula, la corteza frontal medial y la actividad del cerebelo (estructuras cerebrales que modulan las respuestas atencionales-emocionales a estímulos dolorosos), en pacientes con fibromialgia con altos niveles de catastrofización (Gracely y cols., 2002, 2004; Sullivan y cols., 2001).

Por su parte, la anticipación del dolor, caracterizada por cogniciones orientadas al futuro, emociones negativas y activación autonómica, se ha relacionado en pacientes con dolor crónico, incluyendo pacientes con fibromialgia, con una experiencia del dolor exagerada, miedo al dolor, conductas relacionadas con el dolor y la discapacidad funcional (Edwards, Bingham, Bathon, Haythornthwaite, 2006; Geisser y cols., 2003, Giesecke y cols., 2003, Gracely y cols., 2004; Karsdorp y Vlaeyen, 2009; Van Wilgen, van Ittersum, Kaptein y van Wijhe, 2008), factores que pueden exacerbar el sufrimiento de estos pacientes (Ploghaus y cols., 1999). La anticipación del dolor se ha asociado con la activación de estructuras nociceptivas como las cortezas frontal medial, insular y dorsolateral (Burgmer y cols., 2009; Gracely y cols., 2004; Motzkin, Philippi, Wolf, Baskaya y Koenigs, 2014; Ploghaus y cols., 1999), involucradas a su vez en el desarrollo de la hiperalgesia y la Sensibilización Central nociceptiva. En este sentido, existen autores que han interpretado el aumento de la sensibilidad a los estímulos nocivos como una manifestación de hipervigilancia generalizada en la fibromialgia (McDermid, Rollman y McCain, 1996).

Estas estructuras, como se ha apuntado en el párrafo anterior, han mostrado un mayor aumento en actividad en pacientes con fibromialgia con altos niveles de catastrofización (Gracely y cols., 2002, 2004; Sullivan y cols., 2001), estrechando de esta forma la relación entre anticipación al dolor, catastrofización y Sensibilización Central. Jensen y colaboradores (2010) sugieren un potencial efecto de la catastrofización sobre la atención y la anticipación del dolor, ya que cuando éstas son controladas estadísticamente la relación entre catastrofización y la mayor activación cerebral desaparece.

No obstante, la evidencia actual no es concluyente. Por ejemplo, Burgmer y colaboradores (2011) han puesto en entredicho la existencia de una relación estrecha entre anticipación al dolor y catastrofización, sugiriendo que la activación de los sistemas implicados en la modulación del dolor por parte de la anticipación, serían independientes de la estrategia de afrontamiento al dolor utilizada durante ésta.

1.4.3 PERSONALIDAD

La personalidad, a través de diversos mecanismos mediadores (estados emocionales, mecanismos de afrontamiento, relaciones interpersonales, estilo de vida, etc.) puede influir significativamente en el proceso de adaptación al dolor crónico, cómo el dolor es experimentado y evaluado, cómo reaccionamos ante el dolor, el uso de la medicación y los servicios médicos, la adherencia al tratamiento y las prescripciones profesionales etc. Por ello, es necesario tenerla en cuenta a la hora de evaluar y tratar a los pacientes con fibromialgia (Affleck, Tennen, Urrows y Higgins, 1992; Asghari y Nicolas, 2006; Ramírez, Esteve y López, 2001).

Se ha encontrado que las personas afectadas por esta enfermedad presentan mayor incidencia de enfermedades psiquiátricas en comparación con la población general, detectándose también desórdenes de tipo psiquiátrico en sus familiares (Fietta, Fietta y Manganelli, 2007). Además, se ha encontrado una relación significativa entre padecer patología psiquiátrica y puntuar positivamente en los rasgos de personalidad límite y dependiente, relacionándose a su vez este último rasgo con la percepción de un peor estado de salud (Cerón, Centelles, Abellana y García., 2010).

Se han encontrado también en pacientes con fibromialgia puntuaciones elevadas en los patrones de funcionamiento básicos correspondientes a los rasgos paranoide, esquizoide, dependiente, pasivo-agresivo y compulsivo (medidos mediante el cuestionario *Millon Clinical Multiaxial Inventory-III*), obteniéndose para la escala paranoide la puntuación más elevada (Ayats, Martín y Soler, 2006). El patrón de funcionamiento característico de estos pacientes viene caracterizado por la pasividad y

la tendencia a ser introvertidas, perfeccionistas, organizadas, cautelosas, indecisas y dependientes (Ayats y cols., 2006)

Camino, Jiménez, de Castro-Palomino y Fábregas (2009) hablan de personas emocionalmente dependientes, con dificultades para comportarse asertivamente y que, generalmente, se identifican y actúan en función de roles rígidos de funcionamiento relacionados con el "ideal" que se presupone a la figura femenina. En general, se caracterizarían por ser excesivamente responsables y autoexigentes, y con una tendencia a sentirse culpables (Camino y cols., 2009). Otros autores han relacionado el trastorno con la histeria, considerando que la fibromialgia cumple con la descripción clásica de ésta (Barrera, Guerrero, Aguirre, 2005; Carveth y Carveth, 2003;).

Hasset, Cone, Patella y Sigal (2000) hablan de personas cuya personalidad conlleva más vulnerabilidad psicológica, debido a los acontecimientos infantiles traumáticos supuestamente vividos. Estos autores encuentran puntuaciones elevadas en pesimismo, desesperanza, dependencia, pasividad, negación de problemas, atribución de la disfunción psicosocial a los problemas físicos y catastrofismo; junto con sentimientos de inutilidad, fracaso, aversión e ideación suicida. Para estos autores las creencias influirían de manera importante en el dolor y la depresión (Hasset y cols., 2000)

J. Deus (2009) encontró que estos pacientes se caracterizaban por un estado emocional y un estilo de afrontamiento determinados por una significativa elevación de la ansiedad estado-rasgo y del factor neuroticismo, marcada tendencia a la excesiva preocupación por acontecimientos futuros y pasados, marcada ansiedad anticipatoria y evitación del daño, emocional o físico. Las pacientes afectadas de fibromialgia con puntuaciones altas en evitación del daño utilizan en menor medida estrategias de afrontamiento como el humor y la reinterpretación positiva y en mayor medida estrategias de afrontamiento centradas en las emociones, en comparación con pacientes que obtienen puntuaciones bajas en evitación del daño (Cuevas, López, García y Díaz, 2008). Se ha destacado también en pacientes con fibromialgia la falta de asertividad (Jhonson, Paananen, Rahinantti y Hannonen, 1997; Mata y cols., 2009; Peri, 2009).

Las pacientes con fibromialgia suelen mostrar un sentido de coherencia más débil, unos índices menores en calidad de vida y peor estado de salud percibida

(Besteiro y cols., 2008). Las áreas más afectadas en cuanto a la percepción de salud serían la función física, la actividad intelectual, el estado emocional y la calidad del sueño (Munguía y cols., 2007). Lledó y colaboradores (2010) encontraron un papel mediador de la emoción en las creencias sobre la propia competencia y control, y su influencia en el impacto de esta enfermedad en las esferas tanto física como psicosocial: la depresión presentó un fuerte impacto en la faceta física, mientras que la ansiedad afectó al funcionamiento psicosocial. Las creencias de control son también fundamentales en la modulación del estado depresivo de las pacientes (Arnstein, Caudill, Lynn, Norris y Beasley, 1999).

Las vivencias del dolor en pacientes con fibromialgia dependerán de las características de personalidad de éstas. Las que viven el dolor con tensión emocional, ansiedad y depresión, suelen experimentarlo con mayor intensidad y responden peor al tratamiento farmacológico, por el contrario, las que desarrollan conductas adaptativas como creer en sus posibilidades de afrontamiento del dolor, lo viven con menor intensidad, respondiendo mejor al tratamiento (Gatchel y Weisberg, 2000).

Dos de las investigaciones que componen esta Tesis Doctoral están en parte centradas en el estudio de las dimensiones básicas de personalidad identificadas por H.J. Eysenck (neuroticismo, extraversión y psicoticismo) en la fibromialgia, en relación con variables clínicas, emocionales, funcionales y de afrontamiento en el trastorno, y las respuestas de flujo sanguíneo cerebral ante estimulación dolorosa.

En cuanto a estas dimensiones de personalidad, numerosas investigaciones han relacionado la fibromialgia con un mayor neuroticismo (tendencia global a presentar respuestas de ansiedad, a ser vegetativamente hiperreactivo, a mostrar una mayor fatigabilidad física y mental, a ser proclive a la frustración y resistente a cambiar hábitos desadaptativos) y un malestar psicológico desproporcionado en respuesta a los estresores medioambientales (Asghari y Nicolas, 1999; Besteiro y cols., 2008; Netter y Henning, 1998), todo lo cual se ha relacionado con la existencia de alteraciones genéticas que afectarían a la actividad serotoninérgica. Este vínculo podría explicar una posible asociación neuroticismo-depresión-dolor y la correlación significativa con una mayor intensidad del dolor encontrada en otros trastornos crónicos como la artritis reumatoide (Affleck y cols., 1992; Costa y cols., 1985; Costa y McCrae, 1987; Kentle,

1989). Algunos estudios han encontrado menores umbrales de dolor y mayor sensibilidad al dolor en pacientes con fibromialgia con altos niveles de neuroticismo (Netter y Henning, 1998); no obstante, estos resultados no han podido ser replicados en otros estudios como el de Contreras y cols., (2006). Ello sugiere la necesidad de realizar nuevos estudios que analicen la relación entre personalidad y dolor en la fibromialgia.

Algunos estudios con amplias poblaciones de gemelos han asociado el neuroticismo casi exclusivamente con factores ambientales, minimizando así la influencia genética en éste (Koskenvuo, Langinvainio, Kaprio y Sarna 1984). Otros estudios, por el contrario, parecen apoyar la importancia de los factores genéticos en la base del neuroticismo (Lake, Maes, Heath y Martin, 2000). La opinión actual más generalizada considera este rasgo como el resultado de una interacción entre genética y ambiente. En la formulación original y más extendida, Eysenck y Eysenck (1969) relacionó el neuroticismo con la actividad del sistema límbico y del sistema vegetativo y consideró éste como una interacción de factores genéticos y constitucionales. De esta forma, los altos niveles de neuroticismo en la fibromialgia podrían deberse a una interacción entre características innatas y una mayor propensión generada por el mayor estrés sufrido y la propia vivencia de la enfermedad.

En cuanto a la forma de vivir el dolor, se ha comprobado que tanto las personas que puntúan alto en neuroticismo como las personas que padecen fibromialgia, tienden a vivir de forma más catastrófica sus síntomas (Affleck y cols., 1992), experimentan más emociones negativas y toleraran peor el malestar (Costa, 1987; Harkins, Price y Braith, 1989). Los altos niveles de neuroticismo pueden asociarse a catastrofismo frente al dolor y a la puesta en marcha de estrategias de afrontamiento pasivas poco eficaces (Asghari y Nicolas, 2006; Ramírez y cols., 2001). A su vez, las estrategias de afrontamiento pasivas predicen una mayor intensidad del dolor percibido (Affleck y cols., 1992; Bolger, 1990; Brown y Nicassio, 1987). Adicionalmente, las altas puntuaciones en neuroticismo se relacionan con menor satisfacción en los indicadores de calidad de vida, probablemente por los pensamientos pesimistas-catastróficos (McCain, 1996).

En cuanto a la extraversión (interés por el mundo exterior y sociabilidad), hay estudios que afirman que los pacientes con dolor crónico que presentan altas

puntuaciones en extroversión presentan una mayor tolerancia al dolor que los pacientes introvertidos (Eysenck, 1967, Eysenck y Eysenck, 1968). De esta forma, la extroversión sería una variable protectora ante el dolor, lo que podría atenuar la influencia del neuroticismo sobre éste (Ballina, Martín, Iglesias, Hernández y Cueto, 1995) e influir selectivamente en la atención hacia el dolor (Eysenck, 1967). Niveles bajos en extraversión han sido informados en pacientes con fibromialgia (Ayats et al., 2006; Besteiro et al., 2008; Glazer, Buskila, Cohen, Ebstein y Neumann., 2010; Kersh y cols., 2001; Malin & Little John, 2012; Zautra y cols., 2005). El neuroticismo junto con la extraversión han sido los factores más destacados en la diferenciación entre los distintos tipos de personalidad entre pacientes con fibromialgia y controles sanos (Malin y Little John, 2012), siendo a su vez las variables más relacionadas con la calidad de vida de pacientes con fibromialgia (Gómez, y cols., 2008). También han sido estudiadas como determinantes de la calidad de vida otras variables como apertura a la experiencia y responsabilidad, pero en menor medida (Gómez, y cols., 2008).

Respecto a la dimensión de psicoticismo, no existen estudios en la literatura que hayan medido esta dimensión específicamente en el contexto de la fibromialgia, no obstante algunos informes sugieren niveles elevados de la misma (Banic y cols., 2004). En los estudios que componen la presente Tesis Doctoral se pretende también evaluar si esta dimensión se relaciona con algún indicador o síntoma de la fibromialgia. El psicoticismo, según Eysenck, es una dimensión referente a la vulnerabilidad a conductas impulsivas, agresivas o de baja empatía. Siendo las personas que puntúan alto en psicoticismo frías, egocéntricas e irresponsables, pero también más creativas, objetivas, realistas, competitivas, originales y críticas (Eysenck y Eysenck, 1985).

El estudio de la personalidad en la fibromialgia puede adquirir una mayor relevancia en la actualidad, debido a los nuevos criterios diagnósticos propuestos, que como hemos visto, incluyen una escala centrada en la severidad de los síntomas, que mide el sueño no reparador, fatiga, problemas cognitivos y otros síntomas somáticos (Wolfe et al., 2010, 2011). Las escalas de autoinforme pueden ser afectadas por un componente de afectividad negativa, que puede exagerar el informe de síntomas somáticos (Watson y Pennebaker, 1989). Individuos con alta afectividad negativa o neuroticismo normalmente informan de mayores niveles de síntomas somáticos (Lahey, 2009; Watson y Pennebaker, 1989).

1.4.4 ALEXITIMIA

Las diferencias interindividuales en las respuestas emocionales y el estrés pueden ser relevantes en la modulación de los resultados de adaptación y de salud psicosocial en la fibromialgia (Crofford y Demitrack, 1996; Goldenberg, 1996). La vulnerabilidad hacia el estrés y el afecto negativo en fibromialgia pueden deberse en parte a formas desadaptativas de adaptación a la hora de regular las emociones y responder a los estímulos aversivos (Bartley, Rhudy & Williams, 2009; Duschek, Werner, Limbert, Winkelmann y Montoya, 2014). En este contexto la alexitimia (rasgo de personalidad caracterizado por falta de conciencia emocional, dificultades en la identificación y comunicación de sentimientos y un estilo de pensamiento cognitivo orientado externamente; Bagby, Parker y Taylor, 1994; Sifneos, 1973), es considerada un factor relevante (Brosschot y Aarsse, 2001; van Middendorp y cols., 2008). La alexitimia se ha propuesto como un factor mediador entre el afrontamiento maladaptativo y la cronificación del dolor, relacionándose con el dolor clínico y otros factores asociados con la fibromialgia, como el malestar general, la depresión, la ansiedad, la amplificación somatosensorial, el neuroticismo y el psicoticismo (Deary, Scott y Wilson, 1997; Hosoi y cols., 2010; Luminet, Bagby, Wagner, Taylor y Parker, 1999; Sandín, Chorot, Santed y Jiménez, 1996; Wise y Mann, 1994). Sin embargo, el papel preciso de la alexitimia en la fibromialgia aún es poco conocido (Huber, Suman, Biasi y Carli, 2009; Taylor, 2000). Se ha propuesto que la alexitimia interfiere con el éxito en la autorregulación de las emociones negativas, dando lugar a un estado afectivo aversivo sostenido que puede contribuir a la aparición y exacerbación de los síntomas psíquicos y somáticos (Huber y cols., 2009). Individuos con niveles altos en alexitimia pueden, además, tender a malinterpretar la activación emocional como síntomas de enfermedad física, que, por extensión, pueden reforzar los comportamientos maladaptativos relacionados con la enfermedad y la cronificación del dolor (Lumley, Stettner y Wehmer, 1996; Pilowsky y Katsikitis, 1994).

Llegados a este punto hay que hacer referencia a la no existencia de estudios que delimiten la relación entre los factores emocionales y cognitivos en la fibromialgia y su influencia en el proceso de Sensibilización Central al Dolor a través del análisis de los patrones cerebrales temporales de reactividad al dolor. Mediante el análisis de estos

patrones dinámicos se podría obtener datos alternativos que esclarecieran la posible relación existente entre factores psicológico-emocionales y activación del sistema medial del dolor.

1.5 DÉFICITS COGNITIVOS EN LA FIBROMIALGIA

Una de las quejas más comunes informadas por los pacientes con fibromialgia es la existencia de disfunciones cognitivas que afectan a su vida diaria, principalmente en atención y memoria (Glass, Park, Minear y Crofford., 2005). Las pacientes frecuentemente se quejan de confusión mental, pérdida de memoria, dificultad para concentrarse y dificultad para recordar palabras (Glass, 2006; Glass, 2008; Glass y cols., 2005). Estos problemas cognitivos son percibidos como problemáticos particularmente en el contexto laboral. Las pacientes con fibromialgia frecuentemente sienten que estos déficits afectan a su competencia profesional (Glass y cols., 2005). La evidencia clínica y de laboratorio, incluyendo medidas neuropsicológicas estandarizadas, confirman la realidad de éstos déficits. Se han encontrado déficits en memoria a largo plazo (episódica y semántica) y memoria de trabajo, al igual que lentitud en tareas cognitivas complejas (Sephton y cols., 2003). Además, las pacientes con fibromialgia muestran deficiencias en atención selectiva, velocidad de procesamiento cognitivo y control ejecutivo (Dick, Verrier, Harper y Rashiq, 2008; Duschek, Werner, Winkelmann y Wankner, 2013; Glass, 2006; Glass, 2008; Munguía-Izquierdo, Legaz-Arrese, Moliner-Urdiales y Reverter-Masía, 2008; Pericot-Nierga y cols., 2009; Reyes del Paso y cols., 2012; Verdejo-García, López-Torrecillas, Calandre, Delgado-Rodríguez y Bechara, 2009).

Sobre la etiología de estas alteraciones cognitivas no existe acuerdo entre los diferentes autores, algunas hipótesis sugieren que podrían estar asociadas a la depresión (Suhr, 2003). Otros autores han encontrado que los déficits cognitivos son independientes de la depresión y dependen fundamentalmente del nivel de dolor clínico presente (Glass y cols., 2005; Reyes y cols., 2012). Factores como la depresión, la ansiedad y la fatiga jugarían un rol secundario en la función cognitiva en la fibromialgia

(Glass, 2006; Glass, 2008; Munguía-Izquierdo y cols., 2008; Park, Glass, Minear y Crofford., 2001; Reyes del Paso y cols., 2012; Verdejo-García y cols., 2009). Por último, hay autores que consideran estas alteraciones como un resultado del efecto interferidor del dolor junto con el de la ansiedad (Munguía-Izquierdo y cols., 2008). La evidencia actual muestra asociaciones entre la intensidad del dolor clínico y el deterioro cognitivo, señalando el efecto intrusivo del dolor como uno de los factores más importantes que podrían interferir en la cognición (Duschek y cols., 2013; Glass, 2006; Glass, 2008; Grace, Nielson, Hopkins y Berg, 1999; Karp y cols., 2006; Munguía-Izquierdo y cols., 2008; Park y cols., 2001; Reyes del Paso y cols., 2012; Verdejo-García y cols., 2009).

El dolor como condición demandante de atención conlleva la activación de áreas cerebrales asociadas con el procesamiento cognitivo, como las cortezas cingulada y prefrontal (Apkarian, Bushnell, Treede y Zubieta, 2005). Es posible que el procesamiento nociceptivo central reste recursos a la cognición al requerir la activación de áreas cerebrales relacionadas con la cognición (Baliki y cols., 2006; Dick y cols., 2008; Glass, 2008; Munguía-Izquierdo y cols., 2008; Park y cols., 2001). La corteza cingulada anterior desempeña un papel esencial en la atención selectiva, memoria de trabajo y la conciencia (Klein y cols., 2007), mientras que la corteza prefrontal se ha relacionado con el funcionamiento ejecutivo, la memoria de trabajo y el reconocimiento, especialmente en el recuerdo libre (Petrovic y Ingvar, 2002; Rusch y cols., 2007; Turriziani y cols., 2008). Varios estudios ponen de manifiesto que estas áreas, también relacionadas con la experiencia y anticipación del dolor, muestran alteraciones en pacientes con fibromialgia. Concretamente, se ha observado una reducción de la materia gris en el giro parahipocampal izquierdo, en la zona bilateral media y posterior del giro cingulado, en el área izquierda de la ínsula y en la zona medial del cortex frontal (Kuchinad y cols., 2007).

Un factor que ha sido relacionado con el rendimiento cognitivo y la puesta en marcha de las áreas cerebrales involucradas en la realización de una tarea es la capacidad para incrementar el flujo sanguíneo cerebral en dichas áreas en respuesta a las demandas cognitivas (Duschek, Heiss, Schmidt, Werner, & Schuepbach, 2010; Duschek & Schandry., 2003; Duschek, Schuepbach, & Schandry, 2008). Existe un estrecho acoplamiento entre la actividad neuronal y el flujo sanguíneo cerebral, de forma que la

actividad cognitiva induce cambios en la perfusión cerebral (Logothetis, Pauls, Trinath, & Oeltermann, 2001; Mosso, 1881; Roy y Sherrington, 1890; Szirmai, Amrein, Palvogyi, Debreczeni y Kamondi, 2005). Las deficiencias en la evocación de las respuestas de flujo sanguíneo cerebral están asociadas con un menor rendimiento cognitivo (Duschek y Schandry, 2006). Duscheck y Schandry (2006) encontraron una clara relación positiva entre el rendimiento cognitivo, durante la ejecución de una tarea de sustracción serial, y el flujo sanguíneo de la arteria cerebral media (sobre todo respecto a los componentes más tempranos de la respuesta), subrayando así la importancia del ajuste del flujo sanguíneo cerebral a las exigencias existentes para un funcionamiento cognitivo óptimo.

En este contexto, la ya mencionada técnica de *ultrasonografía Doppler transcraneal funcional* podría ser de especial relevancia para valorar los cambios en flujo sanguíneo cerebral asociados a la cognición en la fibromialgia. Un número extenso de estudios han aportado evidencia de que esta técnica constituye una excelente herramienta para la cuantificación de los cambios rápidos en flujo sanguíneo cerebral que acompañan a la actividad cognitiva (Duschek y Schandry, 2003). Aaslid, pionero en la utilización de esta técnica, demostró en sus estudios iniciales un aumento en la velocidad del flujo sanguíneo en las arterias cerebrales posteriores en respuesta a estimulación visual (Aaslid, 1987). Resultados similares se han obtenido con esta técnica en tareas de atención y de memoria (Cupini y cols., 1996; Stroobant y Vingerhoets, 2000).

2. OBJETIVOS

Objetivo general

Evaluar la dinámica temporal de las respuestas de flujo sanguíneo cerebral ante procesamiento nociceptivo y cognitivo en la fibromialgia como indicadores, en el primer caso, de hiperalgesia y sensibilización central al dolor, y en el segundo caso, de los déficits cognitivos asociados al trastorno. Se analizará la asociación entre los componentes de respuesta encontrados en flujo sanguíneo cerebral e indicadores clínicos (dolor, fatiga, insomnio), emocionales (ansiedad y depresión), personalidad (por ejemplo neuroticismo) y mecanismos de afrontamiento (por ejemplo catastrofización). Por último, a partir de los resultados de uno de los estudios, se valorará la asociación entre algunos rasgos de personalidad (neuroticismo, extraversión, alexitimia, etc.) y variables clínicas, emocionales y funcionales en la fibromialgia.

Objetivos específicos

1. Analizar la dinámica temporal de las modulaciones del flujo sanguíneo cerebral en respuesta a estimulación dolorosa en pacientes con fibromialgia, en comparación a participantes sanos equiparados en variables sociodemográficas, utilizando la técnica de ultrasonografía Doppler transcraneal funcional.
2. Examinar la relación entre las respuestas de flujo sanguíneo cerebral en respuesta al dolor y factores clínicos, emocionales y de personalidad en la fibromialgia.
3. Analizar las respuestas de flujo sanguíneo cerebral, mediante técnicas de ultrasonografía Doppler transcraneal funcional, durante el procesamiento aritmético en pacientes con fibromialgia, en comparación con participantes sanos, y evaluar su relación con el rendimiento cognitivo y la intensidad de los síntomas clínicos.
4. Investigar las respuestas de flujo sanguíneo cerebral y tasa cardíaca durante una tarea de tiempo de reacción con estímulo de aviso en pacientes con fibromialgia, en comparación con participantes sanos, y analizar su relación con el rendimiento cognitivo y la intensidad de las manifestaciones clínicas del trastorno.
5. Evaluar las tres dimensiones de personalidad propuestas por H. J. Eysenck en pacientes con fibromialgia, en comparación con participantes sanos, y analizar su

asociación con variables clínicas, emocionales y funcionales, así como estrategias de afrontamiento al dolor.

6. Comparar las dimensiones de alexitimia en pacientes con fibromialgia y controles sanos y analizar su asociación con variables clínicas, emocionales y funcionales, así como estrategias de afrontamiento al dolor.

3. ESTUDIOS

ESTUDIO 1. PATTERNS OF CEREBRAL BLOOD FLOW MODULATIONS DURING PAIN STIMULATION IN FIBROMYALGIA: A TRANSCRANIAL DOPPLER SONOGRAPHY STUDY.

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(Under review, Pain Medicine)

Patterns of cerebral blood flow modulation during painful stimulation in fibromyalgia: a transcranial Doppler sonography study

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Abstract

Objetive: This study analyzed the temporal dynamics of cerebral blood flow (CBF) modulations, during painful stimulation in fibromyalgia syndrome (FMS), using functional transcranial Doppler sonography. **Method:** Blood flow velocities were recorded bilaterally in the anterior (ACA) and middle (MCA) cerebral arteries of 24 FMS patients and 20 healthy individuals during exposure to painful pressure stimulation. Participants were presented with two stimulation blocks: a) fixed pressure (2.4 kg) and b) stimulation pressure, individually calibrated to produce equal subjective and moderate pain intensity in all participants. **Results:** A complex pattern of CBF modulations arose, comprising four main components: an anticipatory increase before stimulation onset, an early increase, a transient decrease to baseline or below and a final increase. Group differences were observed in all components. The anticipatory component only arose in FMS patients, specifically in the ACA. Patients exhibited a greater early CBF increase under the fixed pressure condition, predominantly in the right ACA. A stronger CBF decrease after the early component was observed in patients during the equal pain condition, in the ACA and MCA. Significant associations were found between clinical pain severity and CBF responses in the MCA. **Conclusion:** The results demonstrate that acute pain processing is associated with a complex pattern of CBF modulation, where FMS patients exhibited alterations in all phases of the response. The aberrances may be ascribed to psychophysiological phenomena, including central nervous nociceptive sensitization and protective-defensive reflex mechanisms. The anticipatory CBF response in patients may relate to various cognitive, emotional and behavioral mechanisms involved in pain chronification.

Keywords: Fibromyalgia Syndrome; pain anticipation; defensive reflex; clinical pain; cerebral blow flood; functional transcranial Doppler sonography (fTCD).

Introduction

Fibromyalgia syndrome (FMS) is a chronic disease characterized by generalized diffuse musculoskeletal pain (1). The etiology and pathophysiology of FMS remain to be confirmed, although the general consensus is that central nervous sensitization and deficient pain-inhibiting mechanisms may be involved (2,3). This notion is supported by decreased pain thresholds and tolerance (4), the occurrence of allodynia (5), observations of temporal (windup) and spatial summation (6,7) and exaggerated activity of the central nervous pain neuromatrix (8-10). Neuroimaging techniques such as functional magnetic resonance imaging (fMRI) have been used to analyze cerebral blood flow (CBF) responses to painful stimulation in FMS. During moderate pain stimulation, FMS patients exhibited activation of prefrontal and supplementary motor cortices and the insula, anterior cingulate, sensory-motor cortex, right thalamus and basal ganglia In healthy controls the response was predominantly restricted to the somatosensory cortex (8-11). This anatomical dissociation suggests activation of cerebral areas specifically related to the emotional and cognitive elaboration of pain in FMS patients, in contrast to predominantly sensory pain processing in healthy individuals (11).

One important factor in pain chronification is the anticipation of pain, characterized by future-oriented cognitions, negative emotions and autonomic arousal. In patients with chronic pain, including those with FMS, pain anticipation has been related to exaggerated pain experience, fear of pain, pain-related behaviors and functional disability (12-17), which may in turn exacerbate patients´ suffering (18). Pain anticipation is furthermore associated with the activation of nociceptive structures such as the medial frontal, insular and dorsolateral cortices (11,15,18,19), which are assumed to be involved in the development of hyperalgesia and central nociceptive sensitization.

The above-mentioned brain mapping studies provide evidence concerning the spatial distribution of CBF responses during painful stimulation in FMS. In contrast, evidence concerning the temporal dynamics of these responses remains sparse. The investigation of CBF dynamics provides complementary information to that revealed by classic brain imaging paradigms (20,21). Functional transcranial Doppler sonography (fTCD) allows for continuous, noninvasive measurement of CBF velocities in the basal cerebral

arteries with excellent time resolution (20). Changes in the flow velocity of these arteries reflect changes in blood demand in their perfusion territories as a result of neural activity (20). Several studies have proven the validity of fTCD for the analysis of CBF responses during psychological processes, including the experience of acute pain (21-24). The CBF response observed during pain stimulation consists of two basic components: an early response peaking after approximately 5 s, and a late response peaking around 15 s after stimulus onset (21,22). Both components exhibited a degree of lateralization towards the right hemisphere (21). The pain-related CBF response is relatively slow (latencies of 2-3 s) in comparison to cognitive activity (latencies < 1 s) (21). Previous fTCD studies indicate that interindividual differences in hemodynamic responses, and associations between CBF responses and pain indicators, are time-dependent and usually restricted to specific time frames (21,22). Similarly, associations between CBF responses and clinical parameters (e.g., clinical pain severity, anxiety or depression) are highly dynamic, with correlations typically arising during limited response intervals (23,24).

A previous study, that used fTCD to quantify CBF responses during painful heat stimulation in FMS (21), revealed stronger blood flow increases in FMS patients vs. healthy individuals in the anterior cerebral arteries (ACA), which supply medial-anterior cerebral regions. Two response components where identified; only the early one correlated with clinical pain. The exaggerated CBF response in the ACA has been interpreted in terms of hyperactivity of the medial part of the pain neuromatrix, which comprises structures specifically mediating the affective and cognitive components of pain (21). In contrast, no group difference arose in CBF responses in the middle cerebral arteries (MCA), which supply lateral brain areas including structures associated with the sensory pain component (11).

Transient changes in CBF have been traditionally discussed in the context of orienting (OR) and defense (DR) reflexes and non-associative learning mechanisms, i.e. habituation and sensitization (25-27). These basic reflex mechanisms are implicated in the modulation of sensory input, where they exert opposing effects on sensory processing. During the OR - elicited by novel stimuli of low intensity - receptor and CNS sensitivity is increased, while the DR - elicited by intense, aversive stimulation - is associated with elevated sensory threshold and diminished CNS sensitivity (26). One of

the mechanisms thought to be involved in the modulation of receptor and CNS sensitivity is adjustment of CBF. Increased CBF has been related to the OR and low sensory thresholds, and reduced CBF to the DR and elevated thresholds (26). Further research on the physiological differentiation of the OR and DR revealed a more-complex picture (25,27). The CBF response associated with the DR (measured via photoplethysmography at the forehead or temporal sites) consists of an increase component during the first few seconds after aversive stimulus onset, and a decrease below the baseline level approximately 10 s later. For stimuli eliciting the OR, the first CBF increase component is smaller and the decrease below baseline does not occur (27).

The present fTCD study analyzed the temporal dynamics of CBF responses to painful pressure stimulation in FMS patients and healthy individuals. Blood flow velocities were recorded bilaterally in the ACA and MCA while participants were exposed to painful pressure stimulation. We adapted the protocol designed for the fMRI study of Gracely et al. (8). Participants were presented with two stimulation blocks: a) fixed pressure of 2.4 kg and b) stimulation pressure individually calibrated to produce equal subjective pain intensity in all participants (corresponding to a value of 6 on a 10-point VAS). Associations between clinical pain severity and CBF responses were also investigated. Considering the central nervous nociceptive sensitization involved in FMS, we expected that the fixed pressure condition (2.4 kg) would produce greater CBF responses in the FMS group vs. healthy controls. Based on previous studies (21,22), we furthermore hypothesized that group differences would predominantly arise in the ACA, particularly in the right hemisphere. Assuming greater pain expectancy and catastrophizing in FMS patients (12,15), we expected a stronger CBF response during pain anticipation in FMS patients. According to neuropsychological theories that ascribe particular roles to the anterior cingulate and ventromedial prefrontal cortices during anticipatory processing (19,28-30), the anticipatory CBF component may be particularly pronounced in the ACA. Regarding time dynamics, we predicted a response pattern consisting of a CBF increase before stimulus onset, related to pain anticipation, as well as early- and late-increase component related to nociception. Based on previous observations in FMS (21,22), we hypothesized that group differences would be restricted to the anticipatory and early response components. Similarly, we expected that associations between CBF responses and clinical pain would mainly arise for these

components. Taking into account the hyperalgesia and central nervous nociceptive sensitization associated with FMS, we predicted that painful stimulation would elicit a stronger DR in patients. We finally hypothesized that the DR would be evidenced by a decrease in CBF after the early increase component, and further that this decrease would be of a greater magnitude in FMS patients vs. healthy individuals (27).

Method

Participants

Forty-four women, 24 with FMS and 20 healthy controls, participated in the study. Patients were recruited via the Fibromyalgia Association of Jaén and met the American College of Rheumatology criteria for FMS (31). The presence of cardiovascular diseases, metabolic abnormalities, neurological disorders, drug abuse, or severe somatic (e.g., cancer) or psychiatric (e.g., psychotic) diseases were used as exclusionary criteria. The control group was recruited from women's associations and was matched to the patient group with respect to age, body mass index and educational level. In addition to having any kind of pain disorder, the control group was subject to the same exclusionary criteria applied to patients. All participants were right handed. Table 1 displays the demographic and clinical data of both groups.

* Table 1

Pressure stimulation and pain quantification

Pain was evoked using a wireless pressure algometer (Traker Freedom, JTECH Medical, Lawndale, USA) with a surface area of 1 cm^2. The algometer was connected to a computer, that allowed for the control of pressure and rate of increase (kg/s), and was inserted in a screw-piston specifically designed to fix and press the finger-nails, such that stimulation pressure could be reliably delivered. When stimulation commenced, the piston sent an electrical pulse to the fTCD system signaling the start of a trial. Pain pressure was delivered to the nail of the index finger of the left hand. For the measurement of pain threshold (the pressure at which the participant started to feel pain) and tolerance (the maximum pressure tolerated), pressure was continuously increased at a rate of 1 kg/s. Subjective pain intensity was evaluated using a 10-cm line visual

analogue scale (VAS; “How strong was the pain?”) running from 0 (*not at all*) to 10 (*extremely*). Our stimulation protocol allowed for investigation of the anticipation of pain, because participants could see their nail in the screw-piston and the investigator approaching the device approximately 4 s prior to stimulus onset.

Recording of cerebral blood flow

Blood flow velocity was assessed by fTCD employing a digital Multi-Dop L2 DWL (Elektronische Systeme, Inc., Sipplingen, Germany). Recordings were conducted bilaterally, in both the ACA and MCA, through the temporal bone windows using two 2-MHz transducer probes. Following vessel identification, the probes were fixed to the head via a head harness. The MCA were insonated at a depth of 48÷55 mm, and the ACA at a depth of 60÷70 mm. The spectral envelope curves of the Doppler signal were recorded at 100 Hz. The mean flow velocity index was applied as a measure of CBF. This index is the least vulnerable to artifacts and exhibits the highest correlation with blood volume flowing through an artery per unit of time (20).

The 100 Hz mean flow velocity recording was resampled at 4 Hz. The 30 s period after stimulus onset was defined as the stimulation period; the 4 s period before stimulus onset was the anticipatory period. Mean flow velocity during the 10 s prior to the anticipation period served as the baseline. Responses were expressed as relative (percent) changes in flow velocity (dFV) with respect to baseline (FVbas) according to the formula dFV = (FV[t] - FVbas) *100/FVbas, where FV(t) is the flow velocity over time.

Procedure

The study was performed across two separate sessions that took place on different days. During the first session a clinical psychologist obtained the patients’ clinical history and socio-demographic data, checked the exclusionary criteria, conducted the Structured Clinical Interview for Axis I Disorders of the Diagnostic and Statistical Manual for Mental Disorders (32) and presented the McGill Pain Questionnaire (33). The following parameters were obtained using this instrument: the sensorial, emotional, evaluative, and miscellaneous dimensions of pain, the number of words selected, from a list of 78,

to describe pain and the total score. During administration of the McGill Questionnaire to the control group, participants were asked to refer to possible sporadic pains, or the corporal area in which they usually felt some discomfort. Control group also were asked to provide medication data concerning to sleep problems. Through the second session the experimental procedure took place across two phases, which represented an adaptation of the method used by Gracely at al. (8) study. In the first phase participants were familiarized with the stimulation protocol, while in the second phase the actual experiment was performed. During the first phase participants received instructions pertaining to the concepts of pain threshold and tolerance and the use of the VAS. Threshold and tolerance data were obtained thereafter. In order to reduce anxiety and familiarize participants with the procedure, seven pressure stimuli of 5 s duration were applied with 20 s inter-trial intervals (sequence: 1.35, 4.5, 0.9, 2.7, 0.45, 1.8, and 3.6 kg). Finally, a sequence of 5 s pressure stimuli was applied in ascending order, beginning at 0.45 kg/cm² and increasing in 0.45 kg/cm² intervals until the tolerance level was reached, or to a maximum of 9 kg/cm². With the subjective pain evaluation obtained using this sequence of increases, a psychophysics function relating physical pressure (in kg) to subjective pain ratings (VAS) was computed for each participant. From this regression function, the individual pressure (in kg) required to produce moderate pain (a value of 6 on the 10-point VAS) was individually calculated.

During the second experimental phase, two blocks of 12 pressure stimuli were presented in a counterbalanced order: one block used a fixed pressure of 2.4 kg and the other used an individually calculated pressure in order to evocate a subjective pain intensity of 6 on the VAS. Previous studies showed that pressures of approximately 2.4 kg are associated with low pain ratings in healthy individuals, and with low-to-moderate pain in FMS patients (8,15). In both sequences, stimulation was maintained for 10 s and inter-trial intervals were 60 s.

Given the impossibility of measuring blood flow velocity in the MCA and ACA simultaneously, the entire procedure was repeated for each pair of arteries. The artery starting order (MCA vs. ACA) was counterbalanced across participants. Participants were instructed to refrain from smoking, caffeine, alcohol, and vigorous exercise for 2 hours prior to the experiment. They were also asked not to consume analgesics or other drugs affecting the cardiovascular system beginning 24 hours before the study. All

participants provided informed consent. The study protocol was approved by the Bioethics Committee of the University of Jaén.

Data reduction and analysis

Based on previous fTCD studies conducted in the fields of pain processing (21,22), and on visual inspection of the CBF data, four delimitable response components were identified: 1) an anticipatory increase component (approximately 2 s before stimulus onset), 2) an early increase component (s 1 to 3 after stimulus onset), 3) a decrease component (s 5 to 11), and 4) a late increase component (s 12 to 22). Peak amplitudes during these periods (maximum values for components 1, 2, and 4, and minimum values for component 3) were obtained for each participant. Statistical analysis of the CBF response was conducted using 2x(4) repeated measures ANOVAs, with the between-subjects factor 'group' (i.e., FMS patients vs. control group) and the repeated-measure factor 'CBF component' (i.e. the four response amplitudes). Data were analyzed using the multivariate test statistic Wilks' lambda. Group differences and post-hoc analysis of interactions were evaluated using Student's *t*-test for independent samples. Associations between pain parameters and CBF responses were quantified using Pearson correlations.

Results

Pain parameters and CBF responses

Pain threshold (1.61 ± 0.77 vs. 3.78 ± 2.73, for FMS and controls, respectively; $t = 3.76$, $p = .001$, $\eta^2 = .247$) and tolerance (4.00 ± 1.39 vs. 7.52 ± 3.23, for FMS and controls, respectively; $t = 4.92$, $p < .0001$, $\eta^2 = .360$), and the pressure required to evocate a VAS rating of 6 (3.52 ± 2.12 vs. 5.12 ± 2.15, for FMS and controls, respectively; $t = 2.49$, $p = .017$, $\eta^2 = .126$) were lower in FMS patients vs. controls.

For all cerebral arteries and pain conditions, the repeated-measures factor (response component) was significant (all Fs (3, 40) > 22, all ps < .0001, all η^2s > .62). The response pattern in CBF was characterized by early (peaking at s 2-3 from stimulus onset) and late (peaking at s 17-19 from stimulus onset) increase components. Between these peaks a decrease component (peaking at s 8-9 from stimulus onset) arose, where

CBF fell to the baseline level or below. An anticipation component was present in the right ACA for the fixed pressure (2.4 kg) and equal pain (6 VAS) conditions, and in the left ACA for the equal pain condition, but only in the FMS group (c.f. Figures 1 to 4).

Group × response interactions were observed for the right ACA under the fixed pressure condition ($F(3, 41) = 3.58$, $p = .022$, $\eta^2 = .208$) and for the right ($F(3, 41) = 4.65$, $p = .007$, $\eta^2 = .254$), and left ACA under the equal pain condition ($F(3, 41) = 3.56$, $p = .028$, $\eta^2 = .197$). For the right ACA under the fixed pressure condition, the FMS group displayed greater CBF increases compared to the control group, during both the anticipation and early components. For the right ACA under the equal pain condition, patients exhibited greater CBF responses during anticipation and reduced CBF during the decrease component. For the left ACA under the equal pain condition, the FMS group displayed increased CBF during anticipation (see Table 2). Finally, for the MCA under the equal pain condition, the FMS group exhibited overall decreased CBF, the difference being significant for the right ($F(1, 42) = 5.59$, $p = .023$, $\eta^2 = .118$), and marginally for the left, hemisphere ($F(1, 42) = 3.23$, $p = .079$, $\eta^2 = .071$) (see table 3).

Associations between clinical pain and CBF in the fibromyalgia group

No significant associations between clinical pain ratings and CBF were found for the anticipatory period. For the early component assessed in the MCA, associations depended on the respective pain condition. Regarding the fixed pressure condition, significant positive associations were observed for sensorial pain ($r = .461$, $p = .020$ for the left, and $r = .435$, $p = .034$ for the right, MCA), miscellaneous pain ($r = .527$, $p = .007$ for the left, and $r = .506$, $p = .010$ for the right MCA), emotional pain ($r = .491$, $p = .013$ for the left, and $r = .492$, $p = .012$ for the right MCA), number of words used to describe pain ($r = .484$, $p = .014$ for the left, and $r = .450$, $p = .024$ for the right MCA), and total McGill Pain Questionnaire score ($r = .472$, $p = .017$ for the left, and $r = .458$, $p = .021$ for the right MCA). In contrast, for the equal pain condition associations were lower and negative, and only reached significance for sensorial pain ($r = -.399$, $p = .048$ for the right MCA). Marginal associations were found for total McGill ($r = -.379$, $p = .061$ for the right MCA) and miscellaneous pain ($r = -.332$, $p= .105$ for the right) scores. No associations arose for the early ACA component.

For the decrease component and the MCA, the associations followed the same trend. Regarding the fixed pressure condition, significant positive associations were observed for sensorial pain (r = .458, p = .021 for the left, and r = .402, p = .046 for the right MCA), miscellaneous pain (r = .530, p = .006 for the left, and r = .474, p = .017 for the right MCA), emotional pain (r = .479, p = .016 for the left, and r = .400, p = .047 for the right MCA), number of words used to describe pain (r = .407, p = .043 for the left, and r = .369, p = .069 for the right MCA), and total McGill score (r = .452, p = .023 for the left, and r = .418, p = .038 for the right MCA). With respect to the equal pain condition, and specifically for the right MCA, associations were negative for the number of words used to describe pain (r = -.495, p = .012), sensorial pain (r = -.549, p = .005), miscellaneous pain (r = -.501, p = .011) and total score (r = -.565, p = .003). No associations significant were obtained for the ACA decrease component.

Regarding the late CBF component and the equal pain condition, negative associations arose for the MCA and ACA. However, these associtions only reached significance for emotional pain (r = -.437, p = .029 for the right MCA; r = -.337, p = .107 for the right ACA), while correlations were marginally significant for the number of words used to describe pain (r = -.368, p = .070 for the right MCA, and r = -.355, p = .082 for the right ACA), sensorial pain (r = -.384, p = .058 for the right MCA), and total score (r = -.385, p = .058 for the right MCA, and r = -.337, p = .107 for the right ACA).

Associations of pain threshold and tolerance with CBF

In the FMS group pain threshold was negatively associated with MCA CBF responses during the anticipatory period (r = -.505, p = .010 for left MCA fixed pressure and r = -.489, p = .013 for right MCA fixed pressure) and theearly (r = -.412, p =.040 for right MCA fixed pressure, and r = -.354, p = .083 for left MCA fixed pressure), and late components (r = -.541, p = .005 for left MCA equal pain). Pain tolerance was inversely associated with the late CBF component under the equal pain condition (r = -.652, p = <.001 for left MCA, r = -.495, p =.012 for right MCA), but positively for the decrease component under the fixed pressure condition (r = .430, p = .032 for right ACA).

In the control group these correlations only reached significance for the ACA decrease component under the equal pain condition with regard to pain threshold (r = .465, p =

.039 for the left, and r = .434, p = .049 for the right ACA). For pain tolerance these associations did not reach significance (r = .414 for the left, and r = .379 for the right ACA, n.s.).

Discussion

A complex pattern of CBF modulation during painful pressure stimulation was observed in FMS patients and healthy individuals, underlining the notion that time dynamics are an important aspect of hemodynamic adjustment during central nervous nociceptive processing. Although the CBF pattern differed as a function of group, artery, hemisphere and stimulation condition, it was generally characterized by an increase component during stimulus anticipation, an early increase component after stimulus onset followed by transient CBF decrease to baseline level or below, and a final increase component.

The anticipatory component was observed only in FMS patients, specifically in the ACA. Under the fixed pressure condition (2.4 kg) this component was restricted to the right ACA, while under the equal pain condition (6 VAS), which was of higher average physical intensity (M = 3.52 kg), it arose in both hemispheres. These results support our predictions and accord with neuropsychological theories postulating the involvement of anterior-medial structures, such as the anterior cingulate and ventromedial prefrontal cortices, in anticipatory processing (19,28-30). Pain anticipation encompasses increased negative affect and modulation of attentional and cortical tone, processes that are well-known to be lateralized towards the right hemisphere (24,34,35). This is consistent with the restriction of the response to the right ACA under the fixed pressure condition.

The results concerning the anticipatory CBF component in FMS cohere with the occurrence of a pain sensitization processes in FMS. Pain sensitization could include the presence and development of a cognitive bias, in both the interpretation of pain sensations and attention paid to them (hypervigilance to pain). This bias can lead to individuals ascribing greater relevance to pain in general life, in addition to fear of pain, catastrophizing, pain-related behaviors, emotional alterations, etc. (12-17,21, 29, 36) all of which can in turn reinforce the previous cognitive bias and, by means of a ‘vicious circle’, stimulate a pain chronification process.

As expected, FMS patients exhibited a greater CBF response than did healthy participants under the fixed pressure condition, specifically for the early right component in the ACA. This is congruent with previous evidence of an increased ACA blood flow response during painful heat stimulation in FMS patients (21). Application of mild pressure (2.4 kg) in FMS patients resulted in a stronger CBF response compared to the control group even during the equal pain condition, where an average of 5.12 kg was delivered. This clearly supports theories postulating exaggerated central nervous pain processing in FMS (8-11) and also accords with previous fMRI evidence of activation of larger brain areas in FMS patients during fixed pressure stimulation of 2.4 kg (8). The restriction of the group difference in early CBF modulation to the (right) ACA supports the view of specific hyperactivity of the medial pain matrix, which represents emotional and cognitive pain components (11,22) and is also in line with prefrontal anterior asymmetry theories that postulate right hemispherical dominance of negative emotional and motivational states (34). Previous studies on CBF responses during cognition indicate stronger right hemispherical lateralization of ACA responses in FMS vs. healthy individuals (23,24) even in an arithmetic task for which one would expect left hemispherical dominance. There may be a general tendency towards right hemispherical ACA blood flow increases, possibly due to alterations in arousal regulation or a negatively biased cognitive or emotional style (34,35,37).

During the decrease component, CBF was lower in the FMS vs. control group for the right ACA under the equal pain condition. A marginally significant group difference in the same direction also arose for the left ACA. The CBF decrease, after the early component under the (stronger) equal pain condition, is consistent with traditional reflex theory and suggests the occurrence of a DR in FMS patients (25,27). The CBF reduction below baseline level is in line with previously observed DRs elicited by aversive acoustic stimulation (27). It is commonly assumed that the DR represents a reduction of central nervous and receptor sensitivity during conditions of intense aversive stimulation (25-27). It has been related to Pavlov's concept of protective, or transmarginal, inhibition, which is regarded as a protective mechanism against overstimulation (38). Taking into account central nervous nociceptive sensitization in FMS, it may be hypothesized that the DR helps to limit neural activation during acute painful stimulation, where the reduction of CBF is regarded as one of the mechanisms involved in restricting stimulus processing (25-27). Concerning the MCA, the patients´

DR may have become apparent in a more global CBF reduction during the entire response (especially in the right hemisphere). The MCA supply the somatosensory cortex, where the sensory pain component is processed. This is again in accordance with a proposed protective inhibition that serves to limit stimulus processing and prevent overstimulation (26,27,38). Nociceptive information is predominantly processed contralateral to the stimulated side, which is illustrated by the presently observed overall stronger right hemispherical CBF response. The fact that group differences during the equal pain condition were more pronounced in the right vs. left ACA and MCA supports the occurrence of a DR, functioning to limit central nociceptive activation.

Based on previous fTCD findings in FMS (21), we expected significant associations between CBF modulation and clinical pain severity, especially for the early response component. Such associations may represent the increased pain-related CBF responses due to hyperalgesia that characterize FMS. In our study correlations were higher for the MCA vs. ACA and varied in accordance with stimulation condition. Under the fixed pressure condition correlations were similar for the two hemispheres, while under the equal pain condition, where overall stronger pressures were applied, correlations only reached significance for the right hemisphere. In FMS patients, early MCA blood flow increases under the fixed pressure condition were positively associated with almost all of the McGill Pain questionnaire parameters. In contrast, the magnitude of the early MCA response under the equal pain condition correlated weakly and negatively with clinical pain. The same pattern of correlations was observed for the decrease component. For the late MCA response negative correlations with clinical pain arose under the equal pain condition. Greater clinical pain was associated with higher CBF responses in both MCAs under the fixed pressure condition, but with lower right MCA responses under the equal pain condition. The dissociation in these patterns of associations is consistent with the notion of a DR in FMS patients under the (more intense) equal pain condition. During intense stimulation, protective inhibition may occur in patients to prevent overstimulation, where the threshold and magnitude of inhibition depend on inter-individual differences in hyperalgesia as represented by clinical pain indices. The results support the view that clinical pain level modulates the magnitude of the DR, in the sense that more severe pain is associated with a stronger reduction of MCA perfusion. No significant associations were observed for the ACA, which may suggest that that the influence of clinical pain on CBF modulation is widely

restricted to sensory pain processing in the somatosensory cortex. The fact that negative associations between CBF responses and clinical pain, under the equal pain condition, were only observed for the right hemisphere again suggests the elicitation of a DR that functioned to restrict sensorial processing of aversive stimuli.

Patients´ pain thresholds were inversely associated with CBF responses, in both MCAs under the fixed pressure condition for the anticipatory and early components, and under the equal pain condition for the late component. No correlations reached significance for the ACA, once again suggesting that interindividual differences in pressure pain sensitivity specifically modulate sensory pain processing in the somatosensory cortex. The close association found for the anticipatory component suggests that that the degree of anticipation of painful stimulation varies subject to the extent of hyperalgesia and central nervous sensitization.

In summation, the present study demonstrated that acute pain processing is associated with a complex pattern of CBF modulation, where in FMS patients alterations in each of the specific components was apparent. The aberrances are likely due to psychophysiological phenomena, particularly central nervous sensitization and protective defensive mechanisms. Furthermore, the anticipatory CBF response, which only arose in patients, may relate to various emotional, cognitive and behavioral mechanisms contributing to pain chronification. From a methodological point of view, the study supports the utility of analyzing rapid hemodynamic modulation to complement the analysis of local CBF distribution patterns using neuroimaging.

References

[1] Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P. "The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity". Arthritis Care Res 2010;5:600–10.

[2] Jensen KB, Kosek E, Petzke F, Carville S, Fransson P, Marcus H, Williams SC, Choy E, Giesecke T, Mainguy Y, Gracely R, Ingvar M. Evidence of dysfunctional pain inhibition in fibromyalgia reflected in rACC during provoked pain. Pain 2009;144:95-100.

[3] Price D, Staud R. Neurobiology of fibromyalgia syndrome. J Rehumatol Supplement 2005;32:22-8.

[4] Reyes del Paso GA, Garrido S, Pulgar A, Duschek S. Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia syndrome. J Psychosom Res 2011;70:125–34.

[5] Petzke F, Clauw DJ, Ambrose K, Khine A, Gracely RH. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. Pain 2003;105:403-13.

[6] Staud R, Robinson M, Price D. Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. J Pain 2006;11:893-901.

[7] Staud R, Craggs J, Perlstein W, Robinson M, Price D. Brain activity associated with slow temporal summation of C-fiber evoked pain in fibromyalgia patients and healthy controls. Eur J Pain 2008;12:1078-89.

[8] Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional Magnetic Resonance Imaging Evidence of Augmented Pain Processing in Fibromyalgia. Arthritis Rheum 2002;46:1333-43.

[9] Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH. Functional imaging of pain in patients with primary fibromyalgia. J. Rheumatol 2004;31:364-78.

[10] Pujol J, López-Solà M, Ortiz H. Mapping brain response to pain in fibromyalgia using temporal analysis of fMRI. PLoS ONE 2009;4(4):e5224.

[11] Burgmer M, Pogatzki-Zahn E, Gaubitz M, Wessoleck E, Heuft G, Pfleiderer B. Altered brain activity during pain processing in fibromyalgia. NeuroImage 2009;44:502-8.

[12] Edwards RR, Bingham CO III, Bathon J, Haythornthwaite JA. Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. Arthritis Rheum 2006;55: 325-32.

[13] Geisser ME, Casey KL, Brucksch CB, Ribbens CM, Appleton BB, Crofford LJ. Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia: association with mood, somatic focus, and catastrophizing. Pain 2003;102:243-50.

[14] Giesecke T, Williams DA, Harris RE, Cupps TR, Tian X, Tian TX, Gracely RH, Clauw DJ. Subgrouping of fibromyalgia patients on the basis of pressure- pain thresholds and psychological factors. Arthritis Rheum 2003;48:2916–22.

[15] Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 2004;127:835–43.

[16] Karsdorp PA, Vlaeyen JW. Active avoidance but not activity pacing is associated with disability in fibromyalgia. Pain 2009;147:29-35.

[17] Van Wilgen CP, van Ittersum MW, Kaptein AA, van Wijhe M. Illness perceptions in patients with fibromyalgia and their relationship to quality of life and catastrophizing. Arthritis Rheum 2008;58:3618-26.

[18] Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM. Dissociating Pain from Its anticipation in the human brain. Science 1999;284:1979-81

[19] Motzkin JC, Philippi CL, Wolf RC, Baskaya MK, Koenigs M. Ventromedial prefrontal cortex lesions alter neural and physiological correlates of anticipation. J Neurosci 2014;30:10430-37

[20] Duschek S, Schandry R. Functional transcranial Doppler sonography as a tool in psychophysiological research. Psychophysiology 2003;40:436-54.

[21] Duschek S, Hellmann N, Merzoug K, Reyes del Paso GA, Werner NS. Cerebral blood flow dynamics during pain processing investigated by functional transcranial Doppler sonography. Pain Med 2012;13:419-26.

[22] Duschek S, Mannhart T, Winkelmann A, Merzoug K, Werner NS, Schuepbach D, Montoya P. Cerebral blood flow dynamics during pain processing in patients with fibromyalgia syndrome. Psychosom Med 2012;74:802-9.

[23] Montoro CI, Duschek S, Muñoz Ladrón de Guevara C, Fernández-Serrano MJ, Reyes del Paso GA. Aberrant cerebral blood flow responses during cognition: implications for the understanding of cognitive deficits in fibromyalgia. Neuropsychology 2014; 29:173-82. http://dx.doi.org/10.1037/neu0000138.

[24] Reyes del Paso G, Montoro CI, Duschek, S. Reaction time, cerebral blood flow, and heart rate responses in fibromyalgia: evidence of alterations in attentional control. J Clinic Exp Neuropsyc 2015; *(ahead-of-print):*1-15. DOI:10.1080/13803395.2015.1023265

[25] Cook E III, Turpin G. Differentiating orienting, startle, and defense responses: The role of affect and its implications for psychopathology. In P J Lang, R F Simons, & M Balaban, Attention and orienting: Sensory and motivational processes. New York: Psychology Press; 1997.

[26] Sokolov EN. Perception and the conditioned reflex. Oxfrod: Pergamon; 1963.

[27] Turpin G. Effects of stimulus intensity on autonomic responding: the problem of differentiating orienting and defense reflexes. Psychophysiology 1986;23:1-14.

[28] Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 2000;4:215-22.

[29] Chua P, Krams M, Toni I, Passingham R, Dolan R. A functional anatomy of anticipatory anxiety. NeuroImage 1999;9:563-71.

[30] Straube T, Mentzel, HJ, Miltner, WHR. Waiting for spiders: Brain activation during anticipatory anxiety in spider phobics. NeuroImage 2007;37:1427-36

[31] Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynols WJ, Romano TJ, Rusell IJ, Sheon RP. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.

[32] First MB, Spitzer RL, Gibbon M, Williams JBW. Entrevista clínica estructurada para los trastornos de eje I del DSM-IV (versión clínica) SCID-I; 1999.

[33] Melzack, R. The Mc Gill Pain questionnaire: major properties and scoring methods. Pain 1975;1:277-99.

[34] Sutton ST, Davidson RJ. Prefrontal brain asymmetry: A biological substrate of the behavioral approach and inhibition systems. Psychol Sci 1997;8:204-10.

[35] Posner MI, Petersen SE. The attention system of the human brain. Annu Rev Neurosci 1990;13:25-42

[36] Burgmer M, Petzke F, Giesecke T, Gaubitz M, Heuft G, Pfleiderer B. Cerebral Activation and Catastrophizing During Pain Anticipation in Patients With Fibromyalgia. Psychosom Med 2011;73:751-59.

[37] Duschek S, Werner NS, Limbert N, Winkelmann A, Montoya P. Attentional bias towards negative information in patients with fibromyalgia syndrome. Pain Med, 2014;15:603-12.

[38] Strelau J. Temperament personality activity. Academic Press; 1983.

Table 1. Demographic and clinical characteristics (mean ± SD) and medication use in the FMS and control groups. Results of the group comparisons are also displayed (*t* or χ^2).

	FMS patients	Control group	*t or* χ^2	*P*
Age	48.96±9.15	45.40±5.34	1.540	.131
Body Mass Index	25.31±3.37	24.18±3.98	1.033	.307
Years of education	11.64±3.05	12.80±3.14	-1.251	.218
Depression (%)	13 (52)	2 (10)	8.62	.003
Anxiety disorders (%)	13 (52)	1 (5)	10.60	.001
Antidepressant use (%)	13 (52)	1 (5)	11.20	.001
Anxiolytic use (%)	15 (60)	4 (20)	7.13	.008
Analgesic use (%)	21 (84)	4 (20)	18.02	<.0001
Opiate use (%)	13 (52)	0 (0)	14.30	<.0001
McGill: sensorial	38.56 ± 22.14	10.80±7.52	5.86	<.0001
McGill: emotional	6.40 ± 5.75	1.10±1.68	4.45	<.0001
McGill: miscellaneous	10.08 ± 6.81	3.95±3.07	7.42	<.0001
McGill: evaluative	3.56 ± 1.23	1.90±1.02	4.02	<.0001
McGill: Pain words	26.64 ± 12.50	9.00±5.28	6.38	<.0001
McGill: total score	60.32 ± 38.10	17.95±12.51	5.22	<.0001

Table 2. Mean values (± SD) of relative (%) blood flow velocity changes in the anterior cerebral arteries (ACA) of the right and left hemispheres, under the fixed pressure and equal pain conditions for the anticipatory (1), early increase (2) and decrease (3) and late increase components (4). Results of the group comparisons are also displayed (p, η^2).

	FMS patients	Control group	$t(43)$	p	η^2
Right, fixed pressure, 1	4.85 (1.34)	.78 (.53)	2.70	.011	.127
Right, fixed pressure, 2	5.35 (1.53)	.01 (.77)	2.76	.009	.135
Right, fixed pressure, 3	-3.72 (1.45)	-3.06 (1.37)	.413	.682	.006
Right, fixed pressure, 4	8.75 (1.96)	6.82 (1.05)	.826	.414	.015
Left, fixed pressure, 1	2.49 (.66)	2.52 (.58)	.220	.827	.001
Left, fixed pressure, 2	4.41 (1.16)	2.96 (.63)	1.01	.317	.019
Left, fixed pressure, 3	-5.41 (1.76)	-3.56 (.56)	1.53	.138	.050
Left, fixed pressure, 4	8.15 (2.23)	6.57(.92)	.653	.518	.010
Right, equal pain, 1	5.14 (.94)	1.78 (.57)	2.73	.010	.137
Right, equal pain, 2	4.76 (1.46)	3.61 (.84)	.683	.499	.028
Right, equal pain, 3	-6.46 (1.42)	-2.80 (1.01)	2.19	.035	.097
Right, equal pain, 4	6.03 (.92)	7.23 (.84)	.951	.347	.009
Left, equal pain, 1	3.99 (1.45)	.06 (.71)	2.52	.016	.115
Left, equal pain, 2	5.92 (1.98)	3.35 (.79)	1.25	.222	.036
Left, equal pain, 3	-5.88 (1.06)	-3.69 (.59)	1.79	.081	.067
Left, equal pain, 4	7.01 (1.6)	7.33 (.89)	.170	.886	.001

Table 3. Mean values (± SD) of relative (%) blood flow velocity changes for the middle cerebral arteries (MCA) of the right and left hemispheres under the fixed pressure and equal pain conditions for the anticipatory (1), early increase (2), decrease (3) and late increase components (4). Results of the group comparisons are also displayed (p, η^2).

	FMS patients	Control group	*t*(43)	*p*	η^2
Right, fixed pressure, 1	2.35 (.44)	2.12 (.38)	.713	.480	.004
Right, fixed pressure, 2	2.24 (.52)	2.31 (.47)	.395	.694	.002
Right, fixed pressure, 3	-3.73 (.51)	-3.66 (.62)	.075	.941	.005
Right, fixed pressure, 4	4.56 (.48)	5.30 (.67)	.903	.373	.006
Left, fixed pressure, 1	1.93 (.45)	1.72 (.53)	.145	.705	.003
Left, fixed pressure, 2	3.74 (.47)	3.62 (.54)	.161	.873	.000
Left, fixed pressure, 3	-.64 (.40)	1.05 (.67)	.390	.535	.009
Left, fixed pressure, 4	5.56 (.58)	5.75(.58)	.238	.812	.020
Right, equal pain, 1	2.21 (.45)	2.83 (.54)	.88	.384	.006
Right, equal pain, 2	2.76 (.46)	4.12 (.84)	1.41	.170	.026
Right, equal pain, 3	-2.93 (.49)	-1.57 (.67)	1.65	.106	.048
Right, equal pain, 4	4.49 (.61)	6.29 (1.09)	2.17	.036	.101
Left, equal pain, 1	3.07 (.51)	3.43 (.49)	.498	.621	.018
Left, equal pain, 2	4.91 (.51)	6.12 (.82)	1.315	.196	.050
Left, equal pain, 3	.66 (.62)	3.36 (.91)	1.65	.106	.061
Left, equal pain, 4	6.15 (.50)	8.26 (.89)	1.52	.135	.052

Figure legends:

Figure 1. Grand averages of blood flow velocity responses for the anterior (ACA) and middle (MCA) cerebral arteries under the fixed pressure condition (continuous lines and points represent FMS patients and controls, respectively).

Figure 2. Grand averages of blood flow velocity responses for the anterior (ACA) and middle (MCA) cerebral arteries under the equal pain condition (continuous lines and points represent FMS patients and controls, respectively).

Figure 1

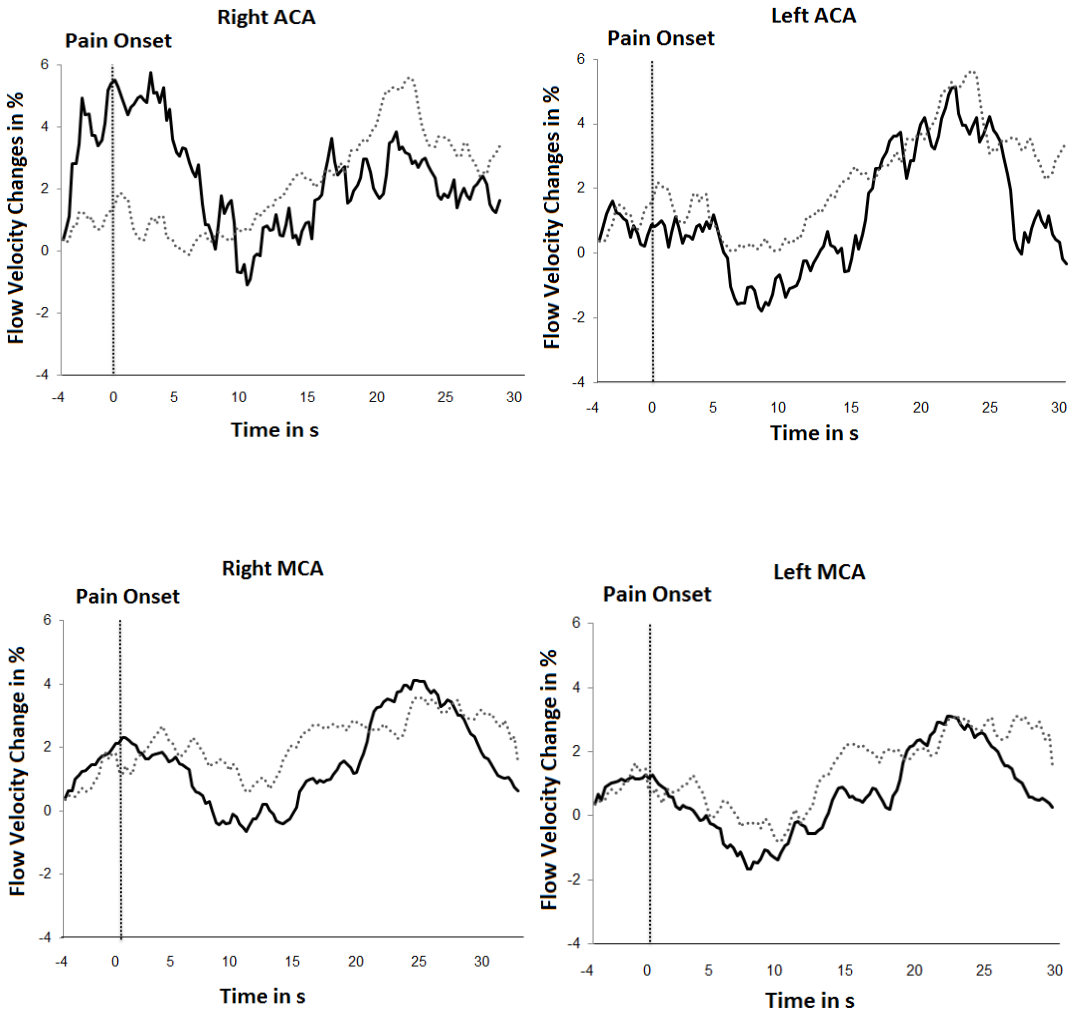
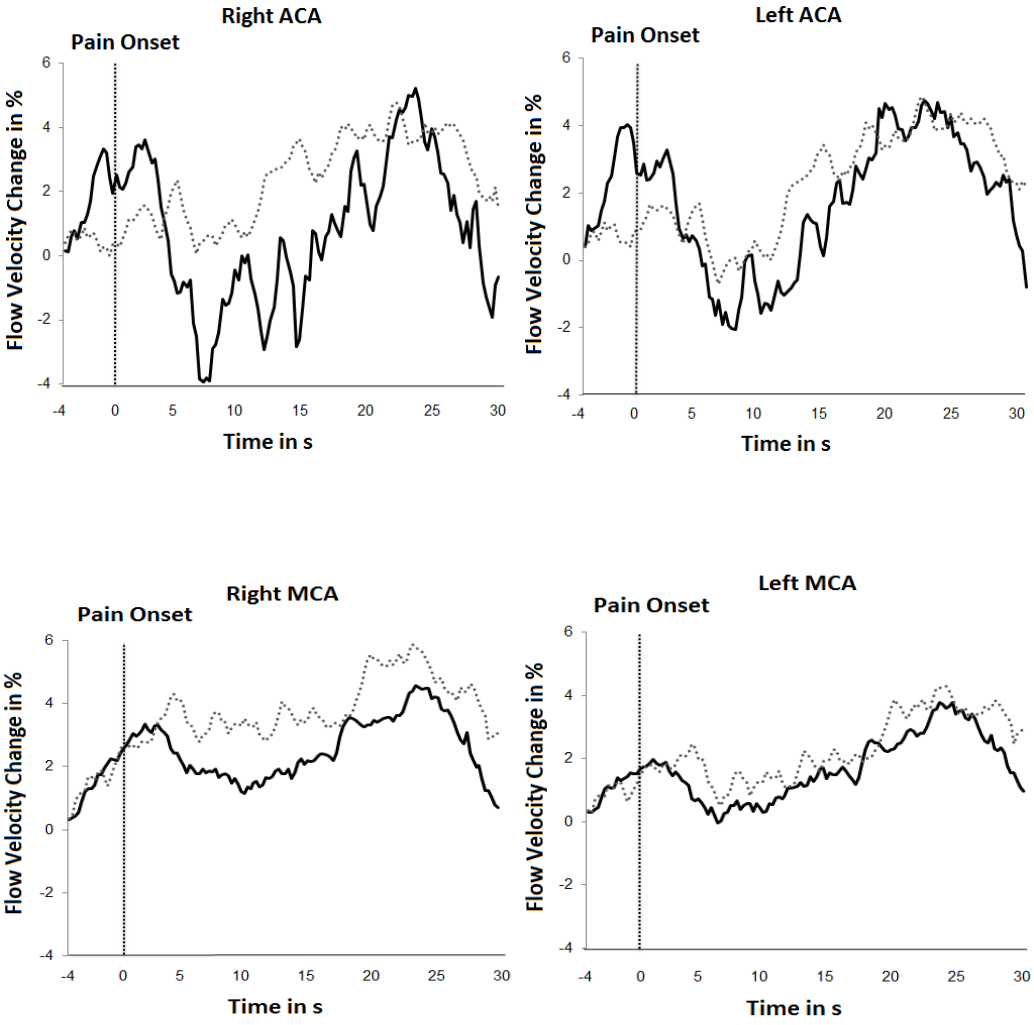

Right ACA
Pain Onset
Flow Velocity Changes in %
Time in s
Left ACA
Pain Onset
Flow Velocity Changes in %
Time in s
Right MCA
Pain Onset
Flow Velocity Change in %
Time in s
Left MCA
Pain Onset
Flow Velocity Change in %
Time in s

Figure 2


Right ACA
Pain Onset
Flow Velocity Change in %
Time in s
Left ACA
Pain Onset
Flow Velocity Change in %
Time in s
Right MCA
Pain Onset
Flow Velocity Change in %
Time in s
Left MCA
Pain Onset
Flow Velocity Change in %
Time in s

ESTUDIO 2. ABERRANT CEREBRAL BLOOD FLOW RESPONSES DURING COGNITION: IMPLICATIONS FOR THE UNDERSTANDING OF COGNITIVE DEFICITS IN FIBROMYAGIA.

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Aberrant Cerebral Blood Flow Responses During Cognition: Implications for the Understanding of Cognitive Deficits in Fibromyalgia

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Objective: There is ample evidence for cognitive deficits in fibromyalgia syndrome (FMS). The present study investigated cerebral blood flow responses during arithmetic processing in FMS patients and its relationship with performance. The influence of clinical factors on performance and blood flow responses were also analyzed. ***Method:*** Forty-five FMS patients and 32 matched healthy controls completed a mental arithmetic task while cerebral blood flow velocities in the middle (MCA) and anterior (ACA) cerebral arteries were measured bilaterally using functional transcranial Doppler sonography (fTCD). ***Results:*** Patients′ cognitive processing speeds were slower versus healthy controls. In contrast to patients, healthy controls showed a pronounced early blood flow response (during seconds 4–6 after the warning signal) in all assessed arteries. MCA blood flow modulation during this period was correlated with task performance. This early blood flow response component was markedly less pronounced in FMS patients in both MCAs. Furthermore, patients displayed an aberrant pattern of lateralization, with right hemispheric dominance especially observed in the ACA. Severity of clinical pain in FMS patients was correlated with cognitive performance and cerebral blood flow responses. ***Conclusions:*** Cognitive impairment in FMS is associated with alterations in cerebral blood flow responses during cognitive processing. These results suggest a potential physiological pathway through which psychosocial and clinical factors may affect cognition.

Keywords: clinical pain, cognitive performance, fibromyalgia syndrome, functional transcranial Doppler sonography (fTCD)

Fibromyalgia syndrome (FMS) is a highly prevalent chronic pain disorder (Wolfe et al., 1990). Among its most frequently presenting symptoms is reduced mental performance. Self-reported cognitive deficits include forgetfulness, concentration difficulties, loss of vocabulary, and mental slowness (Glass, 2006; Glass, 2008; Glass, Park, Minear, & Crofford, 2005). Patients often state that these deficits significantly affect their everyday life, thus they must be considered among the most serious symptoms of the disease (Glass et al., 2005). These cognitive problems are problematic particularly in the context of working life, where patients frequently feel that their professional competence is compromised (Glass et al., 2005). Clinical and laboratory evidence, including that gathered via standardized neuropsychological assessment, confirms the reality of these deficits. FMS patients show substantial impairments in working, episodic, semantic, and implicit memory, selective attention, speed of cognitive processing, and executive control (Dick, Verrier, Harper, & Rashiq, 2008; Duschek, Werner, Winkelmann, & Wankner, 2013; Glass, 2006; Glass, 2008; Munguía-Izquierdo, Legaz-Arrese, Moliner-Urdiales, & Reverter-Masía, 2008; Pericot-Nierga et al., 2009; Reyes del Paso, Pulgar, Duschek, & Garrido, 2012; Verdejo-García, López-Torrecillas, Calandre, Delgado-Rodríguez, & Bechara, 2009).

Current evidence regarding the origin of these cognitive deficits suggests that one of the most important factors relates to the interfering, intrusive effect of pain, and where significant associations between pain intensity and cognitive impairment have been obtained (Duschek et al., 2013; Glass, 2006; Glass, 2008; Grace, Nielson, Hopkins, & Berg, 1999; Karp et al., 2006; Munguía-Izquierdo et al., 2008; Park, Glass, Minear, & Crofford, 2001; Reyes del Paso et al., 2012; Verdejo-García et al., 2009). Pain is an attention-demanding condition that activates brain areas associated with cognitive processing such as the cingulate and prefrontal cortex (Apkarian, Bushnell, Treede, & Zubieta, 2005). It is possi-

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ble that central nociceptive processing detracts from cognition because it requires enhanced neural resources to be employed in the respective brain areas (Baliki et al., 2006; Dick et al., 2008; Glass, 2008; Park et al., 2001; Munguía-Izquierdo et al., 2008). With regard to other factors, such as depression, anxiety, and fatigue, the majority of studies report that these conditions play a secondary role in cognitive function in FMS (i.e., Glass, 2006; Glass, 2008; Munguía-Izquierdo et al., 2008; Park et al., 2001; Reyes del Paso et al., 2012; Verdejo-García et al., 2009).

One factor that has previously been related to cognitive performance is the ability to increase cerebral blood flow in response to cognitive demands (Duschek, Schuepbach, & Schandry, 2008; Duschek, Heiss, Schmidt, Werner, & Schuepbach, 2010). For more than a century it has been known that a coupling exists between neuronal activity and cerebral blood flow. Cognitively induced changes in cerebral perfusion result from the tight coupling between neural activity and brain metabolism (Logothetis, Pauls, Trinath, & Oeltermann, 2001). Mediated by a variety of biochemical factors, such as K^+, H^+, NO, and adenosine, neural activation leads to the dilation of cerebral arterioles and capillaries, followed by an increase in cerebral blood flow (Iadecola, 2004; Paulson, 2002).

Functional transcranial Doppler sonography (fTCD) is used to measure cerebral blood flow and perfusion. This method allows for the continuous noninvasive registration of blood flow velocity changes in the basal cerebral arteries associated with neural activation. Unlike the diameters of the small vessels, those of the basal cerebral arteries, which are insonated by fTCD, remain virtually unchanged under varying conditions of stimulation (Giller, Bowman, Dyer, Mootz, & Krippner, 1993; Kontos, 1989). Therefore, blood flow changes in these arteries do not result from their own vasomotor activity, but rather reflect changing metabolic rates in their perfusion territories. In their pioneering studies with fTCD, Aaslid, Markwalder, and Nornes (1982) reported increases in cerebral blood flow velocities in response to visual stimulation. Subsequent studies reported similar results during attentional (Knecht, Deppe, Backer, Ringelstein, & Henningsen, 1997), memory (Cupini et al., 1996), and other cognitive tasks (see Stroobant & Vingerhoets, 2000). The excellent temporal resolution provided by this technique allows for the assessment of the dynamic component of cerebral perfusion. A large number of studies provide evidence that fTCD is a valuable tool for the quantification of the rapid changes in cerebral blood flow which accompany cognitive activity and other psychological processes (for an overview, see Duschek & Schandry, 2003).

Duschek and colleagues (Duschek, Hadjamu, & Schandry, 2007; Duschek & Schandry, 2004, 2006; Duschek, Schuepbach, & Schandry, 2008; Schuepbach, Boeker, Duschek, & Hell, 2007) have repeatedly reported positive associations between amplitude of cerebral blood flow response and cognitive performance. These studies clearly suggest that, for the correct activation of cerebral areas involved in the resolution of a task, it is necessary to increase cerebral blood flow to these areas (Duschek & Schandry, 2003). Deficiencies in task-induced blood flow responses are associated with reduced cognitive performance (Duschek & Schandry, 2004). Until now no study has investigated the evocation of cerebral blood flow responses consequent on the performance of cognitive tasks in FMS. In this context, one relevant question is whether the performance deficits seen in FMS are associated with deficiencies in task-induced cerebral blood flow responses.

The present study evaluates cerebral blood flow in response to a serial mental arithmetic task, both in patients with FMS and in healthy controls. Additionally, associations between the amplitude of blood flow responses and cognitive performance are assessed. Cerebral perfusion is measured by fTCD bilaterally, in both the middle (MCA) and anterior (ACA) cerebral arteries. In a previous study, which employed a paper-and-pencil serial arithmetic task consisting of the addition of pairs of single digit numbers, FMS patients completed less operations, but there were no differences in success/error rate, in comparison with healthy controls (Reyes del Paso et al., 2012). Based on this finding we presently hypothesize impaired performance in FMS patients, to be evidenced by slower arithmetic processing speeds. We also expect alterations in task-evoked increases in cerebral blood flow in FMS patients, and further that blood flow responses will be associated with performance indices. Given that mental arithmetic is principally associated with activation of the left gyrus angularis (Dehaene, 2000) in the inferior parietal cortex, in addition to the left insular/orbitofrontal cortex (perfusion territories of the MCA; Menon, Rivera, White, Glover, & Reiss, 2000), we predict that performance during the task will be specifically associated with increases in cerebral blood flow in the left MCA. Comorbid emotional disorders, medication use, clinical pain, anxiety, depression, fatigue, and sleep problems are also measured, and their influence on cognitive performance and blood flow responses analyzed. Based on our previous study, which employed a similar task (Reyes del Paso et al., 2012), we do not predict cognitive differences as a function of emotional comorbidity or medication use, but expect that severity of clinical pain will be negatively associated with cognitive performance. Finally, and taking into account the possibility that pain, as an attention-demanding condition, may interfere with performance, negative associations between clinical pain severity and amplitude of blood flow in response to the task are expected.

Method

Participants

Forty-five women with FMS, recruited via the Fibromyalgia Association of Jaén, participated in the study. All patients were examined by a rheumatologist and met the American College of Rheumatology criteria for FMS (Wolfe et al., 1990). Exclusionary criteria comprised cardiovascular disease of any kind, metabolic abnormalities, inflammatory causes of pain, neurological disorders, and severe somatic (e.g., cancer) or psychiatric (e.g., psychotic or bipolar) diseases. The control group, comprising 32 healthy women recruited from women's associations, was matched to patients according to age, body mass index, and educational level. In addition to not being able to have any kind of pain disorder, the control group was subject to the same exclusionary criteria as were the patients. Table 1 displays demographic and clinical data for both groups. The majority of the FMS patients were taking receipt of combined pharmacological therapy: 19 patients (of 45; 42.2%) were taking both antidepressants and anxiolytics, and 10 patients (22.2%) were taking a combination of antidepressants, anxiolytics, analgesics, and opiates. Seven patients (15.5%) were using only nonopiate analgesics and 5 patients

Table 1
Demographic and Clinical Characteristics (Mean ± SD) and Medication Use (Number of Participants and Percentage in Brackets) in FMS and Control Groups

Characteristic	Fibromyalgia	Control group	t or $\aleph^2$	p
Age	49.48 ± 8.23	47.03 ± 9.26	1.504	.224
Body mass index	26.53 ± 3.61	25.35 ± 4.44	1.196	.200
Years of education	12.04 ± 3.16	12.87 ± 3.50	1.679	.278
Depression (%)	22 (48.8)	4 (12.5)	10.56	.001
Anxiety disorders (%)	23 (51.1)	4 (12.5)	11.70	.001
Antidepressant use (%)	23 (51.1)	1 (3.1)	20.07	< .0001
Anxiolytic use (%)	26 (57.7)	10 (31.2)	5.29	.021
Analgesic use (%)	37 (82.2)	5 (15.6)	33.45	< .0001
Opiate use (%)	17 (37.7)	0 (0)	15.51	< .0001
State anxiety (STAI)	31.82 ± 10.18	21.34 ± 9.71	4.39	< .0001
Trait anxiety (STAI)	35.37 ± 8.92	19.93 ± 10.71	6.171	< .0001
Depression (BDI)	21.17 ± 12.12	7.32 ± 7.75	5.61	< .0001
Fatigue (FSS)	49.37 ± 11.96	21.00 ± 8.83	10.97	< .0001
Insomnia (OQSQ)	30.51 ± 3.72	18.09 ± 7.77	7.42	< .0001
Hypersomnia (OQSQ)	8.18 ± 3.74	4.67 ± 1.92	4.78	< .0001
No. pain points	30.62 ± 16.06	4.54 ± 4.82	8.75	< .0001
Pain intensity index	3.62 ± .80	1.09 ± 1.32	10.82	< .0001
No. pain words	24.51 ± 10.60	8.83 ± 5.06	7.54	< .0001
Total McGill	53.42 ± 31.98	18.06 ± 11.93	5.87	< .0001

Note. Results of group comparisons are also reported (Student t test or $\aleph^2$). STAI = State-Trait Anxiety Inventory; BDI = Beck Depression Inventory; FSS = Fatigue Severity Scale; OQSQ = Oviedo Quality of Sleep Questionnaire.

(11.1%) were entirely unmedicated. In the control Group 10 participants (of 32; 31.2%) were using anxiolytics, mainly for sleeping difficulties, and 5 (15.6%) were using analgesics to relieve sporadic pain (e.g., headaches).

Mental Arithmetic Task

A small black cross was displayed on the screen (white background), acting as the fixation point. Its disappearance served as a warning stimulus (S1) for the appearance, 5 s subsequently, of two single-digit numbers (S2). Participants were instructed to add these two numbers together and then to provide their response by typing in the last digit of the resulting sum with the computer keyboard. Performance was assessed in terms of response time (RT) and rate of correct responses. Participants were instructed to work as quickly and accurately as possible. The task consisted of 15 trials with an intertrial interval of 30 s, and was preceded by three practice trials and presented on a computer screen via the software package ePrime (Psychology Software Tools, Inc., Sharpsburg, PA).

Recording and Analyzing Cerebral Blood Flow

Blood flow velocities were assessed by fTCD employing a digital Multi-Dop L2 DWI (Elektronische System eGmbh). Recordings were conducted bilaterally in both the MCA and ACA arteries, and were obtained through the temporal bone windows via two 2-MHz transducer probes. After vessel identification, the probes were fixed to the head via a head harness. The MCA were insonated at a depth of 48–55 mm, and the ACA at a depth of 60–70 mm. The spectral envelope curves of the Doppler signal were recorded at a sampling rate of 100 Hz. The mean flow velocity index was applied as a measure of cerebral blood flow; this index is the least vulnerable to artifacts and has the highest correlation with blood volume flowing through an artery per unit of time (Duschek & Schandry, 2003). This parameter was obtained from the digital 100-Hz mean flow velocity output of the Multi-Dop L2 DWI.

In an initial data reduction step, the 100-Hz mean flow velocity recording was reduced by averaging to 4 Hz (one sample every 250 ms). Mean flow velocity during the 5 s before the warning signal (S1) served as the baseline; the 25 s after S1 were taken as the task period (100 post-S1 values). Time-locked to the S1, responses were expressed as relative (percent) changes in flow velocity during task (dFV) with respect to baseline (FVbas) according to the formula $dFV = (FV[t] - FVbas) * 100/FVbas$, where FV(t) represents flow velocity over the time-course of the task.

Procedure

The study was conducted across two sessions, which took place on different days. In the first session a clinical psychologist recorded patients' clinical histories, medication use, and sociodemographic data, and also confirmed that there were no violations of the exclusionary criteria. To assess possible mental disorders, the Structured Clinical Interview for Axis I Disorders of the *Diagnostic and Statistical Manual for Mental Disorders* (First, Spitzer, Gibbon, Williams, 1999) was employed. Clinical pain was evaluated through the McGill Pain Questionnaire (Melzack, 1975; Lázaro et al., 1994), a widely used instrument which provides reliable measures of the sensory, affective and evaluative characteristics of pain. Four parameters were obtained: (a) the number of 'pain points' marked on a picture of the human body; (b) the present pain index as an indicator of current pain intensity; (c) the number of words selected from a list of 66 features describing pain; and (d) the total pain index, given by the sum of sensory, affective, and evaluative pain descriptors. Depression was evalu-

ated via the Beck Depression Inventory (Sanz et al., 2003). Anxiety was assessed using the State–Trait Anxiety Inventory (Spielberger et al., 1986). Fatigue was quantified via a Spanish adaptation of the Fatigue Severity Scale (Krupp et al., 1989; Bulbena et al., 2000). Sleep quality was indexed by the Oviedo Quality of Sleep Questionnaire (Bobes et al., 2000) from which the insomnia and hypersomnia indices were derived.

Some studies have suggested that low cognitive effort leads to reduced validity of neuropsychological testing in a subset of FMS patients (e.g., Johnson-Greene et al., 2013). To control for this, the present participants completed the 15-item Rey Memory Test (an index of possible simulated memory problems) and an *n*-back −1 and −2 task (a measure of working memory performance, which secondarily indicates cognitive effort-engagement; Jaeggi, Buschkuehl, Perrig, & Meier, 2010). The Rey Memory Test (Rey, 1964) assesses immediate visual memory. Its use for simulation detection is based on the premise that malingerers drastically overestimate the difficulties experienced by those with mild memory impairment and thus exaggerate their deficits to the extent that they score less than do individuals with genuine memory impairments. Many studies have reported that both probable malingerers (Greiffenstein, Baker, & Gola, 1994) and individuals simulating memory impairment (Arnett, Hammeke, & Schwartz, 1995) perform significantly worse on the test than do those with actual brain damage, whereas control subjects score higher than all of them. A score below 6 is commonly taken as indicative of simulation. *n*-back tasks provide a measure of working memory: subjects are presented with a continuous stream of items (letters) and are instructed to press a key when they detect a repetition at a specified delay (we used delays of 1 and 2 items).

During the second session the actual experiment was undertaken, supervised by a second experimenter, in a sound-attenuated room set at a constant temperature of 22°C. Because it is not possible to reliably measure both MCA and ACA simultaneously, the entire procedure was repeated twice, once for each pair of arteries. The artery starting order (MCA vs. ACA) was counterbalanced across participants. The distance between the participant and the task monitor was fixed at 0.75 m; participants were also asked to avoid making movements and to fixate upon the cross during the tasks. Participants had been previously instructed to refrain from smoking, caffeine, alcohol, and vigorous exercise for 2 hours before the start of the experiment. They were also asked not to consume analgesics, or other drugs that affect the cardiovascular system, in the 24 hours before the study. Two FMS patients were removed because of outliers; that is, RTs longer than 9 s.

Individual differences in temporal bone thickness affect the possibility of insonation of the cerebral arteries. Furthermore, insonation of the ACA is more difficult than that of the MCA (which is longer, thicker, and has more flow; Duschek & Schandry, 2003). Given this fact, the number of participants with available data was different for each artery. Analyses were performed on the total number of participants in which data from each artery were available. Sample sizes were as follows: left MCA: 41 patients, 32 controls; right MCA: 40 patients, 32 controls; left ACA: 32 patients, 26 controls; and right ACA: 34 patients, 25 controls (complete data on the four arteries were available for 29 patients and 22 controls). The results of the comparison between FMS patients and controls did not differ when the total data set, or only participants with data for all four arteries, was used. Given that the use of all participants with available data increased statistical power (especially in correlational analyses), we performed the analyses for all participants with available data for each artery, as described above. All participants provided informed consent. The study protocol was approved by the Bioethics Committee of the University of Jaén and is part of a larger project investigating neuropsychological performance and psychophysiological processes in FMS.

Statistical Analysis

Visual inspection of the pattern of blood flow velocity modulations revealed three response components: (a) an early increase component associated with the end of the warning period and presentation of the numbers, (b) a late component occurring approximately 5 s subsequent to presentation of the numbers, and (c) a progressive final blood flow decrease (in some cases below baseline level). Peak amplitudes of the three components were computed between 5 and 6 s, 10 and 11 s and 21 and 22 s.

Group differences in cognitive performance, clinical parameters, and amplitudes of the three blood flow components were analyzed via Student *t* test for independent samples. In the FMS group, potential differences related to medication use and comorbid emotional disorders were analyzed using Student *t* tests comparing patients using and not using each medication (separately for antidepressants, anxiolytics, analgesics and opiates) and for patients suffering or not suffering from depression and anxiety disorders. Relationships between cognitive performance, blood flow responses, and clinical variables were quantified by means of Pearson correlations. Correlations were computed for the whole sample and for each group separately. Correlation coefficients involving clinical parameters were only computed separately for each group to avoid spurious results owing to expected large group differences. To optimize the reliability of the analysis concerned with cognitive performance, parameters of the arithmetic task were aggregated for both performances of the test.

The Kolmogorov–Smirnov and the Levene test were used to test normality and homogeneity of variances, respectively. No violations of these assumptions were found (all $p > .05$).

Results

Performance Measures and Their Relationship to Clinical Variables

FMS patients took longer to resolve the arithmetic addition problems, where this difference in performance was present on both occasions upon which the task was performed ($ps < .01$; see Table 2). No group differences were observed in the rate of correct responses. In FMS patients no performance differences were observed as a function of antidepressant, anxiolytic, analgesic or opiate use (all $ts < .5$, all $ps > .5$). The same holds true for effects of comorbid depression (all $ts < 1.50$, all $ps > .13$) and anxiety disorders (all $ts < 1.7$, all $ps > .1$). In the FMS sample present pain intensity, $r = .342$, $p = .024$ and state anxiety, $r = .343$, $p = .023$ were associated with longer RT; hypersomnia level was associated with a lower rate of correct responses, $r = -.344$, $p = .023$. In the control group trait anxiety was associated with longer RT, $r =$

Table 2
Cognitive Performance Data (Mean ± SD)

Task	Fibromyalgia	Control group	*t*	*p*
RT (in s) (ACA)	3.64 ± 1.28	2.70 ± 1.25	2.88	.005
RT (in s) (MCA)	3.84 ± 1.48	2.93 ± 1.00	3.19	.002
% successes (ACA)	96.96 ± 5.79	95.80 ± 6.4	.738	.463
% successes (MCA)	95.21 ± 5.09	96.25 ± 6.76	.702	.485
n-back−1 success	26.66 ± 4.55	28.04 ± 2.86	1.40	.165
n-back−1 false alarms	2.09 ± 2.71	.81 ± 1.11	2.32	.023
n-back−2 success	21.35 ± 5.22	21.22 ± 8.09	.085	.932
n-back−2 false alarms	8.20 ± 5.37	8.00 ± 6.60	.151	.991
15-item Rey Memory test	11.82 ± 2.86	13.40 ± 1.64	2.62	.011

Note. For the mental arithmetic task, response time (RT) and rate of correct responses (% successes) are displayed. For the *n*-back task, number of correct responses (successes) and false alarms are displayed for the −1 and −2 version of the task (because the numbers of trials were 100 in each *n*-back series, these values are also equivalent to percentages). Results of group comparisons are also provided (Student *t* test). The mental arithmetic task was performed twice, once for the recording of the anterior cerebral artery (ACA) and once for the recording of the middle cerebral artery (MCA).

.517, $p = .004$. No overall group difference was found for performance on the *n*-back task; only a difference in the −1 false alarm was observed (see Table 2). FMS patients performed poorer than controls on the 15-item Rey Memory Test (see Table 2), but none of the participants met the simulation criterion (test score < 6).

Blood Flow Responses to Cognitive Task

The response patterns are characterized by two increases in blood flow velocity: an early component associated with the end of the warning period and presentation of the numbers, and a late component approximately 5 s subsequent to presentation of the numbers. The late component is of much greater amplitude versus the early component. From the peak of the late component a progressive decrease and recovery of blood flow velocity is observable (see Figures 1 and 2).

Group comparisons regarding both the left and right MCA revealed differences for the first increase component and the decrease component, where the FMS group displayed lower blood flow velocity (see Table 3). Regarding the left ACA, the groups differed in the decrease component, where the FMS group exhibited lower blood flow velocity. Finally, for the right ACA, the late increase component was higher in the FMS group (see Table 3).

Response in the MCA for the late component was lateralized to the left hemisphere for the control group, $t = 2.41$, $p = .022$, but not for the FMS group, $t = 1.52$, $p = .137$. Lateralization in the ACA to the left hemisphere remained marginally significant in the control group, $t = 1.85$, $p = .079$, and was absent in the FMS group, $t = -.88$, $p = .385$. In the early component no lateralization was observed in the control group, but in the FMS group the response was lateralized to the right hemisphere in the ACA, $t = -2.13$, $p = .043$.

Associations Between Blood Flow Responses and Performance

Across the entire sample, RT was associated with the amplitude of the first component in the MCA, both in the left, $r = -.320$, $p = .006$, and right, $r = -.271$, $p = .021$, hemispheres, and with the amplitude of the decrease component in the right MCA, $r = -.293$, $p = .012$. RT was also associated with the amplitude of the decrease component in the right ACA, $r = -.288$ $p = .029$, and marginally with the amplitude of the first component in the left ACA, $r = -.251$, $p = .057$. In the FMS group, RT was associated with the amplitude of the first component in the right MCA, $r = -.339$, $p = .032$, and the second component in the left MCA, $r = -.354$, $p = .023$. In the control group, the amplitude of the second component in the right ACA was associated with longer RT, $r = .444$, $p = .034$, and a lower rate of correct responses, $r = -.450$, $p = .031$.

Associations Between Blood Flow Responses and Clinical Parameters

In the FMS group blood flow velocities in the left MCA were negatively associated with current pain intensity ($r = -.384$ for the first and $r = -.355$ for the second component, $ps < .05$), total score on the McGill Pain Questionnaire ($r = -.320$, $r = -.396$, and $r = -.317$, respectively for the first, second and third com-

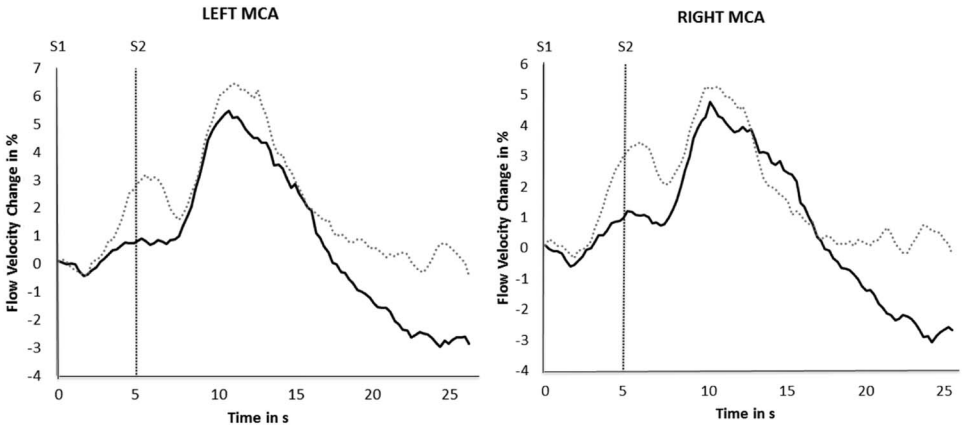

Figure 1. Blood flow velocity response for the left and right MCAs (continuous line represents the fibromyalgia group, dotted line represents the control group).

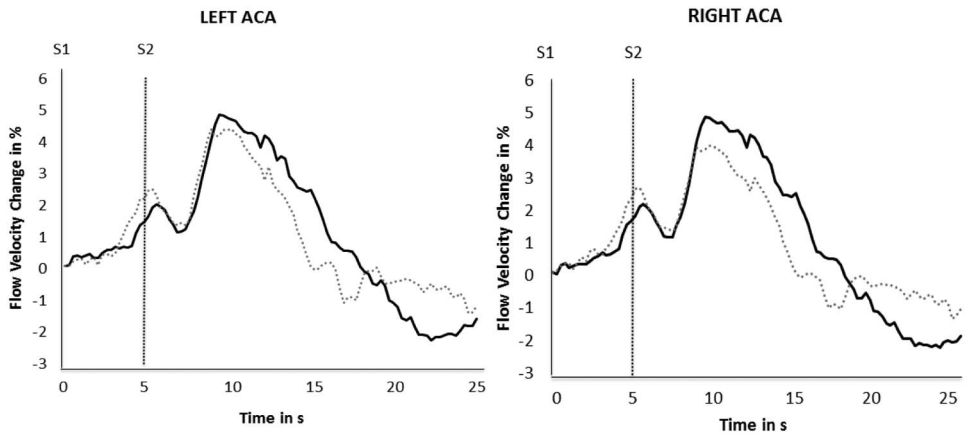

Figure 2. Blood flow velocity response for the left and right ACAs (continuous line represents the fibromyalgia group, dotted line represents the control group).

ponents, *p*s $< .05$), and hypersomnia level ($r = -.382$ for the second and $r = -.366$ for the third component, *p*s $< .05$). Furthermore, current pain intensity was associated with the amplitude of the second component in the right MCA, $r = -.328$, $p = .039$, and the decrease component in the ACA of the right, $r = -.404$, $p = .018$, and left, $r = -.368$, $p = .038$, hemispheres. State anxiety, also in the FMS group, was associated with lower blood flow during the recuperation component in the right MCA ($r = -.340$, $p = .032$; $r = -.308$, $p = .053$ for trait anxiety); insomnia was associated with reduced amplitude of the first component in the right ACA, $r = -.358$, $p = .038$. In the control group, state anxiety was negatively associated with the amplitude of the first component in the MCA of both the left, $r = -.404$, $p = .030$, and right, $r = -.403$, $p = .030$, hemispheres. Finally, in the control group, fatigue was related to lower amplitude of the first component in the left MCA, $r = -.386$, $p = .039$.

Table 3
Peak Amplitudes (Mean ± SD) of the Three Identified Blood Flow Velocity Components (1 = Early Increase, 2 = Late Increase, 3 = Recovery) as a Function of Artery (A = Anterior Cerebral Artery, M = Medial Cerebral Artery) and Group (FMS Patients vs. Control Group), and Results of the Group Comparison (t and p)

Artery/velocity component	FMS	Control group	*t*	*p*
M left (1)	1.14 ± 2.80	3.05 ± 3.25	−2.65	.010
M left (2)	5.55 ± 4.39	6.30 ± 4.88	−.68	.495
M left (3)	−2.31 ± 4.03	−.07 ± 3.62	−2.51	.014
M right (1)	1.38 ± 2.95	3.28 ± 3.65	−2.46	.016
M right (2)	4.60 ± 4.31	5.10 ± 4.98	−.63	.645
M right (3)	−2.58 ± 4.37	.58 ± 2.93	−3.52	.001
A left (1)	1.79 ± 3.84	3.18 ± 3.49	−1.45	.153
A left (2)	4.50 ± 3.60	5.08 ± 4.75	−.53	.596
A left (3)	−2.40 ± 4.37	−.07 ± 3.76	−2.17	.034
A right (1)	2.18 ± 4.01	2.78 ± 2.59	−.64	.522
A right (2)	4.93 ± 4.35	2.86 ± 2.83	2.20	.032
A right (3)	−2.20 ± 4.14	−.71 ± 2.65	−1.68	.097

Discussion

Despite the simplicity of the task employed, FMS patients exhibited impaired cognitive performance, evidenced by slower mental additions. This suggests reduced cognitive processing speed, or mental slowness, in the context of arithmetic processing. These results corroborate previous evidence pertaining to cognitive deficiencies in FMS, and more specifically confirm a slowness in cognitive processing, as reported previously (Cherry et al., 2014; Reyes del Paso et al., 2012; Veldhuijzen, Sondaal, & Oosterman, 2012). As expected, and also in corroboration of previous researches (e.g., Reyes del Paso et al., 2012), the presence of comorbid emotional disorders or medication use did not affect cognitive performance in the FMS group.

Clinical pain severity, as expected, was associated with cognitive slowness, thereby supporting previous evidence for an interfering effect of pain on cognition (Grace et al., 1999; Park et al., 2001; Dick et al., 2008; Glass, 2008, Munguía-Izquierdo et al., 2008; Reyes del Paso et al., 2012; Verdejo-García et al., 2009). Anxiety was associated with longer RT both in FMS patients and in healthy controls, indicating that emotional state interferes with performance. Similarly, Munguía-Izquierdo et al. (2008) reported a negative association between anxiety and cognitive performance in FMS patients, and Reyes del Paso et al. (2012) obtained this same relationship in a healthy population. Finally, hypersomnia level was associated with a lower rate of correct responses in the FMS group, pointing toward a negative effect of sleep problems, which are frequently associated with the disorder.

No significant overall effect for performance on the *n*-back task was found (only in the parameter −1 false alarm). Based on the lack of group differences in correct responses both on the arithmetic task and the n-back test, lower effort is most likely not an explanation of the group differences found in processing speed. Together with the finding that none of the participants met the simulation criteria of the 15-item Rey Memory Test, this finding supports the validity of the mental arithmetic task as a measure of cognitive performance.

To discern a possible mediating mechanism for group differences in cognitive performance, we also analyzed task-elicited

blood flow responses. To activate cerebral regions involved in the resolution of a task it is necessary to increase cerebral blood flow to these areas (Duschek & Schandry, 2003). In this way, one factor relevant to successful cognitive performance is the ability to increase cerebral blood flow in response to cognitive demands (Duschek & Schandry, 2006). fTCD has been applied to the investigation of cerebral hemodynamic modulation during arithmetical processing. Increased blood flow velocities in the anterior and medial cerebral arteries of both hemispheres have been documented during the execution of arithmetical additions, consisting of the obtained response in a biphasic blood flow increase (Duschek, Werner, Kapan, & Reyes del Paso, 2008; Szirmai et al., 2005).

The performance of the mental arithmetic task was associated with a certain pattern of response in cerebral blood flow, consisting of two distinct periods of increase: an early increase associated with the processing of the warning signal and anticipation of the numbers to be added, and a late increase occurring approximately 5 to 6 s subsequent to the presentation of the numbers. This latter increase component is characterized by a higher amplitude versus the early component. The early increase, which onsets before actual presentation of the numbers, can be accounted for in terms of anticipatory attention, whereas the late increase is associated with arithmetical processes (Bäcker et al., 1999).

It has been hypothesized that the connection between neural activity and cerebral blood flow modulation is closer during the initial period of the hemodynamic response than it is during its later components (Sheth, Nemoto, Guiou, Walker, & Toga, 2005), and further that the early response may be particularly useful for the investigation of brain-behavior relationships (Duschek, Schuepbach, & Schandry, 2008; Duschek et al., 2010). In support of this suggestion, in the present study the amplitude of the early component (especially that of the MCA) was most strongly associated with cognitive performance in terms of negative correlations with RT. The association between blood flow responses and RT accords with studies conducted by Duschek et al. (Duschek & Schandry, 2004, 2006; Duschek et al., 2007; Duschek, Schuepbach, & Schandry, 2008; Schuepbach et al., 2007), who repeatedly observed positive associations between amplitude of early cerebral blood flow response and cognitive performance.

Taking into account the arithmetical nature of our task, and in accordance with previous evidence demonstrating specific activation of the left gyrus angularis and the left insular/orbitofrontal cortexes during arithmetic calculations (Dehaene, 2000; Menon et al., 2000), we expected the left MCA to exhibit a greater association with cognitive performance. In line with our hypothesis, the amplitude of the early component in the left MCA was the period most closely associated with RT. This suggests a role for anticipatory attention in modulating task performance. In the FMS group, amplitude of the second increase component in the left MCA was also positively associated with performance. In contrast, the amplitude of the second increase component of the ACA, whose perfusion territories are not essential for completion of the task, was not associated with cognitive performance across the entire sample. Specifically, the amplitude of the right ACA late component in the control group was associated with increased RT and a lower rate of correct responses.

With regard to group differences in blood flow response, the early component in both MCAs—which exhibits a stronger relationship with performance—was strongly reduced in the FMS group. This may indicate that the cerebral areas involved in the correct resolution of tasks of this nature are not fast-activated. Given the reduced activation of these areas during the critical time window in the FMS group, impaired performance should be expected, and was indeed observed. The amplitude of the late increase component for both MCAs did not significantly differ across groups. With regard to the ACAs, the most relevant finding concerns the right ACA. Specific to this artery, the late increase component exhibited greater amplitude in the FMS versus the control group. Activation of cerebral areas irrigated by the right ACA are irrelevant for the resolution of the arithmetic task and, as shown in the control group, its activation was negatively associated with performance in healthy individuals. The cerebral territories of the ACA (such as the ventral-medial frontal cortex), especially with regard to the right hemisphere, are not required for the arithmetic task. Activation of these areas in the FMS group could interfere with task performance by reducing available resources in the appropriate areas irrigated by the MCA.

The left asymmetry expected in the context of an arithmetic task (see Duschek & Schandry, 2006; Duschek, Werner, et al., 2008) was observed in the control group with reference to the late component (which related to arithmetic processing), and especially for the MCA. However, this asymmetry was not observed in the FMS group. These results point toward an aberrant pattern of lateralization in FMS during arithmetic processing, and further suggest that patients with FMS activate the right hemisphere, specifically its anterior middle and ventral structures, even when performing tasks which do not require these cerebral centers. This recruitment of task-irrelevant brain areas may act as an interference mechanism since it can reduce resources in task-relevant cerebral areas. Alternatively, one may discuss that to maintain accuracy in task performance, FMS patients needed to recruit additional brain areas. However, taking into account that the additional cerebral areas specifically activated in the FMS group (e.g., ventral-medial right frontal cortex) are task-irrelevant, this additional recruitment would be useless to improve task accuracy and speed.

A recent study using fTCD in FMS showed that levels of clinical pain severity are positively associated with increases in ACA blood flow during experimentally evoked heat pain, suggesting that cerebral territories supplied by the ACA are implicated in the occurrence of hyperalgesia (Duschek, Mannhart, et al., 2012). Another fTCD study in healthy subjects revealed a close association between flood flow modulation in the ACA during heat stimulation and the subjective sensory and affective pain responses (Duschek, Hellmann, Merzoug, Reyes del Paso, & Werner, 2012a). Together, these results are compatible with the notion that brain structures in the perfusion territory of the ACA might mediating the interfering effect of pain on cognition.

Another difference between the response patterns of the two groups related to the recuperation phase; that is, to decrements in blood flow following the late component. For all four arteries, this decrease component was greater for the FMS group, such that blood flow reached levels lower than baseline. This might be explained as representing an exaggerated counterresponse to the late increase component, which may in turn be indicative of

aberrant homeostatic regulatory mechanisms in FMS (which act to maintain the constancy of cerebral blood flow). Interestingly, RT was associated with blood flow during this recuperation phase in the right arteries (i.e., greater response decrements were associated with longer RT), suggesting that homeostatic regulatory mechanisms might relate in some way to cognitive performance. In light of this possibility, a limitation of the present study might be that the observed, lower blood flow velocity during the final recuperation period in the FMS group may have persisted to some degree during the baseline period which followed, which in turn may have affected the results. This is a relevant point for future studies employing fTCD techniques, and suggests a need for longer interstimulus intervals.

In the FMS sample, clinical pain severity was associated with blood flow velocity responses in the left MCA, that is, stronger pain related to lower amplitudes of both the early (anticipatory attention) and late (arithmetic processing) increase components. Furthermore, pain severity was negatively associated with blood flow during the decrease component, suggesting a possible role of pain in modulating regulatory homeostatic mechanisms. Similarly, greater hypersomnia levels were associated with lower blood flow during the second increase and recuperation components in the left MCA, whereas insomnia was inversely related to the amplitude of the first increase component in the right ACA. In the control group, both anxiety and fatigue were negatively associated with the amplitude of the first component in the MCA.

These results indicate that the disruptive effect of pain and other clinical variables on cognitive performance in FMS might be partly meditated by aberrant cerebral blood flow regulation during task performance. Specifically, our results suggest that pain intensity and insomnia interfered with blood flow response related to anticipatory attention (i.e., the first increase component) and pain intensity, and hypersomnia interfered with blood flow response during arithmetic processing (i.e., the second left MCA increase component).

We have previously found that parameters of systemic hemodynamics (i.e., blood pressure and heart rate) can to some extent modulate cerebral blood flow supply (Duschek, Werner, et al., 2008; Duschek et al., 2010), and further that FMS patients exhibit aberrant autonomic cardiovascular regulation, including in their response to mental and physical stress (Reyes del Paso et al., 2010, 2011). Thus we cannot rule out that some of the group differences in blood flow response might be attributable, to some degree, to these related autonomic cardiovascular deficits.

In conclusion the results of the present study demonstrate that selective cognitive deficits in FMS may be associated with deficiencies in task-evoked increases in cerebral blood flow, specifically the large reduction in early component increases in blood flow, associated with the processing of the warning signal and anticipatory attention to the presentation of task material in both MCAs. Furthermore, results point toward aberrances in blood flow response in FMS: allocation of resources in task-irrelevant areas (especially of the right hemisphere) that could interfere with performance by reducing available resources for activation of the crucial cerebral structures needed for task completion. Moreover, certain of the characteristic clinical features of FMS (such as pain and sleep problems) might modulate these abnormalities in cerebral blood flow. In summation, our study suggests a potential physiological pathway by which psychosocial factors can affect cognition; that is, cerebral blood flow modulation during cognitive processing.

Future research should focus on resolving some of the questions that arose during this initial study of the application of fTCD to the understanding of cognitive deficits in FMS. Important issues include replication of, and explanation for, the large reduction of the early component in the MCAs in the FMS group; the origin of the greater activation of the right ACA in FMS; observation and replication of the aberrant asymmetry we found during the arithmetic task in FMS, via study of the lateralization of other psychological functions in the disorder (such as language, emotions, etc.); and an explanation for the exaggerated decrement in blood flow following the late component observed in FMS patients, via replication of this effect with other types of tasks, and through employment of longer interstimulus intervals.

References

Aaslid, R., Markwalder, T. M., & Nornes, H. (1982). Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *Journal of Neurosurgery, 57,* 769–774. doi:10.3171/jns.1982.57.6.0769

Apkarian, A. V., Bushnell, M. C., Treede, R. D., & Zubieta, J. K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain, 9,* 463–484. doi:10.1016/j.ejpain.2004.11.001

Arnett, P. A., Hammeke, T. A., & Schwartz, L. (1995). Quantitative and qualitative performance on Rey's 15-item test in neurological patients and dissimulators. *Clinical Neuropsychologist, 9,* 17–26. doi:10.1080/13854049508402052

Bäcker, M., Knecht, S., Deppe, M., Lohmann, H., Ringelstein, E. B., & Henningsen, H. (1999). Cortical tuning: A function of anticipated stimulus intensity. *Neuroreport, 10,* 293–296. doi:10.1097/00001756-199902050-00016

Baliki, M. N., Chialvo, D. R., Geha, P. Y., Levy, R. M., Harden, R. N., Parrish, T. B., & Apkarian, A. V. (2006). Chronic pain and the emotional brain: Specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *The Journal of Neuroscience, 26,* 12165–12173. doi:10.1523/JNEUROSCI.3576-06.2006

Bobes, J., González, M. P., Sáiz, P. A., Bascarán, M. T., Iglesias, C., & Fernández, J. M. (2000). Propiedades psicométricas del cuestionario Oviedo de sueño. *Psicothema, 12,* 107–112.

Bulbena, A., Berrios, G. E., & Fernández de Larrinoa, P. (2000). *Medición Clínica en Psiquiatría y Psicología.* Barcelona, Spain: Masson.

Cherry, B. J., Zettel-Watson, L., Shimizu, R., Roberson, I., Rutledge, D. N., & Jones, C. J. (2014). Cognitive performance in women aged 50 years and older with and without fibromyalgia. *The Journals of Gerontology: Series B: Psychological Sciences and Social Sciences.* doi:10.1093/geronb/gbs122

Cupini, L. M., Matteis, M., Troisi, E., Sabbadini, M., Bernardi, G., Caltagirone, C., & Silvestrini, M. (1996). Bilateral simultaneous transcranial Doppler monitoring of flow velocity changes during visuospatial and verbal working memory tasks. *Brain, 119,* 1249–1253. doi:10.1093/brain/119.4.1249

Dehaene, S. (2000). Cerebral bases of number processing and calculation. In S. Gazzaniga (Ed.), *The new cognitive neurosciences.* London, UK: MIT Press.

Dick, B. D., Verrier, M. J., Harper, K. T., & Rashiq, S. (2008). Disruption of cognitive function in fibromyalgia syndrome. *Pain, 139,* 610–616. doi:10.1016/j.pain.2008.06.017

Duschek, S., Hadjamu, M., & Schandry, R. (2007). Enhancement of cerebral blood flow and cognitive performance due to pharmacological

blood pressure elevation in chronic hypotension. *Psychophysiology, 44,* 145–153. doi:10.1111/j.1469-8986.2006.00472.x

Duschek, S., Heiss, H., Schmidt, F. H., Werner, N., & Schuepbach, D. (2010). Interactions between systemic hemodynamics and cerebral blood flow during attentional processing. *Psychophysiology, 47,* 1159–1166.

Duschek, S., Hellmann, N., Merzoug, K., Reyes del Paso, G. A., & Werner, N. S. (2012). Cerebral blood flow dynamics during pain processing investigated by functional transcranial Doppler sonography. *Pain Medicine, 13,* 419–426. doi:10.1111/j.1526-4637.2012.01329.x

Duschek, S., Mannhart, T., Winkelmann, A., Merzoug, K., Werner, N. S., Schuepbach, D., & Montoyo, P. (2012). Cerebral blood flow dynamics during pain processing in patients with fibromyalgia syndrome. *Psychosomatic Medicine, 74,* 802–809. doi:10.1097/PSY.0b013e3182676d08

Duschek, S., & Schandry, R. (2003). Functional transcranial Doppler sonography as a tool in psychophysiological research. *Psychophysiology, 40,* 436–454. doi:10.1111/1469-8986.00046

Duschek, S., & Schandry, R. (2004). Cognitive performance and cerebral blood flow in essential hypotension. *Psychophysiology, 41,* 905–913. doi:10.1111/j.1469-8986.2004.00249.x

Duschek, S., & Schandry, R. (2006). Deficient adjustment of cerebral blood flow to cognitive activity due to chronically low blood pressure. *Biological Psychology, 72,* 311–317. doi:10.1016/j.biopsycho.2005.12.003

Duschek, S., Schuepbach, D., & Schandry, R. (2008). Time-locked association between rapid cerebral blood flow modulation and attentional performance. *Clinical Neurophysiology, 119,* 1292–1299. doi:10.1016/j.clinph.2008.01.102

Duschek, S., Werner, N., Kapan, N., & Reyes del Paso, G. A. (2008). Patterns of cerebral blood flow and systemic hemodynamics during arithmetic processing. *Journal of Psychophysiology, 22,* 81–90. doi:10.1027/0269-8803.22.2.81

Duschek, S., Werner, N. S., Winkelmann, A., & Wankner, S. (2013). Implicit memory function in fibromyalgia syndrome. *Behavioral Medicine, 39,* 11–16. doi:10.1080/08964289.2012.708684

First, M., Spitzer, R., Gibbon, M., & Williams, J. (1999). *Entrevista Clínica Estructurada para los Trastornos del Eje I del DSM–IV (SCID-I).* Barcelona, Spain: Masson.

Giller, C. A., Bowman, G., Dyer, H., Mootz, L., & Krippner, W. (1993). Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery, 32,* 737–742. doi:10.1227/00006123-199305000-00006

Glass, J. M. (2006). Cognitive dysfunction in fibromyalgia and chronic fatigue syndrome: New trends and future directions. *Current Rheumatology Reports, 8,* 425–429. doi:10.1007/s11926-006-0036-0

Glass, J. M. (2008). Fibromyalgia and cognition. *Journal Clinical Psychiatry, 69,* 20–24.

Glass, J. M., Park, D. C., Minear, M., & Crofford, L. J. (2005). Memory beliefs and function in fibromyalgia patients. *Journal of Psychosomatic Research, 58,* 263–269. doi:10.1016/j.jpsychores.2004.09.004

Grace, G. M., Nielson, W. R., Hopkins, M., & Berg, M. A. (1999). Concentration and memory deficits in patients with fibromyalgia syndrome. *Journal of Clinical and Experimental Neuropsychology, 21,* 477–487. doi:10.1076/jcen.21.4.477.876

Greiffenstein, M. F., Baker, W. J., & Gola, T. (1994). Validation of malingered amnesia measures with a large clinical sample. *Psychological Assessment, 6,* 218–224. doi:10.1037/1040-3590.6.3.218

Iadecola, C. (2004). Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nature Reviews Neuroscience, 5,* 347–360. doi:10.1038/nrn1387

Jaeggi, S. M., Buschkuehl, M., Perrig, W. J., & Meier, B. (2010). The concurrent validity of the N-back task as a working memory measure. *Memory, 18,* 394–412. doi:10.1080/09658211003702171

Johnson-Greene, D., Brooks, L., & Ference, T. (2013). Relationship between performance validity testing, disability status, and somatic complaints in patients with fibromyalgia. *The Clinical Neuropsychologist, 27,* 148–158. doi:10.1080/13854046.2012.733732

Karp, J. F., Reynolds, C. F., 3rd, Butters, M. A., Dew, M. A., Mazumdar, S., Begley, A. E., . . . Weiner, D. K. (2006). The relationship between pain and mental flexibility in older adult pain clinic patients. *Pain Medicine, 7,* 444–452. doi:10.1111/j.1526-4637.2006.00212.x

Knecht, S., Deppe, M., Backer, M., Ringelstein, E. B., & Henningsen, H. (1997). Regional cerebral blood flow increases during preparation for and processing of sensory stimuli. *Experimental Brain Research, 116,* 309–314. doi:10.1007/PL00005758

Kontos, H. A. (1989). Validity of cerebral arterial blood flow calculations from velocity measurements. *Stroke, 20,* 1–3. doi:10.1161/01.STR.20.1.1

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology, 46,* 1121–1123. doi:10.1001/archneur.1989.00520460115022

Lázaro, C., Bosch, F., Torrubia, R., & Baños, J. E. (1994). The development of a Spanish questionnaire for assessing pain: Preliminary data concerning reliability and validity. *European Journal of Psychological Assessment, 10,* 145–151.

Logothetis, N. K., Pauls, J., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412,* 150–157. doi:10.1038/35084005

Melzack, R. (1975). The McGill Pain Questionnaire: Mayor properties and scoring method. *Pain, 1,* 277–299. doi:10.1016/0304-3959(75)90044-5

Menon, V., Rivera, S. M., White, C. D., Glover, G. H., & Reiss, A. L. (2000). Dissociating prefrontal and parietal cortex activation during arithmetic processing. *NeuroImage, 12,* 357–365. doi:10.1006/nimg.2000.0613

Munguía-Izquierdo, D., Legaz-Arrese, A., Moliner-Urdiales, D., & Reverter-Masía, J. (2008). Neuropsicología de los pacientes con síndrome de fibromialgia: Relación con dolor y ansiedad. *Psicothema, 20,* 427–431.

Park, D. C., Glass, J. M., Minear, M., & Crofford, L. J. (2001). Cognitive function in fibromyalgia patients. *Arthritis Rheumatism, 44,* 2125–2133. doi:10.1002/1529-0131(200109)44:9<2125::AID-ART365>3.0.CO;2-1

Paulson, O. B. (2002). Blood-brain barrier, brain metabolism, and cerebral blood flow. *European Neuropsychopharmacology, 12,* 495–501. doi:10.1016/S0924-977X(02)00098-6

Pericot-Nierga, I., Hernández-Ferràndiz, M., Lozano-Gallego, M., Vilalta-Franch, J., Cruz-Reina, M. M., & López-Pousa, S. (2009). Cognitive profile in fibromyalgia. Comparison with a mild cognitive impairment group. *Medicina Clínica (Barcelona), 133,* 91–94. doi:10.1016/j.medcli.2008.10.051

Rey, A. (1964). *L'examen Clinique en Psychologie* [*The clinical examination in psychology*]. *Paris, France: Presses Universitaires de France.*

Reyes del Paso, G. A., Garrido, S., Pulgar, A., & Duschek, S. (2011). Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia syndrome. *Journal of Psychosomatic Research, 70,* 125–134. doi:10.1016/j.jpsychores.2010.09.012

Reyes del Paso, G. A., Garrido, S., Pulgar, A., Martín-Vázquez, M., & Duschek, S. (2010). Aberrances in autonomic cardiovascular regulation in fibromyalgia syndrome and their relevance for clinical pain reports. *Psychosomatic Medicine, 72,* 462–470. doi:10.1097/PSY.0b013e3181da91f1

Reyes del Paso, G. A., Pulgar, Á., Duschek, S., & Garrido, S. (2012). Cognitive impairment in fibromyalgia syndrome: The impact of cardiovascular regulation, pain, emotional disorder sand medication. *European Journal of Pain, 16,* 421–429. doi:10.1002/j.1532-2149.2011.00032.x

Sanz, J., Navarro, M. E., & Vázquez, C. (2003). Adaptación española del Inventario para la Depresión de Beck-II (BDI-II): I. Propiedades psicométricas en estudiantes universitarios. *Análisis y Modificación de Conducta, 29,* 239–288.

Schuepbach, D., Boeker, H., Duschek, S., & Hell, D. (2007). Rapid cerebral hemodynamic modulation during mental planning and movement execution: Evidence of time-locked relationship with complex behavior. *Clinical Neurophysiology, 118,* 2254–2262. doi:10.1016/j.clinph.2007.07.013

Sheth, S. A., Nemoto, M., Guiou, M. W., Walker, M. A., & Toga, A. W. (2005). Spatiotemporal evolution of functional hemodynamic changes and their relationship to neuronal activity. *Journal of Cerebral Blood Flow and Metabolism, 25,* 830–841. doi:10.1038/sj.jcbfm.9600091

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1986). *Cuestionario de Ansiedad Estado-Rasgo (STAI): Manual* (2nd ed.). Madrid, Spain: TEA Ediciones.

Stroobant, N., & Vingerhoets, G. (2000). Transcranial Doppler ultrasonography monitoring of cerebral hemodynamics during performance of cognitive tasks: A review. *Neuropsychology Review, 10,* 213–231. doi:10.1023/A:1026412811036

Szirmai, I., Amrein, I., Pálvögyi, L., Debreczeni, R., & Kamondi, A. (2005). Correlation between blood flow velocity in the middle cerebral artery and EEG during cognitive effort. *Cognitive Brain Research, 24,* 33–40. doi:10.1016/j.cogbrainres.2004.12.011

Veldhuijzen, D. S., Sondaal, S. F. V., & Oosterman, J. M. (2012). Intact cognitive inhibition in patients with fibromyalgia but evidence of declined processing speed. *The Journal of Pain, 13,* 507–515. doi:10.1016/j.jpain.2012.02.011

Verdejo-García, A., López-Torrecillas, F., Calandre, E. P., Delgado-Rodríguez, A., & Bechara, A. (2009). Executive function and decision-making in women with fibromyalgia. *Archives of Clinical Neuropsychology, 24,* 113–122. doi:10.1093/arclin/acp014

Wolfe, F., Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., . . . Sheon, R. P. (1990). The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheumatism, 33,* 160–172. doi:10.1002/art.1780330203

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Correction to Sacchetti et al. (2014)

In the article "Ipsilesional Neglect: Behavioral and Anatomical Correlates" by Daniela L. Sacchetti, Kelly M. Goedert, Anne L. Foundas, and A. M. Barrett (*Neuropsychology*, Advance online publication. September 1, 2014. http://dx.doi.org/10.1037/neu0000122), the funding source information was missing from the author note. The research in this article was funded by the National Institutes of Health (K02NS047099, K24HD062647, R01 NS055808, Barrett), National Institute on Disability and Rehabilitation Research (H133G120203, Barrett), and the Kessler Foundation. This does not imply endorsement of the manuscript contents by the federal government.

Likewise, A. M. Barrett's institutional affiliation was incorrect. It should read: Kessler Foundation and Rutgers-New Jersey Medical School.

All versions of this article have been corrected.

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ESTUDIO 3. REACTION TIME, CEREBRAL BLOOD FLOW, AND HEART RATE RESPONSES IN FIBROMYALGIA: EVIDENCE OF ALTERATIONS IN ATTENTIONAL CONTROL.

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Reaction time, cerebral blood flow, and heart rate responses in fibromyalgia: Evidence of alterations in attentional control

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The study investigated cerebral blood flow (CBF) and heart rate (HR) responses during a cued reaction time (RT) task in patients with fibromyalgia syndrome (FMS). CBF velocities in the middle (MCA) and anterior (ACA) cerebral arteries of both hemispheres were recorded in 46 patients and 32 healthy control participants using functional transcranial Doppler sonography (fTCD). Patients exhibited markedly longer RT than healthy participants. Group differences in CBF responses were mainly observed for both ACAs, with greater right hemispherical increases but lower left hemispherical increases in FMS patients than in healthy participants. HR deceleration around the imperative stimulus was more pronounced in healthy participants. RT was inversely related to increases in CBF in both right arteries and in the left ACA in the FMS group, but was positively associated with CBF responses in all four arteries in healthy participants. The magnitude of task-induced HR deceleration correlated negatively with RT in both groups. Patients' clinical pain severity was positively associated with RT and CBF responses; trait anxiety and insomnia were secondary negative predictors of CBF responses. The study provided evidence of a deficit in the alertness component of attention in FMS at behavioral, CBF, and autonomic levels. These results may be interpreted in terms of the neural efficiency hypothesis of intelligence (i.e., less efficient brain activation during cognition in FMS) and the interfering effect of clinical factors on cognition. Clinical factors such as pain, anxiety, and sleep disturbances can affect cognition in FMS by interfering with CBF adjustment to cognitive demands.

Keywords: Fibromyalgia syndrome; Reaction time; Cerebral blood flow; Functional transcranial Doppler sonography.

Fibromyalgia syndrome (FMS) is a noninflammatory chronic disorder characterized by persistent and widespread musculoskeletal pain accompanied by symptoms such as morning stiffness, depression, fatigue, and sleep disturbance. The prevalence of FMS is projected at 2–4% in the general population; sufferers are predominantly females (Wolfe, Ross, Anderson, Russell, & Hebert, 1995). While its precise etiology remains unknown, FMS symptoms substantially reduce quality of life and can lead to extensive use of health care systems (Clauw, 2009; Penrod et al., 2004).

Subjective cognitive complaints are also frequently reported by FMS patients, including memory problems, forgetfulness, concentration difficulties, and loss of vocabulary (Glass, 2008; Glass, Park, Minear, & Crofford, 2005). Objective neuropsychological testing has confirmed at least mild cognitive deficits in FMS patients, characterized by poorer working, episodic, semantic, and implicit memory performance than in healthy individuals, in addition to selective attention and executive function impairment (Berryman et al., 2013; Dick, Verrier, Harper,

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& Rashiq, 2008; Duschek, Werner, Winkelmann, & Wankner, 2013; Glass, 2008; Leavitt & Katz, 2006; Munguía-Izquierdo, Legaz-Arrese, Moliner-Urdiales, & Reverter-Masía, 2008; Pericot-Nierga et al., 2009; Reyes del Paso, Pulgar, Duschek, & Garrido, 2012; Verdejo-García, López-Torrecillas, Calandre, Delgado-Rodríguez, & Bechara, 2009). However, objectively assessed deficits are typically smaller in magnitude than might be expected on the basis of subjective reports; furthermore, several studies reported no performance differences between FMS patients and healthy individuals (e.g., Glass et al., 2011; Leavitt & Katz, 2008; Walitt, Roebuck-Spencer, Bleiberg, Foster, & Weinstein, 2008).

In explaining the observations of impaired cognition in FMS, most studies suggest, as a central component, the interfering-intrusive effect of pain, where it is usual that cognitive deficits are positively associated with the severity of clinical pain (Apkarian, Bushnell, Treede, & Zubieta, 2005; Duschek, Werner, et al., 2013; Glass, 2008; Glass et al., 2005; Grace, Nielson, Hopkins, & Berg, 1999; Karp et al., 2006; Munguía-Izquierdo et al., 2008; Park, Glass, Minear, & Crofford, 2001; Reyes del Paso et al., 2012; Verdejo-García et al., 2009). Pain is an attention-demanding condition that activates brain areas also associated with cognitive processing (e.g., cingulate, insula and prefrontal cortex, see Apkarian et al., 2005; Duschek et al., 2012; Klein et al., 2007; Kuchinad et al., 2007), thereby taking processing resources away from cognition (Baliki et al., 2006; Dick et al., 2008; Glass, 2008). Other possible mediating factors, such as depression, anxiety, and fatigue, have received less support (i.e., Glass, 2008; Munguía-Izquierdo et al., 2008; Park et al., 2001; Reyes del Paso et al., 2012; Verdejo-García et al., 2009).

At the physiological level, one factor that has been previously related to cognitive performance is the ability to increase cerebral blood flow (CBF) during cognitive demands (Duschek, Heiss, Schmidt, Werner, & Schuepbach, 2010; Duschek, Schuepbach, & Schandry, 2008). Low magnitudes of task-induced CBF responses are associated with weak performance (Duschek & Schandry, 2004; Schuepbach, Boeker, Duschek, & Hell, 2007). Owing to the functional coupling that exists between neuronal activity and CBF, increases in local brain activity activate subsequent increases in regional CBF (Iadecola, 2004). Currently, the relationship between cognitive processing and regional CBF is most frequently studied using neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These imaging methods provide high spatial resolution, but due to their relatively low temporal resolutions their suitability for the study of the dynamics of CBF response in cognitive task paradigms is limited (Duschek & Schandry, 2003; Stroobant & Vingerhoets, 2000).

Functional transcranial Doppler sonography (fTCD) allows for the continuous noninvasive registration of CBF changes in the basal cerebral arteries. A large number of studies support fTCD as an excellent tool for the quantification of the rapid changes in CBF flow that accompany cognitive activity (for an overview see Duschek et al., 2010; Duschek & Schandry, 2003; Duschek, Werner, Kapan, & Reyes del Paso, 2008; Stroobant & Vingerhoets, 2000). The principal advantage conferred by fTCD is an excellent temporal resolution, higher than that of the neuroimaging methods fMRI and PET. Typically, the temporal resolution of fTCD is limited to the duration of a heart cycle. However, in event-related designs, such as that applied in the present study, response times can be measured to an accuracy of approximately 100 ms (Duschek & Schandry, 2003).

In a recent study we assessed CBF responses in the anterior and medial cerebral arteries (ACA and MCA) during a mental arithmetic task (addition of one-digit numbers) in FMS patients using fTCD (Montoro, Duschek, Múñoz Ladrón de Guevara, Fernández-Serrano, & Reyes del Paso, 2015). The patients' processing speed was slower than that of healthy controls and was associated with irregularities in task-induced CBF modulation, specifically the absence of an early CBF increase in the ACA, which was observed in healthy individuals during stimuli anticipation and the initial task execution phase. Patients furthermore showed aberrant lateralization of the CBF response, evidenced by pronounced activation of the right hemisphere, which is purportedly of little relevance in arithmetical processing (Duschek, Werner, et al., 2008). Finally, patients' responses were characterized by an exaggerated decrement in CBF below baseline during the recuperation period following task completion. Severity of clinical pain was correlated with CBF responses and cognitive performance (Montoro et al., 2015). Earlier studies addressing cognitive processing speed in FMS are equivocal. While some studies suggest mental slowness (e.g., Cherry et al., 2012; Reyes del Paso et al., 2012; Veldhuijzen, Sondaal, & Oosterman, 2012), negative findings have also been reported (e.g., Glass et al., 2011; Leavitt & Katz, 2008; Walitt et al., 2008). Task complexity may be a relevant parameter here: Speed differences have been observed in relatively simple tests (such as reading words,

naming colors, or adding two 1-digit numbers; Leavitt & Katz, 2008; Montoro et al., 2015; Reyes del Paso et al., 2012), but not in more complex tasks (including n-back, paced auditory serial arithmetic and Trail-Making tests; Leavitt & Katz, 2008; Montoro et al., 2015).

In the present study, fTCD was applied in order to analyze CBF modulations in FMS during a cued reaction time (RT) task, which can be regarded as one of the simplest tests measuring cognitive processing speed. Tasks of this type aim at preparatory processes, in terms of engendering an increase of attentiveness during the anticipation of a significant event. This function of "phasic alertness" is linked to the arousal component of the attentional system, which is of huge importance in everyday life (Posner & Petersen, 1990). Previous studies consistently revealed correlations between performance on cued RT tasks and CBF modulations during their execution (Duschek et al., 2010; Duschek & Schandry, 2004; Duschek, Schuepbach, et al., 2008). At the cerebral level, the component of phasic alertness is represented by cortical as well as subcortical areas, including reticular structures, the anterior cingulate, and also the dorsolateral frontal and the inferior parietal lobes. Although right hemispherical dominance of the alertness system is commonly assumed, more recent fMRI studies also revealed activation of left hemispherical areas in cued RT tasks (e.g., Coull, Nobre, & Frith, 2001; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005).

Attentional processing is closely related to autonomic regulation, in particular of the cardiovascular system (Duschek et al., 2010, Duschek, Wörsching, & Reyes del Paso, 2013). Heart rate (HR) modulations have been interpreted as indicative of vigilance and attentional control in the occidental tradition of psychophysiology (e.g., Lacey & Lacey, 1970), as well as in the Russian tradition (Sokolov, 1963). In cued RT tasks, HR decelerates during the S1 and S2 period, and this deceleration has been interpreted as indicative of increased attentiveness and preparation for speeded action (Jennings & van der Molen, 2005; Lacey & Lacey, 1970; Porges, 1992). Some authors have also postulated a right hemispherical dominance for cardiovascular regulation (e.g., Lane & Jennings, 1994). According to this perspective, lesions of the right hemisphere disrupt both alertness and HR responses to warning signals (e.g., Yokoyama, Jennings, Aekles, Hood & Boller, 1987).

In the current study, CBF and HR responses during a cued RT task were quantified in FMS patients and healthy individuals, thereby assessing possible associations between task performance and the extent of modulations in CBF and HR. We predicted slower RT in patients, which in turn was expected to be associated with smaller increases in task-induced CBF responses. Given the importance of the right frontal lobe for the control of alertness, we expected that group differences in CBF, as well as its association with performance, would arise particularly in the right ACA, which supplies large portions of the frontal cortex. In line with the findings of Montoro et al. (2015), more pronounced decrements in CBF during the recovery period were furthermore hypothesized in FMS patients. Finally, smaller HR deceleration around the imperative stimulus in FMS was predicted in patients versus healthy subjects.

Furthermore, at an exploratory level, the possible influence of clinical factors on RT and CBF was analyzed. Among these factors, comorbid emotional disorders, medication use, sleep disorders, and levels of clinical pain, anxiety, depression, and fatigue were considered. Based on our previous study (Montoro et al., 2015), we expected that clinical pain would be most closely associated to both cognitive performance and CBF responses.

METHOD

Participants

Due to the higher prevalence of FMS in females than in males, and to avoid possible gender-related confounding factors, only females were included in the study. Forty-six female patients, recruited via the Fibromyalgia Association of Jaén, participated in the study. All of the participants were examined by a rheumatologist and diagnosed as suffering from FMS. Exclusionary criteria comprised the presence of psychomotor–mental retardation or slowing, cardiac disease, metabolic abnormalities, neurological disorders, and severe somatic (e.g., cancer) or psychiatric (e.g., bipolar or psychotic) diseases. The healthy group included 32 women recruited from women's associations. The healthy participants did not differ significantly from the FMS patients in age, body mass index, or education level. In addition to any kind of pain disorder, the healthy group was subject to the same exclusionary criteria as were the patients. All participants were right-handed. Table 1 displays the demographic and clinical data of both groups and the group comparison statistics.

TABLE 1
Demographic and clinical data in the FMS and healthy groups

Demographic and clinical data	*FMS (n = 46)*	*Healthy (n = 32)*	*t or* χ^2	*p*	η^2
Age (years)	49.48 ± 8.23	47.03 ± 9.26	1.50	.224	.017
Body mass index	26.53 ± 3.61	25.35 ± 4.44	1.19	.200	.023
Years of education	12.04 ± 3.16	12.87 ± 3.50	1.67	.278	.015
Antidepressant use (%)	21 (54.3)	1 (3.1)	16.85	<.0001	.524
Anxiolytic use (%)	26 (56.5)	9 (28.1)	6.15	.020	.305
Analgesic use (%)	36 (78.2)	5 (15.6)	29.69	<.0001	.707
Opiate use (%)	16 (34.7)	0 (0)	14.00	<.0001	.446
Depression (%)	22 (48.8)	4 (12.9)	10.52	.001	.392
Anxiety disorders (%)	23 (51.1)	4 (12.9)	11.67	.001	.412
State anxiety	31.93 ± 10.27	21.46 ± 9.97	4.28	<.0001	.207
Trait anxiety	35.59 ± 8.91	20.28 ± 10.73	6.56	<.0001	.380
Depression	21.02 ± 12.21	7.20 ± 7.85	5.47	<.0001	.293
Fatigue	49.27 ± 12.08	20.71 ± 8.86	10.78	<.0001	.624
Insomnia	30.63 ± 6.74	18.16 ± 7.89	7.28	<.0001	.424
No. pain points	30.38 ± 16.17	4.56 ± 4.90	8.46	<.0001	.499
Sensorial pain	34.54 ± 19.21	10.80 ± 7.37	6.44	<.0001	.366
Emotional pain	6.04 ± 4.82	1.26 ± 1.65	5.21	<.0001	.274
Cognitive pain	3.36 ± 1.08	1.86 ± 0.97	6.09	<.0001	.340

Note. Means; standard deviations in parentheses. Results of the group comparison (t, χ^2, p, and η^2) are also displayed. FMS = fibromyalgia syndrome.

Cued reaction time task

A small white cross was displayed on the screen (black background) as a fixation point. The disappearance of this cross served as a warning stimulus (S1). Five seconds after this event a larger green cross (imperative stimulus, S2) appeared, to which the subjects had to respond to as quickly as possible via a keystroke performed with the right hand on a computer keyboard. The task consisted of 15 trials with intertrial intervals of 30 s. The task was preceded by three practice trials. It was programmed in the software ePrime (Psychology Software Tools, Inc., Sharpsburg, PA, USA). Reaction time was indexed by time elapsed between stimulus onset and the keystroke.

Recording and analysis of cerebral blood flow

CBF velocities were assessed by way of a digital Multi-Dop L2 (DWL Elektronische Systeme, Sipplingen, Germany). Recordings were conducted bilaterally in both MCA and ACA through the temporal bone windows using two 2-MHz transducer probes. Following vessel identification, the probes were fixed to the head using a head harness. The MCA were insonated at a depth of 48–55 mm and the ACA at a depth of 60–70 mm. The spectral envelope curves of the Doppler signal were recorded at a rate of 100 samples per second. The mean flow velocity index was applied as a measure of CBF velocity as this index is the least vulnerable to artifacts and has the highest correlation with blood volume flowing through an artery per unit of time (Duschek & Schandry, 2003).

In an initial data reduction step, the 100-Hz mean flow velocity recording was resampled to 4 Hz. Mean flow velocity during the 5 s prior to S1 served as the baseline; the 25 s after S1 were defined as the task period. Time-locked to S1, responses were expressed as relative (percentage) changes in flow velocity during task (dFV) with respect to baseline (FVbas) according to the formula $dFV = [FV(t) - FVbas] \times 100/FVbas$, where $FV(t)$ represents flow velocity over time.

HR was derived from intersystolic (peak amplitude values) intervals of the CBF velocity signal and was expressed as differential 0.5 s by 0.5 s HR values with respect to the mean HR during the 5 s prior to the S1.

Procedure

The study was conducted across two sessions, which took place on different days. In the first session a clinical psychologist recorded patients' clinical history and sociodemographic data and evaluated whether they satisfied the inclusion criteria. To assess possible mental disorders, the Structured Clinical Interview for Axis I Disorders of the Diagnostic and Statistical Manual for Mental Disorders (First, Spitzer, Gibbon, & Williams, 1999) was employed. Clinical pain was evaluated through the McGill Pain Questionnaire

(Melzack, 1975; Lázaro, Bosch, Torrubia, & Baños, 1994), from which four parameters were obtained: (a) sensorial pain, (b) emotional pain, (c) cognitive–evaluative pain, and (d) number of "pain points" marked on a picture of the human body. Depression was evaluated using the Beck Depression Inventory (Sanz, Navarro, & Vázquez, 2003), and anxiety was assessed via the State Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1986). The Spanish adaptation of the Fatigue Severity Scale (Bulbena, Berrios, & Fernández de Larrinoa, 2000; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) was employed in order to estimate levels of fatigue. Finally, sleep was evaluated via the Oviedo Quality of Sleep Questionnaire (Bobes et al., 2000), from which the insomnia index was derived. To control for possible simulation of cognitive impairment, participants completed the 15-item Rey Memory Test. A score below 6 in this test was taken as indicative of simulation (Arnett, Hammeke, & Schwartz, 1995). None of the participants fulfilled this criterion.

In the second session, the actual experiment was carried out. As signals from the MCA and ACA cannot be recorded simultaneously, the entire procedure was conducted twice, once for each pair of arteries. The sequence of recordings (MCA vs. ACA) was counterbalanced across participants. The distance between the participant and the monitor was fixed at 0.75 m. Participants were instructed to refrain from smoking, caffeine, alcohol, and vigorous exercise for 2 hours prior to the experiment and to wear their glasses/contact lenses if necessary. They were also asked not to consume analgesics or other drugs that affect the cardiovascular system for at least 24 hours prior to the start of the study. All participants gave their informed consent. The study protocol was approved by the Bioethics Committee of the University of Jaén.

Individual differences in temporal bone density affect the feasibility of fTCD recordings (Duschek & Schandry, 2003). Furthermore, signals are more difficult to obtain from the ACA than the MCA (which is longer and has a larger diameter). Therefore, the amount of available data differed between participants as follows: left MCA, 42 patients, 32 healthy individuals; right MCA, 41 patients, 32 healthy individuals; left ACA, 33 patients, 26 healthy individuals; right ACA, 35 patients, 25 healthy individuals. Complete data for the four arteries were available from 30 patients and 22 healthy subjects.

Statistical analysis

Based on visual inspection of the response patterns, three response components were identified peaking approximately in the following time frames subsequent to S1: Component 1, s 4 to s 6; Component 2, s 10 to s 11; Component 3, s 19 to s 20. Peak amplitudes for the three components were computed.

Group differences were tested for significance using Student's t tests for independent samples. The same procedure was applied to evaluate differences in the FMS group related to the presence of comorbid emotional disorders (depression/anxiety) and medication use (antidepressants, anxiolytics, analgesics, and opiates). Analysis of CBF responses was achieved through 2 (× 3) repeated measures analyses of variance (ANOVAs) with the between-subjects factor of group (FMS vs. healthy participants) and the repeated measures factor of response pattern (peak amplitudes for the three components). Additionally, possible RT changes across the 15 trials were analyzed using a 2 (× 15) repeated measures ANOVA to check for possible learning processes or occurrence of fatigue during the task. The F values of the multivariate test statistic Wilks's lambda are reported. Interactions between group and response pattern were analyzed by means of post hoc group comparisons (Student's t tests for independent samples). Analysis of lateralization of the CBF components was based on Student's t tests for dependent samples. HR was evaluated by computing peak HR deceleration in the time frame around S2 (±1 s). Relationships between variables were initially quantified using Pearson correlations. Subsequently, any significant associations revealed by the correlation analysis were subjected to stepwise multiple regression analyses, with RT and CBF responses as dependent variables (in separate analysis) and clinical factors as predictors. The maximal number of predictors entered in the regression analysis was three in the FMS group and two in the healthy group. From these analyses standardized β coefficients and adjusted r^2 values were obtained (when only one significant predictor was entered into the regression model, standardized β values equated to the r coefficient). Associations involving clinical parameters were computed separately for each group, in order to avoid distortion of the findings due to the expected large group differences.

RESULTS

Attentional performance

FMS patients had significantly slower RT than did healthy participants. This was the case both for the trials during which the MCA [859 ± 563 vs. 563 ± 335 ms, $t(72) = 3.18$, $p = .002$, $\eta^2 = .159$] and those in which the ACA [881 ± 659 vs. 530 ± 277 ms, $t(58) = 2.77$, $p = .008$, $\eta^2 = .121$] were insonated. Analysis of possible RT changes across the 15 trials did not reveal a main effect of the repeated measure factor (all ps > .314, all η^2s < .1) nor an interaction between the repeated measures factor and study group (all ps > .448, all η^2s < .1).

Task-induced blood flow responses

The CBF response patterns for the four arteries are displayed in Figure 1. As shown by the figures, the magnitude of the second response component greatly exceeded those of the first and third components. In most cases blood flow velocity fell below baseline levels during the recovery period towards the end of the task period.

For the left MCA the response pattern, $F(2, 71) = 62.21$, $p < .0001$, $\eta^2 = .647$, differed as a function of group [interaction effect: $F(2, 71) = 5.58$, $p = .005$, $\eta^2 = .143$]. No group differences were obtained for the two first components, but blood flow velocity was significantly lower during the recovery component in patients (see Table 2).

For the right MCA the response pattern, $F(2, 70) = 74.89$, $p < .0001$, $\eta^2 = .681$, also differed between groups [interaction effect: $F(2, 70) = 4.50$, $p = .014$, $\eta^2 = .114$]. As in the left MCA, no group differences arose for the first two components, but patients exhibited lower blood flow velocity than did healthy subjects during the recovery component (Table 2).

The response pattern for the left ACA, $F(2, 56) = 28.58$, $p < .0001$, $\eta^2 = .510$, was similar in both patients and healthy subjects [interaction effect: $F(2, 56) = 1.18$, $p = .315$, $\eta^2 = .041$], but a main effect of group was found, $F(1, 57) = 17.81$,

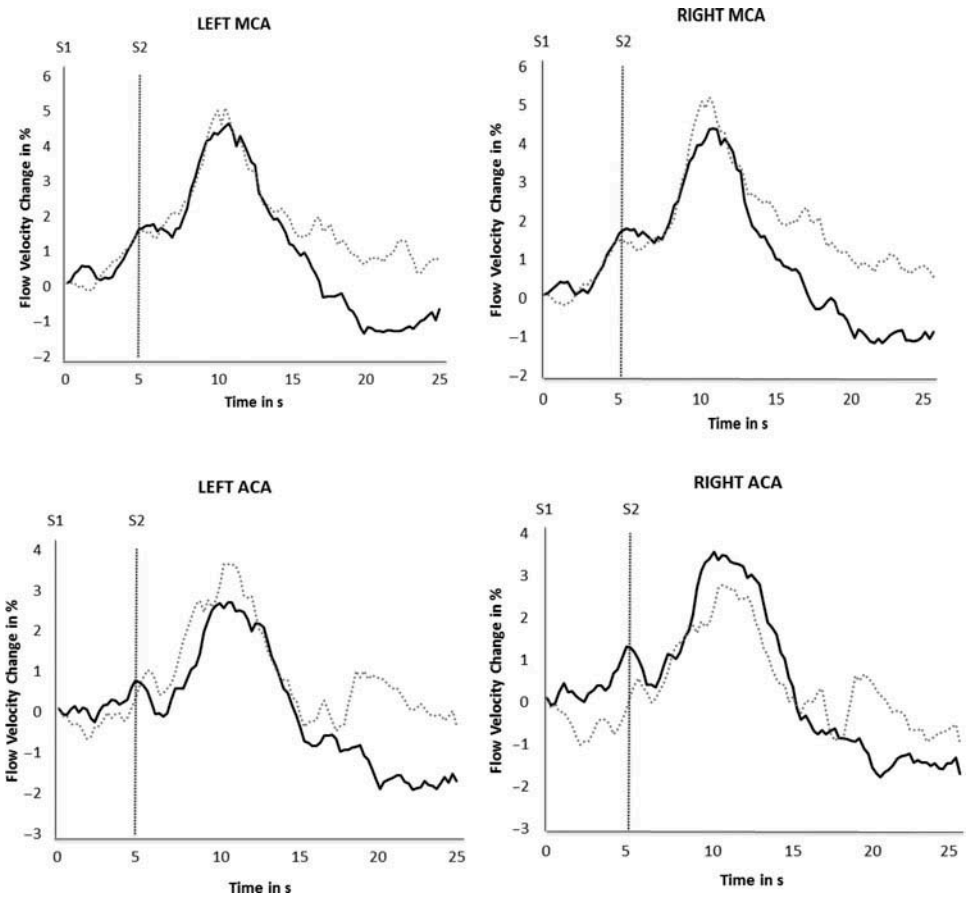

Figure 1. Blood flow velocity response for the left and right middle (MCA) and anterior (ACA) cerebral arteries. Continuous line: fibromyalgia syndrome (FMS) patients; dashed line: healthy individuals.

TABLE 2
Peak amplitudes of the three blood flow velocity components as a function of artery and group

Artery	*FMS*	*Healthy*	*t*	*p*	η^2
ACA left (1)	1.07 ± 2.69	3.21 ± 2.71	–2.99	.004	.138
ACA left (2)	2.39 ± 2.69	4.14 ± 2.69	–2.51	.015	.103
ACA left (3)	–1.74 ± 3.38	1.40 ± 3.38	–3.79	<.0001	.214
ACA right (1)	2.28 ± 2.80	0.47 ± 2.57	2.46	.017	.101
ACA right (2)	4.56 ± 3.28	2.47 ± 2.96	2.47	.017	.100
ACA right (3)	–0.90 ± 3.56	1.37 ± 2.92	–2.67	.010	.104
MCA left (1)	1.98 ± 2.98	1.52 ± 2.00	0.77	.442	.008
MCA left (2)	4.86 ± 4.27	4.95 ± 3.33	–0.99	.921	.000
MCA left (3)	–1.13 ± 3.23	0.76 ± 2.78	–2.65	.010	.089
MCA right (1)	2.05 ± 3.28	1.47 ± 2.51	0.84	.400	.009
MCA right (2)	4.73 ± 4.09	5.39 ± 3.22	–0.77	.442	.008
MCA right (3)	–0.77 ± 2.46	0.99 ± 2.46	–2.78	.007	.094

Note. Means; standard deviations in parentheses. FMS = fibromyalgia syndrome; ACA = anterior cerebral artery; MCA = middle cerebral artery; 1 = early increase; 2 = late increase; 3 = recovery. Groups: FMS patients versus healthy individuals. Results of the group comparison (*t, p,* and η^2) are also displayed. Degrees of freedom were 57 for ACA left, 58 for ACA right, 72 for MCA left, and 71 for MCA right.

$p < .0001$, $\eta^2 = .241$. For all three components, lower amplitudes were observed in the FMS group than in healthy subjects (Table 2).

The response in the right ACA, $F(2, 57) = 18.05$, $p < .0001$, $\eta^2 = .429$, differed as a function of group [interaction effect: $F(2, 57) = 9.17$, $p < .0001$, $\eta^2 = .276$]. While the FMS group showed greater blood flow increases than did healthy subjects in the first two components, lower values were observed in this group during recovery (Table 2).

In the FMS group, the second component of the ACA was lateralized to the right hemisphere, $t(32) = 2.94$, $p = .006$; $\eta^2 = .236$. In healthy subjects, both the first, $t(24) = 4.21$, $p < .0001$, $\eta^2 = .459$, and the second, $t(24) = 2.28$, $p = .036$, $\eta^2 = .206$, increases in components of the ACA were lateralized to the left hemisphere. No lateralization was observed for the MCA in any of the groups or components (all $ts < 1.2$, all $ps > .2$, all η^2s $> .026$).

Task-induced heart rate modulations

HR response patterns are displayed in Figure 2. HR deceleration around S2 was greater in the healthy group than in patients. Group differences were significant for the 0.5 s just before, $t(72) = 3.93$, $p = .05$, $\eta^2 = .035$, and after S2, $t(72) = 6.82$, $p = .01$, $\eta^2 = .087$.

Associations between RT, cerebral blood flow, and heart rate

Table 3 displays the correlations between RT and the amplitudes of the three CBF velocity components for the four arteries. In the FMS group, RT was negatively associated with amplitudes of the second and third components in both the right MCA and the right ACA, and in the second component of the left ACA. In the healthy group, RT correlated positively with the amplitude of the second component in all four arteries. Peak HR deceleration was positively associated with RT in the FMS group ($r = .398$, $p = .007$). A nonsignificant trend in the same direction was found in healthy participants ($r = .255$, $p = .173$).

Effects of clinical factors on RT and cerebral blood flow

No significant RT differences arose between FMS patients suffering or not suffering from comorbid depression or anxiety disorders or as a function of medication use (Table 4). A slight trend was observed toward slower RT in FMS patients taking anxiolytics, $t(44) = 1.54$, $p = .131$, $\eta^2 = .054$, and opiates, $t(44) = 1.42$, $p = .164$, $\eta^2 = .046$, versus patients not taking this medication. In the FMS group, state anxiety ($r = .312$, $p = .039$), trait anxiety ($r = .305$, $p = .044$), emotional pain ($r = .315$, $p = .037$), and the cognitive–evaluative dimension of pain ($r = .372$, $p = .013$) were associated with slower RT. Multiple regression analysis using trait anxiety and the emotional and cognitive–evaluative pain components as predictors in the FMS group (trait anxiety was not entered due to collinearity resulting from a high correlation with state anxiety) revealed that only the cognitive–evaluative dimension of pain (McGill Pain Questionnaire) was a significant predictor of RT [$\beta = .372$, $r^2 = .12$, $t(45) = 2.60$, $p = .013$]. No associations were observed in the healthy group.

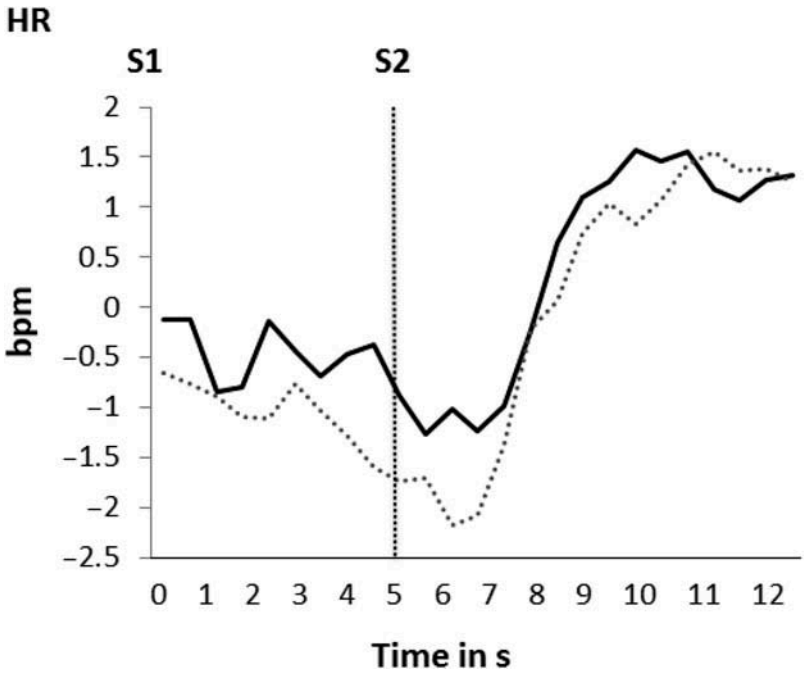

Figure 2. Changes in heart rate (HR) during the cued reaction time task. Continuous line: fibromyalgia syndrome (FMS) patients; dashed line: healthy individuals.

TABLE 3
Correlations between peak amplitudes of the three blood flow velocity components, reaction time, and the number of pain points

Artery		*FMS*	*FMS pain*	*Healthy*
ACA	Left (1)	–.132	.281	–.138
	Left (2)	–.344*	.340*	.449*
	Left (3)	–.257	.484*	–.283
	Right (1)	–.303	.205	.036
	Right (2)	–.386*	.301	.399*
	Right (3)	–.426*	.378*	–.203
MCA	Left (1)	–.294	.346*	–.127
	Left (2)	–.225	.342*	.462*
	Left (3)	–.538*	.245	–.210
	Right (1)	–.275	.405*	.024
	Right (2)	–.440*	.340*	.441*
	Right (3)	–.563*	.337*	–.144

Note. McGill Pain Questionnaire. Values for pain points are based only on the patients subsample. FMS = fibromyalgia syndrome; ACA = anterior cerebral artery; MCA = middle cerebral artery; 1 = early increase; 2 = late increase; 3 = recovery. Sample size for ACA left was 33 in FMS patients and 26 in healthy participants, for ACA right 35 in FMS patients and 25 in healthy participants, for MCA left 42 in FMS patients and 32 in healthy participants, and for MCA right 41 in FMS patients and 32 in healthy participants.

*$p < .05$.

TABLE 4
Mean reaction time as a function of the presence of comorbid depression or anxiety disorders and medication use in FMS patients

Clinical factors	*Present*	*Not present*
Depression	885 ± 429	829 ± 527
Anxiety	801 ± 416	918 ± 537
Antidepressants	885 ± 475	826 ± 486
Anxiolytics	948 ± 501	726 ± 416
Analgesics	873 ± 467	770 ± 550
Opiates	983 ± 485	777 ± 461

Note. Reaction time in ms. FMS = fibromyalgia syndrome.

No significant effects of comorbid depression or antidepressant use on CBF responses were found (all $ps > .34$, all $\eta^2s > .060$). The presence of anxiety disorders was associated with lower amplitudes of the second MCA components [3.62 ± 3.80 vs. 6.28 ± 3.51, $t(40) = 2.19$, $p = .035$, $\eta^2 = .093$; 3.19 ± 3.82 vs. 6.38 ± 3.50, $t(39) = 2.73$, $p = .010$, $\eta^2 = .097$; respectively, for the left and right components for patients suffering and not suffering from anxiety disorders] and trends toward lower CBF responses for the first right MCA, first left MCA, and first left ACA components [4.91 ± 2.45 vs. 6.77 ± 3.44, $t(39) = 1.98$, $p = .055$, $\eta^2 = .093$; 4.96 ± 2.52 vs. 6.54 ± 2.67, $t(40) = 1.87$, $p = .069$, $\eta^2 = .089$; 4.16 ± 1.96 vs. 5.45 ± 2.06, $t(31) = 1.76$, $p = .088$, $\eta^2 = .097$; respectively, for the right first MCA, left first MCA, and left first ACA components for patients suffering and not suffering from anxiety disorders]. The use of anxiolytics was associated with a trend toward stronger CBF responses in the left second MCA component (6.84 ± 3.76 vs.

4.47 ± 3.90, respectively, for patients taking and not taking anxiolytics), $t(40) = 1.84$, $p = .073$, $\eta^2 = .086$. Patients using analgesics exhibited stronger CBF responses in the left second MCA component than did patients not using this medication (6.44 ± 3.79 vs. 3.85 ± 3.52, respectively, for patients taking and not taking analgesics), $t(40) = 2.41$, $p = .021$, $\eta^2 = .139$, and a trend in the same direction for the right second MCA component (6.12 ± 3.77 vs. 3.42 ± 4.78, respectively, for patients taking and not taking analgesics), $t(39) = 1.78$, $p = .083$, $\eta^2 = .077$.

In FMS patients, the number of pain points correlated positively with CBF amplitude for the three right MCA components, the left second and third ACA components, left first and second MCA components, and right third ACA component (Table 3). In patients, trait anxiety was negatively associated with peak amplitude of the right first ACA component (Table 5). This association was also present in the healthy group regarding the left first and third ACA and right second ACA components. Fatigue was unrelated to CBF in FMS but correlated negatively with the amplitude of the three left ACA and right first ACA components in the healthy group. Finally, insomnia was negatively associated in the FMS group with amplitudes of the right first and second ACA components (Table 5). No associations between insomnia and CBF were found in healthy participants.

In stepwise multiple regression analyses for the FMS sample (with the number of pain points, trait anxiety, and insomnia as predictors) the number of pain points (McGill Pain Questionnaire) predicted the three right MCA components, the first and second left MCA components, the second and third left ACA components, and the third right ACA component (same values of β, i.e., r, and p as in the correlation analysis). In a second regression model, trait anxiety significantly predicted the first right MCA [$\beta = .435$, $t(40) = 3.13$, $p = .003$, for number of pain points; $\beta = -.356$, $t(40) = -2.56$, $p = .015$, for trait anxiety; $r^2 = .252$] and first left MCA components [$\beta = .386$, $t(41) = 2.60$, $p = .012$, for number of pain points; $\beta = -.347$, $t(41) = -2.34$, $p = .025$, for trait anxiety; $r^2 = .195$]. For the third right ACA component, insomnia was a significant predictor in a second regression model [$\beta = .499$, $t(34) = 3.09$, $p = .004$, for number of pain points; $\beta = -.402$, $t(34) = -2.49$, $p = .019$, for insomnia; $r^2 = .242$]. Insomnia was the main predictor of the first and second right ACA components (same values of β, i.e., r, and p as in the correlation analysis); number of pain points was also a significant secondary predictor for the first right [$\beta = -.487$, $t(34) = -2.95$, $p = .006$, for insomnia; $\beta = .358$, $t = 2.13$, $p = .041$ for number of pain points; $r^2 = .208$] and second right ACA components [$\beta = -.514$, $t(34) = -3.26$, $p = .003$, for insomnia; $\beta = .438$, $t = 2.78$, $p = .009$, for number of pain points; $r^2 = .275$]. In the healthy group, fatigue was the only predictor of the three left ACA components, and trait anxiety was the only predictor of the first and second right ACA components (same values of β, i.e., r, and p as in the correlation analysis).

DISCUSSION

On a behavioral level, markedly slower cued RTs were observed in FMS patients than in healthy participants. Pain severity (i.e., the cognitive–evaluative pain component of the McGill Pain Questionnaire) was the strongest (negative) predictor of reaction time. This is in contrast to previous studies, which failed to observe differences in RT between FMS patients and healthy controls. In a

TABLE 5
Correlations between peak amplitude of the three blood flow velocity components of the anterior cerebral artery and levels of anxiety (trait), fatigue, and insomnia in the two groups

	Anxiety		*Fatigue*		*Insomnia*	
Artery	*FMS*	*Healthy*	*FMS*	*Healthy*	*FMS*	*Healthy*
Left (1)	–.197	–.559*	–.088	–.565*	–186	–.244
Left (2)	–.196	–.360	–.048	–.492*	–.130	–.255
Left (3)	–.081	–.399*	.059	–.530*	.021	–.084
Right (1)	–.405*	–.555*	–.113	–.541*	–.449*	–.243
Right (2)	–.261	–.386*	–.032	–.319	–.382*	–.002
Right (3)	–.227	–.205	–.001	–.347	–.281	–.173

Note. FMS = fibromyalgia syndrome; 1 = early increase; 2 = late increase; 3 = recovery. Groups: FMS patients versus healthy individuals. Sample size for the left artery was 33 in FMS patients and 26 in healthy participants and for the right artery 35 in FMS patients and 25 in healthy participants.

*$p < .050$.

relatively small sample of 18 patients and 14 healthy participants, Glass et al. (2011) did not report an RT difference on a go/no-go task. Similarly, no difference in simple RTs was observed in a study by Walitt et al. (2008). Differences in task methodology in these studies may account for the divergent findings. First, the 15 trials used for the present task was a smaller amount than is typically employed in RT tasks. Furthermore, at 30 s the interstimulus intervals were relatively long, to allow CBF to return to baseline level between responses. These have rendered the task more tedious than typical RT tasks, thereby increasing the difficulty of maintaining attention for its duration. RT did not significantly change across trials in either study group, indicating that neither a learning effect (i.e., faster RT) nor fatigue (i.e., slower RT) occurred. This may be explained by the small number of trials and the long interstimulus intervals. Both factors may also account for the relatively long RTs, for example as compared to the Glass et al. (2011) and Walitt et al. (2008) studies. It is also important to note that cued RT tasks are concerned with clearly distinct cognitive processes to those involved in these studies. While the go/no-go task of Glass et al. (2011) aimed to quantify executive functioning—that is, response inhibition—performance on simple (noncued) RT tasks such as that used by Walitt et al. (2008) depends on tonic attentional arousal and motor speed. In contrast, the presently used cued RT task was concerned primarily with phasic alertness—that is, alterations in attentiveness during anticipation of a significant event (Posner & Petersen, 1990).

As stated above, task complexity may be another mediating factor of group differences in cognitive performance. For example, Leavitt and Katz (2008) reported no deficits in 7 of their 10 speed measures (i.e., in their more complex measures, such as paced auditory serial arithmetic, digits symbol substitution, and Trail-Making tests, etc.), but observed noticeably slower cognitive processing speed in the two simplest tasks (involving naming speed; reading words and naming colors). Similarly, Montoro et al. (2015) reported no group difference in the n-back test (1- and 2-back versions), but FMS patients were characterized by longer latencies when adding pairs of one-digit numbers. These results suggest that processing speed deficits in FMS may be selective; paradoxically, speed deficiencies are more readily observed in tasks aiming to evaluate simple, low-level cognitive processes (Leavitt & Katz, 2008). These findings are in accordance with those obtained in the present study, with markedly slower RTs in FMS than in healthy participants.

The observed group differences in reaction speed suggest lower attentional arousal and diminished ability to enhance alertness during the preparation of the response to an announced signal in patients than in healthy individuals. This finding is in accordance with previous reports of impaired processing speed and attentional function in FMS (Cherry et al., 2012; Leavitt & Katz, 2009; Miró et al., 2011; Montoro et al., 2015; Reyes del Paso et al., 2012; Veldhuijzen et al., 2012; however, cf. Glass et al., 2011; Leavitt & Katz, 2008; Walitt et al., 2008, for equivocal results).

A response pattern in CBF with two increase components was observed in all four cerebral arteries under study: a first increase starting about 2 s before S2, probably associated to anticipatory attention, and a late increase peaking 5 to 6 s after S2, which may predominantly reflect psychomotor processes. In contrast to our expectations, patients did not consistently exhibit smaller cognitively induced CBF modulations in their cerebral arteries than did healthy individuals. While they exhibited lower CBF during the three left ACA components and the recovery phase after the behavioral response in both MCA and ACA, even larger task-related flow increases were observed in the right ACA. CBF increases in the right MCA and ACA, as well as in the left ACA, correlated negatively with RT in patients. Just as with the right hemispherical lateralization of the ACA response in FMS patients, the closer association obtained for the right vessels is in accordance with the assumed right dominance of the neuronal network controlling attentional arousal (Posner & Petersen, 1990). However, and representing another unexpected result, ACA blood flow lateralization towards the left, as well as positive associations of RT with CBF during the later increase phase in each of the insonated vessels, was seen in healthy subjects. The left lateralization of the second component of the ACA response, which may be ascribed to psychomotor processing, may be explained by the fact that motor responses were carried out using the right hand. At this, it should, however, not be overlooked that left lateralization was restricted to the ACA, where motor areas are also supplied by the MCA.

The relationships between RT and CBF may be explained according to the framework of the neural efficiency hypothesis of intelligence (e.g., Neubauer & Fink, 2009). This hypothesis states that higher mental performance is related to lower (and thus more efficient) brain activation during cognitive processing. Several studies point towards inverse associations between brain activation during cognitive testing and performance

scores (i.e., higher achieving subjects exhibited lower brain metabolic rates, lower glucose consumption, and less energy expenditure and pupil dilatation, etc.) than lower achieving subjects (see Neubauer & Fink, 2009, for a review). According to the theory, efficient brain activity is furthermore characterized by a restriction of activation to specific task-relevant brain structures, while task-irrelevant areas are inhibited. In addition, a higher magnitude of global brain activity implies lower efficiency (Haier et al., 1988; Neubauer & Fink, 2009). Even though a number of individual and task-related factors moderate the relationship between neural activity and cognitive performance, this hypothesis as a whole has received abundant empirical support (e.g., Deary, Penke, & Johnson, 2010; Haier et al., 1988; Neubauer & Fink, 2009).

In the context of this theory, one may argue that in a simple test like a cued RT task, individuals with higher attentional capacity activate fewer cerebral resources than do those with lower capacity. In the present case, FMS patients, who exhibited slower processing speeds, may have activated larger brain areas during the task than those with more rapid reactions, which in turn was accompanied by stronger metabolic demands and higher CBF. This may explain the negative correlation between RT and flow velocity responses in the FMS patients. On the other hand, the higher achieving participants from the healthy group needed less effort in order to resolve the task and therefore exhibited less pronounced cerebral activation, resulting in a positive correlation between RT and CBF increase. The strong CBF responses observed in FMS patients using anxiolytics and analgesics is also congruent with this interpretation. It might be hypothesized that comparatively large neural resources need to be activated in order to compensate for the sedative effect of these drugs, which in turn may result in pronounced CBF responses. Furthermore, regression analysis in the FMS group revealed that the number of pain points marked on the McGill Pain Questionnaire were the most important (positive) predictor of CBF responses in all assessed arteries. The interfering effect of pain on cognition may be of relevance in this regard; this has been frequently invoked to explain the occurrence of cognitive impairment in FMS (cf. Duschek, Werner, et al., 2013; Reyes del Paso et al., 2012). To compensate for the interference of nociceptive processing on cognition, it is possible that greater neural resources are activated by patients experiencing more intense pain than by those with lower pain levels. This view is also consistent with fMRI studies, which indicate hyperactivation of task-irrelevant cerebral areas in FMS patients during cognitive task execution (e.g., Glass et al., 2011). These results have been interpreted as reflecting a compensatory cortical mechanism aiming to overcome the interfering influence of pain in order to maintain adequate cognitive performance.

Nonetheless, it must be acknowledged that the interpretations presented herein, to a certain degree, are speculative and occasionally contradictory with earlier findings. This is particularly applicable to the observations pertaining to positive associations between MCA blood flow modulations and cued RT performance in healthy groups (Duschek et al., 2010; Duschek & Schandry, 2004; Duschek, Schuepbach, et al., 2008). These studies, however, used young, healthy participants, composed almost exclusively of university students, such that their results cannot be directly compared to those of the present study. It should also be noted that the literature on the interaction between central nervous system activation and cognitive performance remains inconsistent. While several studies support the notion of a connection between stronger neural activation and superior performance (e.g., Schuepbach, et al., 2007;Unterrainer et al., 2004), other studies accord with the neural efficiency hypothesis of intelligence, which predicts an inverse relationship (for overview, cf. Deary et al., 2010; Neubauer & Fink, 2009). The direction of associations may vary according to numerous factors, such as the cognitive functions addressed, task difficulty, characteristics of the samples, and the neural structures under study and methods used to assess their activity (Deary et al., 2010). Furthermore, the contributions of irregularities in CBF regulation to cognitive impairment in FMS are complex and may depend on certain of these factors. Therefore, addressing this issue represents an important target for future studies, in which task characteristics could be systematically varied; the clinical characteristics of patient samples should also be carefully assessed.

Similarly to the present findings, Montoro et al. (2015) observed that FMS patients had a stronger right hemispherical and weaker left hemispherical ACA response than did healthy individuals during a mental arithmetic task. This may be indicative of greater dominance in the right anterior hemisphere in attention regulation and executive control in FMS relatively independent of the task applied. The response asymmetry may also reflect a more general tendency towards greater right hemispherical activation in FMS patients than in healthy persons. Various studies have demonstrated exaggerated negative affective and cognitive processing

of painful stimuli in FMS patients, which is also related to the right hemisphere (Cook et al., 2004; Kwan, Crawley, Mikulis, & Davis, 2000; Peyron, Laurent, & García-Larrea, 2000; Rainville, 2002). Moreover, a negatively biased affective style, which is well documented in FMS, is related to right frontal activity (Wheeler, Davidson, & Tomarken, 1993).

The left hemispherical lateralization of CBF velocities in healthy subjects is in accordance with some fMRI studies demonstrating an involvement of left hemispherical structures in the control of attentional arousal and orienting (e.g., Coull et al., 2001; Fan et al., 2005). Structures exhibiting predominantly right hemispherical activity during cued RT tasks include the right thalamus, the frontal, parietal, and superior temporal gyrus, and the superior colliculus, whereas left hemispherical dominance occurs in the left thalamus, left inferior parietal lobe, fusiform gyrus, inferior frontal gyrus, and superior parietal lobe (e.g., Fan et al., 2005). The dissociation we observed in ACA lateralization as a function of group may be indicative of differences in the structures activated during the cued RT task: right structures such as the right thalamus and prefrontal and superior colliculus in the FMS group versus left structures such as left thalamus, left parietal lobe, and left frontal gyrus in healthy individuals.

Confirming previous findings (Montoro et al., 2015), CBF in each of the four insonated vessels decreased more during recovery in FMS patients than in healthy persons. This supports the notion of exaggerated counterregulation following the actual CBF response. This overcompensation may reflect aberrances in homeostatic regulatory mechanisms responsible for the maintenance of constant CBF in FMS. Interestingly, the amplitude of this "rebound" component correlated negatively with RT in the FMS group, suggesting that the functioning of this regulatory mechanism is positively related to attentional performance. In this sense, greater blood flow dynamics may be associated with improved cognitive function.

Across the entire study group, the classical biphasic HR response was observed during the cued RT task (Jennings & van der Molen, 2005): HR decelerated during the S1–S2 interval and accelerated after S2. As predicted, HR decreased less in the patients than in the healthy group. Additionally, HR around S2 correlated positively with RT (i.e., greater HR deceleration was associated with better performance). This result is in line with traditional psychophysiological research, which takes HR as an index of attention and action preparedness (e.g., Jennings & van der Molen, 2005; Lacey & Lacey, 1970; Porges, 1992; Sokolov, 1963). Therefore, this finding shows that attentional deficits in FMS also become apparent at the level of autonomic cardiovascular control. The finding is also in line with observations of blunted autonomic responses to both psychological (Reyes del Paso, Garrido, Pulgar, Martín-Vázquez, & Duschek, 2010; Thieme et al., 2006) and physical (Raj, Brouillard, Simpson, Hopman, & Abdollah, 2000; Reyes del Paso, Garrido, Pulgar, & Duschek, 2011) stressors in FMS. HR deceleration during RT tasks results from parasympathetic activation (Porges, 1992), and diminished cardiac parasympathetic tone has been documented in FMS (Reyes del Paso et al., 2010, 2011). Although powerful mechanisms exist for the maintenance of CBF regardless of changes in systemic hemodynamics (blood pressure, cardiac output, HR, etc.; Sándor, 1999), acute changes in cardiovascular parameters to a certain degree affect CBF responses (Duschek et al., 2010; Duschek & Schandry, 2004; Duschek, Werner, et al., 2008). In light of this, the aforementioned deficits in autonomic cardiovascular regulation in FMS may also contribute to the alterations in CBF responses.

Only slight effects of medication on RT were observed. The trend toward slower RT in patients taking anxiolytics is congruent with the pharmacological action of these drugs. The slower RT associated with the use of analgesics (especially opiates) may be explained by their inhibitory–sedative effect. The presence of anxiety disorders was associated with lower CBF responses in the first and second components, suggestive of an interference effect of anxiety on attentional activation (cf. Munguía-Izquierdo et al., 2008). This assumption is partly supported by the association found between trait anxiety and the first CBF components. Insomnia was negatively associated with right hemispherical ACA blood flow responses in FMS patients. This may also indicate that sleep disturbances contribute to altered central nervous adjustment to attentional demands. While fatigue was negatively associated with CBF amplitudes in the healthy group, no association arose in FMS patients. This is in line with former studies suggesting that fatigue plays only a minor role in explaining cognitive deficits in FMS (Montoro et al., 2015; Reyes del Paso et al., 2012).

A relevant limitation of the study pertains to there being different numbers of participants in which data for the four arteries were available, which resulted in differential statistical power across the respective analyses. Another caveat

relates to the computation of HR from the fTCD signal, which is certainly not as precise as an electrocardiogram (ECG). However, the HR response has been averaged across 15 trials, limiting the possible effect of measuring error. In future studies it may be useful to assess CBF response together with hemodynamic and autonomic parameters, such as blood pressure or cardiac output. Another limitation is that the lower CBF velocity during the final recovery period in the FMS group may have persisted to some degree during the following baseline period, which may have affected the results. This suggests the need for using longer interstimulus intervals when employing fTCD in the study of cognitive function in FMS. Finally, the abovementioned characteristics of our RT task (i.e., the low number of trials and long interstimulus intervals) must be taken into account when comparing our data to those of previous studies of RT in FMS.

In summation, the present study provides evidence of deficits in the control of attentional arousal in FMS, as indexed by (a) slow response speed, (b) altered CBF modulation during the RT task, and (c) a blunted cardiac autonomic response. Clinical pain severity was most closely associated with performance and CBF modulation in FMS patients, in whom anxiety and insomnia may play secondary roles in the suboptimal adjustment of CBF to cognitive demands. These results suggest that clinical factors (such as pain, anxiety, and sleep disturbances) can affect cognition in FMS by interfering with the elicitation of CBF responses to cognitive demands.

REFERENCES

Apkarian, A. V., Bushnell, M. C., Treede, R. D., & Zubieta, J. K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain*, *9*, 463–484.

Arnett, P. A., Hammeke, T. A., & Schwartz, L. (1995). Quantitative and qualitative performance on Rey's 15-item test in neurological patients and dissimulators. *The Clinical Neuropsychologist*, *9*, 17–26.

Baliki, M. N., Chialvo, D. R., Geha, P. Y., Levy, R. M., Harden, R. N., Parrish, T. B., & Apkarian, A. V. (2006). Chronic pain and the emotional brain: Specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *The Journal of Neuroscience*, *26*, 12165–12173.

Berryman, C., Stanton, T. R., Bowering, K. J., Tabor, A., McFarlane, A., & Moseley, G. L. (2013). Evidence for working memory deficits in chronic pain: A systematic review and meta-analysis. *Pain*, *154*, 1181–1196.

Bobes, J., González, M. P., Sáiz, P. A., Bascarán, M. T., Iglesias, C., & Fernández, J. M. (2000). Propiedades psicométricas del cuestionario Oviedo de sueño [Psychometric properties of Oviedo sleep Questionnaire]. *Psicothema*, *12*, 107–112.

Bulbena, A., Berrios, G. E., & Fernández de Larrinoa, P. (2000). *Medición clínica en psiquiatría y psicología*. Barcelona: Masson.

Cherry, B. J., Zettel-Watson, L., Shimizu, R., Roberson, I., Rutledge, D. N., & Jones, C. J. (2012). Cognitive performance in women aged 50 years and older with and without fibromyalgia. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*. Advance online publication. doi:10.1093/geronb/gbs122

Clauw, D. J. (2009). Fibromyalgia: An overview. *American Journal of Medicine*, *122*, 3–13.

Cook, D. B., Lange, G., Ciccone, D. S., Liu, W. C., Steffener, J., & Natelson, B. H. (2004). Functional imaging of pain in patients with primary fibromyalgia. *The Journal of Rheumatology*, *31*, 364–378.

Coull, J. T., Nobre, A. C., & Frith, C. D. (2001). The noradrenergic alpha2 agonist clonidine modulates behavioural and neuroanatomical correlates of human attentional orienting and alerting. *Cerebral Cortex*, *11*, 73–84.

Deary, I. J., Penke, L., & Johnson, W. (2010). The neuroscience of human intelligence differences. *Nature Reviews Neuroscience*, *11*, 201–211.

Dick, B. D., Verrier, M. J., Harper, K. T., & Rashiq, S. (2008). Disruption of cognitive function in fibromyalgia syndrome. *Pain, 139*, 610–616.

Duschek, S., Heiss, H., Schmidt, F. H., Werner, N., & Schuepbach, D. (2010). Interactions between systemic hemodynamics and cerebral blood flow during attentional processing. *Psychophysiology*, *47*, 1159–1166.

Duschek, S., Mannhart, T., Winkelmann, A., Merzoug, K., Werner, N. S., Schuepbach, D., & Montoya, P. (2012). Cerebral blood flow dynamics during pain processing in patients with fibromyalgia syndrome. *Psychosomatic Medicine*, *74*, 802–809.

Duschek, S., & Schandry, R. (2003). Functional transcranial Doppler sonography as a tool in psychophysiological research. Psychophysiology, 40, 436–454.

Duschek, S., & Schandry, R. (2004). Cognitive performance and cerebral blood flow in essential hypotension. Psychophysiology, 41, 905–913.

Duschek, S., Schuepbach, D., & Schandry, R. (2008). Time-locked association between rapid cerebral blood flow modulation and attentional performance. *Clinical Neurophysiology*, *119*, 1292–1299.

Duschek, S., Werner, N., Kapan, N., & Reyes del Paso, G. A. (2008). Patterns of cerebral blood flow and systemic hemodynamics during arithmetic processing. *Journal of Psychophysiology*, *22*, 81–90.

Duschek, S., Werner, N. S., Winkelmann, A., & Wankner, S. (2013). Implicit memory function in fibromyalgia syndrome. *Behavioral Medicine*, *39*, 11–16.

Duschek, S., Wörsching, J., & Reyes del Paso, G. A. (2013). Interactions between autonomic cardiovascular regulation and cortical activity: A CNV study. *Psychophysiology*, *50*, 388–397.

Fan, J., McCandliss, B. D., Fossella, J., Flombaum, J. I., & Posner, M. I. (2005). The activation of attentional networks. *NeuroImage*, *26*, 471–479.

First, M., Spitzer, R., Gibbon, M., & Williams, J. (1999). *Entrevista Clínica Estructurada para los Trastornos del Eje I del DSM-IV (SCID-I)*

[Structured clinical interview for DSM-IV Axis I Disorders (SCID-I)]. Barcelona: Masson.

Glass, J. M. (2008). Fibromyalgia and cognition. *The Journal of Clinical Psychiatry*, *69*, 20–24.

Glass, J. M., Park, D. C., Minear, M., & Crofford, L. J. (2005). Memory beliefs and function in fibromyalgia patients. *Journal of Psychosomatic Research*, *58*, 263–269.

Glass, J. M., Williams, D. A., Fernández-Sánchez, M. L., Kairys, A., Barjola, P., Heitzeg, M. M., … Schmidt-Wilcke, T. (2011). Executive function in chronic pain patients and healthy controls: Different cortical activation during response inhibition in fibromyalgia. *Journal of Pain*, *12*, 1219–1229.

Grace, G. M., Nielson, W. R., Hopkins, M., & Berg, M. A. (1999). Concentration and memory deficits in patients with fibromyalgia syndrome. *Journal of Clinical and Experimental Neuropsychology*, *21*, 477–487.

Haier, R. J., Siegel, B. V., Nuechterlein, K. H., Hazlett, E., Wu, J. C., Paek, J., … Buchsbaum, M. S. (1988). Cortical glucose metabolic rate correlates of abstract reasoning and attention studied with positron emission tomography. *Intelligence*, *12*, 199–217.

Iadecola, C. (2004). Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nature Reviews Neuroscience*, *5*, 347–360.

Jennings, J. R., & van der Molen, M. W. (2005). Preparation for speeded action as a psychophysiological concept. *Psychological Bulletin*, *131*, 434–459.

Karp, J. F., Reynolds, C. F, III, Butters, M. A., Dew, M. A., Mazumdar, S., Begley, A. E., … Weiner, D. K. (2006). The relationship between pain and mental flexibility in older adult pain clinic patients. *Pain Medicine*, *7*, 444–452.

Klein, T. A., Endrass, T., Kathmann, N., Neumann, J., Von Cramon, D. Y., & Ullsperger, M. (2007). Neural correlates of error awareness. *NeuroImage*, *34*, 1774–1781.

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology*, *46*, 1121–1123.

Kuchinad, A., Schweinhardt, P., Seminowicz, D. A., Wood, P. B., Chizh, B. A., & Bushnell, M. C. (2007). Accelerated brain gray matter loss in fibromyalgia patients: Premature aging of the brain? *The Journal of Neuroscience*, *27*, 4004–4007.

Kwan, C. L., Crawley, A. P., Mikulis, D. J., & Davis, K. D. (2000). An fMRI study of the anterior cingulate cortex and surrounding medial wall activations evoked by noxious cutaneous heat and cold stimuli. *Pain*, *85*, 359–374.

Lacey, J. I., & Lacey, B. C. (1970). Some autonomic-central nervous system interrelationships. In P. Black (Ed.), *Physiological correlates of emotion* (pp. 205–227). New York, NY: Academic Press.

Lane, R. D., & Jennings, J. R. (1994). Hemispheric asymmetry, autonomic asymmetry, and the problem of sudden cardiac death. In R. J. Davidson & K. Hugdahl (Eds.), *Brain asymmetry* (pp. 271–304). Cambridge, MA: MIT Press.

Lázaro, C., Bosch, F., Torrubia, R., & Baños, J. E. (1994). The development of a Spanish questionnaire for assessing pain: Preliminary data concerning reliability and validity. *European Journal of Psychology Assessment*, *10*, 145–151.

Leavitt, F., & Katz, R. S. (2006). Distraction as a key determinant of impaired memory in patients with fibromyalgia. *Journal of Rheumatology*, *33*, 127–132.

Leavitt, F., & Katz, R. S. (2008). Speed of mental operations in fibromyalgia. A selective naming speed deficit. *Journal of Clinical Rheumatology*, *14*, 214–218.

Leavitt, F., & Katz, R. S. (2009). Normalizing memory recall in fibromyalgia with rehearsal: A distraction-counteracting effect. *Arthritis & Rheumatism*, *61*, 740–744.

Melzak, R. (1975). The McGill Pain Questionnaire: Major properties and scoring method. *Pain*, *1*, 277–299.

Miró, E., Lupiánez, J., Hita, E., Martínez, M. P., Sánchez, A., & Buela-Casal, G. (2011). Attentional deficits in fibromyalgia and its relationships with pain, emotional distress and sleep dysfunction complaints. *Psychology & Health*, *26*, 765–780.

Montoro, C., Duschek, S., Muñoz Ladrón de Guevara, C., Fernández-Serrano, M. J., & Reyes del Paso, G. A. (2015). Aberrant cerebral blood flow responses during cognition: Implications for the understanding of cognitive deficits in fibromyalgia. *Neuropsychology*, *29*(2), 173–182. doi:10.1037/neu0000138

Munguía-Izquierdo, D., Legaz-Arrese, A., Moliner-Urdiales, D., & Reverter-Masía, J. (2008). Neuropsicología de los pacientes con síndrome de fibromialgia: Relación con dolor y ansiedad [Neuropsychological performance in patients with fibromyalgia syndrome: Relation to pain and anxiety]. *Psicothema*, *20*, 427–431.

Neubauer, A. C., & Fink, A. (2009). Intelligence and neural efficiency. *Neuroscience & Biobehavioral Reviews*, *33*, 1004–1023.

Park, D. C., Glass, J. M., Minear, M., & Crofford, L. J. (2001). Cognitive function in fibromyalgia patients. *Arthritis & Rheumatism*, *44*, 2125–2133.

Penrod, J. R., Bernatsky, S., Adam, V., Baron, M., Dayan, N., & Dobkin, P. L. (2004). Health services costs and their determinants in women with fibromyalgia. *The Journal of Rheumatology*, *31*, 1391–1398.

Pericot-Nierga, I., Hernández-Ferràndiz, M., Lozano-Gallego, M., Vilalta-Franch, J., Cruz-Reina, M. M., & López-Pousa, S. (2009). Cognitive profile in fibromyalgia. Comparison with a mild cognitive impairment group. *Medicina Clinica*, *133*, 91–94.

Peyron, R., Laurent, B., & García-Larrea, L. (2000). Functional imaging of brain responses to pain. A review and meta-analysis. *Clinical Neurophysiology*, *30*, 263–288.

Porges, S. W. (1992). Autonomic regulation and attention. In B. A. Campbell, H. Hayne, & R. Richardson (Eds.), *Attention and information processing in infants and adults* (pp. 201–223). Hillsdale, NJ: Lawrence Erlbaum Associates.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience*, *13*, 25–42.

Rainville, P. (2002). Brain mechanisms of pain affect and pain modulation. *Current Opinion in Neurobiology*, *12*, 195–204.

Raj, S., Brouillard, D., Simpson, C. S., Hopman, W. M., & Abdollah, H. (2000). Dysautonomia among

patients with fibromyalgia: A non-invasive assessment. *Journal of Rheumatology*, *27*, 2660–2665.

Reyes del Paso, G. A., Garrido, S., Pulgar, A., & Duschek, S. (2011). Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia syndrome. *Journal of Psychosomatic Research, 70*, 125–134.

Reyes del Paso, G. A., Garrido, S., Pulgar, A., Martín-Vázquez, M., & Duschek, S. (2010). Aberrances in autonomic cardiovascular regulation in fibromyalgia syndrome and their relevance for clinical pain reports. *Psychosomatic Medicine, 72*, 462–470.

Reyes del Paso, G. A., Pulgar, A., Duschek, S., & Garrido, S. (2012). Cognitive impairment in fibromyalgia syndrome: The impact of cardiovascular regulation, pain, emotional disorders and medication. *European Journal of Pain, 16*, 421–429.

Sándor, P. (1999). Nervous control of the cerebrovascular system: Doubts and facts. *Neurochemistry International*, *35*, 237–259.

Sanz, J., Navarro, M. E., & Vázquez, C. (2003). Adaptación española del Inventario para la Depresión de Beck-II (BDI-II): I. Propiedades psicométricas en estudiantes universitarios [Spanish adaptation of the Beck Depression Inventory-II (BDI-II): I. Psychometric features in university students]. *Análisis y Modificación de Conducta*, *29*, 239–288.

Schuepbach, D., Boeker, H., Duschek, S., & Hell, D. (2007). Rapid cerebral hemodynamic modulation during mental planning and movement execution: Evidence of time-locked relationship with complex behavior. *Clinical Neurophysiology*, *118*, 2254–2262.

Sokolov, E. N. (1963). Higher nervous functions: The orienting reflex. *Annual Review of Physiology*, *25*, 545–580.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1986). *Cuestionario de Ansiedad Estado-Rasgo (STAI)* [State-Trait Anxiety Inventory (STAI)]. Manual (2nd ed., pp. 545–580). Madrid: TEA Ediciones.

Stroobant, N., & Vingerhoets, G. (2000). Transcranial Doppler ultrasonography monitoring of cerebral hemodynamics during performance of cognitive tasks: A review. *Neuropsychology Review*, *10*, 213–231.

Thieme, K., Rose, U., Pinkpank, T., Spies, C., Flor, H., & Turk, D. C. (2006). Psychophysiological responses in patients with fibromyalgia syndrome. *Journal of Psychosomatic Research*, *61*, 671–679.

Unterrainer, J. M., Rahm, B., Kaller, C. P., Ruff, C. C., Spreer, J., Krause, B. J., … Halsband, U. (2004). When planning fails: Individual differences and error-related brain activity in problem solving. *Cerebral Cortex*, *14*, 1390–1397.

Veldhuijzen, D. S., Sondaal, S. F., & Oosterman, J. M. (2012). Intact cognitive inhibition in patients with fibromyalgia but evidence of declined processing speed. *Journal of Pain*, *13*, 507–515.

Verdejo-García, A., López-Torrecillas, F., Calandre, E. P., Delgado-Rodríguez, A., & Bechara, A. (2009). Executive function and decision-making in women with fibromyalgia. *Archives of Clinical Neuropsychology, 24*, 113–122.

Walitt, B., Roebuck-Spencer, T., Bleiberg, J., Foster, G., & Weinstein, A. (2008). Automated neuropsychiatric measurements of information processing in fibromyalgia. *Rheumatology International*, *28*, 561–566.

Wheeler, R. E., Davidson, R. J., & Tomarken, A. J. (1993). Frontal brain asymmetry and emotional reactivity: A biological substrate of affective style. *Psychophysiology*, *30*, 82–89.

Wolfe, F., Ross, K., Anderson, J., Russell, I. J., & Hebert, L. (1995). The prevalence and characteristics of fibromyalgia in the general population. *Arthritis & Rheumatism*, *38*, 19–28.

Yokoyama, K., Jennings, R., Aekles, P., Hood, P., & Boller, F. (1987). Lack of heart rate changes during an attention-demanding task after right hemisphere lesions. *Neurology*, 37, 624–630.

ESTUDIO 4. AN EXPLORATORY ANALYSIS OF THE INFLUENCE OF PERSONALITY AND EMOTIONAL FACTORS ON CEREBRAL BLOOD FLOW RESPONSES DURING PAINFUL STIMULATION IN FIBROMYALGIA.

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(Submitted)

An exploratory analysis of the influence of personality and emotional factors on cerebral blood flow responses during painful stimulation in fibromyalgia

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Abstract

This exploratory study investigated the influence of personality traits (neuroticism, extraversion, psychoticism), emotional variables (depression, catastrophizing, alexithymia) and insomnia on cerebral blood flow responses to painful stimulation in fibromyalgia syndrome (FMS), using functional transcranial Doppler sonography. Blood flow velocities were recorded bilaterally in the anterior (ACA) and middle (MCA) cerebral arteries of 24 FMS patients during exposure to painful pressure stimulation. Participants were presented with two stimulation conditions: a) fixed pressure of 2.4 kg and b) stimulation pressure individually calibrated to produce equal subjective and moderate pain intensity in all participants (average, 3.5 kg). Psychological factors were assessed by means of questionnaires. Neuroticism, psychoticism and the externally-oriented thinking dimension of alexithymia were positively, and extraversion was inversely, associated with specific components of ACA and MCA blood flow responses. Regarding catastrophizing and depression, correlations were positive for the less intense fixed pressure and negative for the more intense equal subjective intensity condition. The findings support the notion that alterations in central nervous pain processing in FMS vary according to psychological factors. While most of the observed associations reflect a linear increase in nociceptive processing with the magnitude of negative cognitive and emotional states, the inverse associations for catastrophizing and depression during more intense painful stimulation may be ascribed to anti-nociceptive effects due to activation of the defense reflex.

Keywords: Fibromyalgia, chronic pain, cerebral blood flow, neuroticism, extroversion, psychoticism, alexithymia, catastrophizing, depression, insomnia

Introduction

Fibromyalgia syndrome (FMS) is a complex disorder of unknown etiology characterized by persistent and widespread musculoskeletal pain in addition to symptoms like depression, fatigue, sleep disturbance and impaired mental performance (Van Middendorp et al., 2008; Wolfe et al., 2010; Yunus 2007). The prevalence of FMS is estimated at 2 to 4% in the general population, and women are more likely to be affected (Wolfe, Ross, Anderson, Russell & Hebert, 1995). Research on FMS pathogenesis has revealed evidence of central nervous system (CNS) sensitization to pain and deficient pain-inhibiting mechanisms. Exaggerated activity of the pain neuromatrix is believed to contribute to the hyperalgesia related to FMS (Clauw, 2014; Gracely & Ambrose, 2011; Jensen et al., 2009), where brain regions involved in processing of the emotional and cognitive pain components may play a particular role (Burgmer et al., 2009; Duschek et al., 2012; Pujol, López-Solà & Ortiz 2009). This notion accords with numerous studies implicating emotional and cognitive factors in FMS pain (Clauw & Crofford, 2003; Duschek, Werner, Limbert, Winkelmann & Montoya, 2014; Gracely et al., 2004). Pain catastrophizing and depression constitute the major features investigated in this context (Edwards, Bingham, Bathon & Haythomthwaite, 2006; Giesecke et al., 2005; Gracely et al., 2004; Karsdorp & Vlaeyen, 2009; Van Wilgen, Van Ittersum, Kaptein & Van Wijhe, 2008). Increased pain severity and pain-related disability have been repeatedly associated with pain catastrophizing in FMS (Geisser & Roth, 1998; Geisser et al., 2003; Keefe, Brown, Wallston & Caldwell, 1989) and catastrophizing and pain anticipation are likely to be involved in CNS sensitization (Gracely et al., 2004). This is supported**,** for example, by brain imaging studies demonstrating greater pain-related increases in activity in the anterior cingulate cortex (ACC), insula, and medial frontal cortex (brain structures that modulate attention and emotional reactions to painful stimulation) in FMS patients with high vs. low catastrophizing levels (Gracely et al., 2004; Gracely, Petzke, Wolf & Clauw., 2002; Sullivan et al., 2001). Depression is well-known to be accompanied by cognitive, behavioral and neurobiological changes that increase vulnerability to clinical pain (Gupta et al., 2007). The central nervous pathways related to negative emotions overlap with structures relevant to the affective and motivational aspects of pain (Eisenberger, 2012; Eisenberger & Lieberman, 2004; Meerwijk, Ford & Weiss, 2013), such that emotional and nociceptive processing closely interact (Edwards et al., 2006;

De Souza, Potvin, Goffaux, Charest & Marchand, 2009; Godinho, Magnin, Frot, Perchet & Garcia-Larrea, 2006; Ploghaus et al., 2001). While FMS is associated with high prevalence of depression (Epstein et al., 1999; Van Middendorp et al., 2008), research on the central nervous correlates of this linkage has revealed controversial results. Giesecke et al. (2005), for example, showed increased pain-induced activity in the insula and amygdala, regions related to the affective-motivational pain component, in FMS patients with comorbid depression vs. those without depression. Contrariwise, findings by Jensen et al. (2010) suggest that altered central nervous nociceptive processing in FMS patients occurs virtually independent of alterations related to depression.

Personality factors are also believed to affect nociception and pain (Affleck, Tennen, Urrows & Higgins, 1992; Asghari & Nicholas, 2006; Ramírez, Esteve & Lopez, 2001). FMS has been repeatedly related to traits such as neuroticism and alexithymia (Besteiro et al., 2008; Castelli et al., 2012; Huber, Suman, Biasi & Carli, 2009; Malin & Little John, 2012; Montoro & Reyes del Paso, 2015; Steinweg, Dallas, & Rea, 2011), which in turn correlate with clinical pain and other symptoms of FMS including maladaptive coping, sleep disturbance, somatosensory amplification, anxiety and depression (Asghari & Nicholas, 2006; Deary, Scott & Wilson, 1997; Hosoi et al., 2010; Malin & Littlejohn, 2012; Martínez, Sánchez, Miró, Medina & Lami, 2011; Martínez et al., 2015; Montoro & Reyes del Paso, 2015; Ramírez et al, 2001; Wise & Mann, 1994). However, studies concerning the possible impact of personality on altered nociceptive processing, particularly CNS sensitization to pain, are still lacking in FMS. In the present study, H. J. Eysenck´s three personality dimensions were considered. Neuroticism entails, among other features, great reactivity to – and low tolerance of – negative physical (e.g., pain) and psychological (e.g., conflict or frustration) states (Eysenck, 1967; Lynn & Eysenck, 1961). At the biological level, it has been hypothesized that differential limbic system activation is responsible for interindividual differences in this trait (Eysenck, 2013). Furthermore, neuroticism has been linked to reduced connectivity between the left amygdala and the ACC, structures involved in the perception and cognitive control of negative stimuli, which may imply a negative bias in attention, selective recall of negative information, increased emotional reactivity and dysfunctional coping (c.f. Ormel et al., 2013 for a review). Extraversion (i.e., interest in the outside world and sociability) has been associated with low levels of CNS

activation, especially in the ascending reticular activating system, frontal lobes, septal regions, and hippocampus, which in turn is accompanied by reduced cortical representation of afferent information (Eysenck, 1967; Gray, 1970). This notion is consistent with the view of extraversion as a protective factor against pain, contributing to the maintenance of well-being (Ballina, Martín, Iglesias, Hernández & Cueto, 1995; Montoro & Reyes del Paso 2015). Moreover, some regional cerebral blood flow (CBF) studies demonstrated lower CBF in the temporal lobes and posterior insula in extraverts vs. introverts (Johnson et al., 1999; Stenberg, Risberg, Warkentin & Rosen, 1990), structures which are likely to be involved in the development of central nociceptive sensitization and hyperalgesia (Burgmer et al., 2011). Psychoticism (i.e., vulnerability to impulsive, aggressive or low empathy behaviors), has been associated with greater divergent thinking, high creative ability (Eysenck, 1995; Woody & Claridge, 2011), and greater objectivity, realism and hardiness in daily life, including situations involving pain (Carrillo, Collado & Rojo, 2005).

Highly expressed alexithymia, a personality trait involving a lack of emotional awareness, difficulties in identifying and communicating feelings and an externally-oriented cognitive style (Bagby, Parker, & Taylor, 1994; Sifneos, 1973), was repeatedly demonstrated in individuals suffering from FMS (Castelli et al., 2012; Huber et al., 2009; Steinweg et al., 2011; Weiß, Winkelmann & Duschek, 2013). The tendency to focus on and amplify somatic sensations accompanying emotional arousal is a typical manifestation of this trait (Taylor & Bagby, 1997). As such, alexithymia has been proposed as a factor mediating the relationship between maladaptive coping and pain chronification (Lumley, Stettner & Wehmer, 1996; Pilowsky & Katsikitis, 1994). Alexithymia is thought to impede the regulation of negative emotions, resulting in increased negative affect, sympathetic overarousal and impaired immune system status, which may contribute to the development or exacerbation of somatic disease and pain (Beales & Dolton, 2000). It was suggested that alexithymia is linked to a lack of adequate neuronal connections between the limbic system and neocortex (Nemiah, Sifneos & Apfel-Savitz, 1997). Individuals with high alexithymia showed enhanced activity in the insula, somatosensory and motor cortices, especially in the left hemisphere, in addition to reduced activity in the ACC (Karlsson, Näätänen & Stenman, 2008; Lane et al., 1998), areas relevant to emotional awareness as well as attentional and pain processing (Devinsky, Morrell & Vogt, 1995; Lane, 2000).

A large proportion of FMS patients suffer from sleep disturbance (Wolfe et al., 2010). The neuromatrix theory of pain suggests that numerous factors contribute to nociception and pain perception, including psychological and general health characteristics such as sleep problems (Melzack & Loeser, 1978). Disturbed sleep has been related to increased pain sensitivity and vulnerability to FMS (Affleck, Urrows, Tennen, Higgins & Abeles, 1996; Bigatti, Hernández, Cronan & Rand, 2008). However, studies on CNS connecting sleep problems with FMS pain are not yet available.

The studies reviewed above explored relationships between psychological factors and spatial distributions of pain-related CBF responses mostly using functional magnetic resonance imaging (fMRI). The investigation of temporal dynamics of CBF can provide complementary information to that revealed by classic brain imaging techniques. Functional transcranial Doppler sonography (fTCD) allows for the continuous noninvasive measurement of CBF velocities in the basal cerebral arteries and provides excellent time resolution (Duschek & Schandry, 2003). Changes in flow velocity in these arteries reflect changes in the blood demand in their perfusion territories as a result of the close coupling between neural and vascular activity (Duschek & Schandry, 2003). In the current study, we bilaterally recorded blood flow velocities in the anterior cerebral arteries (ACA), which supply medial-anterior cerebral regions comprising structures specifically mediating the affective and cognitive pain components, and the middle cerebral arteries (MCA), which supply lateral brain areas including structures associated with the sensory pain component (Burgmer et al., 2009; Duschek, Hellmann, Merzoug, Reyes del Paso & Werner, 2012).

This exploratory study aimed to investigate the impact of personality (neuroticism, extraversion, psychoticism, alexithymia), emotional (depression and catastrophizing) and clinical (insomnia) variables on CBF responses during painful pressure stimulation in FMS patients. The study was based on a reanalysis of previously recorded data on CBF responses during painful stimulation in FMS patients and healthy individuals (Montoro, Duschek, Muñoz & Reyes del Paso, 2015). Participants were administered two stimulation conditions (Gracely et al., 2002; 2004): a fixed pain pressure condition evoking low-to-moderate pain, and an equal pain condition, in which stimulation pressures were individually calibrated to produce equal, moderate pain intensity in all participants. In the study of Montoro et al. (2015), a complex pattern of CBF

modulations was observed, comprising four main components: an anticipatory increase before stimulation onset, an early increase, a transient decrease to baseline or below, and a final increase. Differences between patients and healthy subjects were observed in all components, most of them reflecting augmented central nervous pain processing in FMS. Furthermore, significant associations arose between clinical pain severity and alterations in CBF responses.

Based on the considerations presented above, the study tested the following hypotheses: (a) amplitudes of the CBF response components are positively related to neuroticism and inversely related to extraversion; (b) high levels of depression, catastrophizing and alexithymia are associated with stronger CBF responses; and (c) the magnitude of sleep disturbance correlates positively with CBF responses. Considering that the perfusion territory of the ACA includes structures relevant to the processing of the affective and cognitive pain components, overall closer associations were expected for CBF responses in the ACA vs. the MCA, particularly regarding neuroticism, depression, catastrophizing and alexithymia.

Method

Participants

Twenty-four women with FMS participated in the study. They were recruited via the Fibromyalgia Association of Jaén and met the American College of Rheumatology criteria for FMS (Wolfe et al., 1990). The presence of cardiovascular diseases, metabolic abnormalities, inflammatory causes of pain, neurological disorders, drug abuse, or severe somatic (e.g., cancer) or psychiatric (e.g., psychotic or bipolar) diseases were used as exclusionary criteria. All participants were right handed. Table 1 displays the demographic and clinical data of the sample.

Table 1. Demographic and clinical characteristics (mean ± SD) and medication use (number of patients and %).

	FMS patients
Age	48.96±9.15
Body Mass Index	25.31±3.37
Years of education	11.64±3.05
Depression (%)	13 (52)
Anxiety disorders (%)	13 (52)
Antidepressant use (%)	13 (52)
Anxiolytic use (%)	15 (60)
Analgesic use (%)	21 (84)
Opiate use (%)	13 (52)
Neuroticism	4.80±1.12
Extraversion	3.56±1.39
Psychoticism	2.84±.80
Catastrophizing	18.84±6.47
Difficulty Identifying Feelings	20.57±7.46
External Oriented Thinking	21.87±4.64
Depression	22.92±11.24
Insomnia	31.40±6.01

Psychological measures

In addition to a semi-structured interview assessing clinical history and demographic data, participants were evaluated with the following self-reported questionnaires:

Spanish Adaptation of the Eysenck Personality Questionnaire Revised-Abbreviated (EPQR-A). This scale was developed by Francis, Brown & Philipchalk (1992), and was validated in Spanish samples by Sandín, Valiente, Olmedo, Chorot & Santed (2002). It consists of 24 items spread among four subscales (6 items each): Neuroticism, Extraversion, Psychoticism and social desirability (sincerity). Scores range between 0 and 6 on all subscales (answer format = YES/NO). Due to its relative brevity, this questionnaire is particularly suited for use in clinical settings and correlates adequately with its predecessor, the EPQ. Internal consistency (Cronbach's α) is .74 for neuroticism, .78 for extroversion, .63 for psychoticism and .54 for the sincerity scale.

Beck Depression lnventory (BDI) (Beck, Ward & Mendelson, 1961); Spanish adaptation by Sanz, Navarro & Vázquez (2003). This instrument consists of 21 items rated on 4-point Likert scales according to symptom severity. The internal consistency of the Spanish version ranges between .76 and .95.

Coping Strategies Questionnaire (CSQ, Rosenstiel & Keefe, 1983); Spanish adaptation by Rodríguez, Cano & Blanco (2004). The CSQ is a self-administered questionnaire that includes a frequently used 6-item catastrophizing subscale. The scale requires subjects to provide 7-point ratings concerning the extent of catastrophizing as a coping strategy in the specific context of pain. The internal consistency (Cronbach's α) of the questionnaire is .89.

Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994); Spanish version adapted by Martínez-Sánchez (1996). The TAS-20 measures alexithymia on three sub-scales with 5-point Likert scales ranging from 1 to 5: Difficulty Identifying Feelings (inability to distinguish between specific emotions, or between emotions and bodily sensations); Difficulty Describing Feelings (inability to verbalize one's emotions); and Externally-Oriented Thinking (tendency to focus attention externally rather than on inner emotional experience). Due to the overlap and high correlation between Difficulty Describing Feelings and Difficulty Identifying Feelings (Kooiman, Spinhoven & Trijsburg, 2002;

Taylor, Parker, Bagby & Acklin, 1992), only Difficulty Identifying Feelings and Externally-Oriented Thinking were taken from the TAS-20 in the present study. The internal consistency of the questionnaire is .76.

Oviedo Quality of Sleep Questionnaire (COS, Bobes et al., 2000). Completed during interview, this questionnaire has 15 items scored on 5-point Likert scales. The global internal consistency of the questionnaire is 0.77. Only the Insomnia index was taken from this instrument by the present study.

Pressure stimulation and pain quantification

Pain was evoked using a wireless pressure algometer (Traker Freedom, JTECH Medical, Salt Lake City, UT, USA) with a surface area of 1 cm^2. The algometer was inserted in a screw-piston specifically designed to fixate and press the finger-nails. When stimulation commenced, the piston sent an electrical pulse to the fTCD system, signaling the start of a trial. Pain pressure was delivered to the nail of the index finger of the left hand. Participants were exposed to two blocks of 12 pressure stimuli presented in a counterbalanced order: (a) one block used a fixed pressure of 2.4 kg, associated with low pain ratings in healthy individuals and with low-to-moderate pain in FMS patients (Gracely et al., 2002; 2004), and (b) an individually calculated pressure in order to evocate a moderate-to-high subjective pain intensity (i.e., score of 6 on a 10 point VAS) in all participants. Mean pressure during this condition was 3.5 kg (SD = 2.1 kg). Stimulus duration was 10 s; inter-trial intervals were 60 s. The stimulation protocol allowed for investigation of the anticipation of pain, because participants could see their nail in the screw-piston and the investigator approaching the device approximately 4 s prior to stimulus onset (c.f. Montoro et al., 2015).

Recording of cerebral blood flow

Blood flow velocity was assessed by fTCD employing a digital Multi-Dop L2 DWL (Elektronische Systeme, Inc., Sipplingen, Germany). Recordings were conducted bilaterally, in both the ACA and MCA, through the temporal bone windows using two 2-MHz transducer probes. Following vessel identification, the probes were fixed to the head via a head harness. The spectral envelope curves of the Doppler signal were recorded at 100 Hz. The mean flow velocity index was applied as a measure of CBF.

This index is the least vulnerable to artifacts and exhibits the highest correlation with blood volume flowing through an artery per unit of time (Duschek & Schandry, 2003).

The 30 s period after stimulus onset was defined as the stimulation period; the 4 s period before stimulus onset was the anticipatory period. Mean flow velocity during the 10 s prior to the anticipation period served as the baseline. Responses were expressed as relative (percent) changes in flow velocity (dFV) with respect to baseline (FVbas) according to the formula dFV = (FV[t] - FVbas) *100/FVbas, where FV(t) is the flow velocity over time.

Procedure

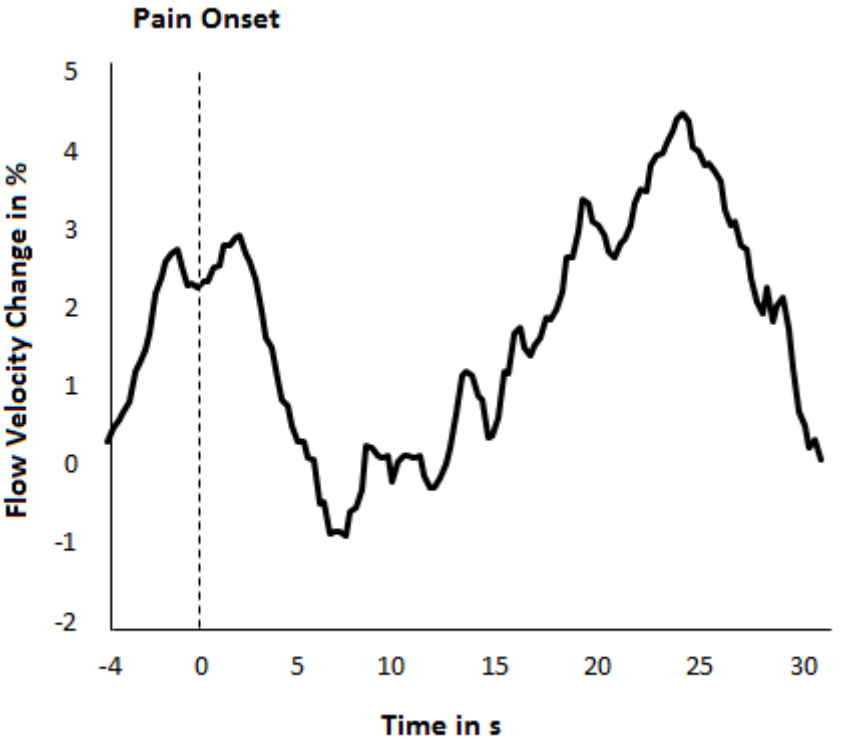
Data were acquired within two sessions: in the first session, a clinical psychologist recorded patients' clinical histories, confirmed that there were no violations of the exclusionary criteria and administered the BDI and OQSQ questionnaires. In the second session, participants completed the remaining questionnaires (EPQR-A, CSQ and TAS-20) and the pain experiment was performed. All participants provided informed consent. The study protocol was approved by the Bioethics Committee of the University of Jaén.

Data reduction and analysis

Grand averages of the CBF response pattern during the two pain conditions are displayed in Figure 1. Four delimitable components were identified in the CBF response: 1) an anticipatory increase component (2 s before stimulus onset), 2) an early increase component (s 1 to 3 after stimulus onset), 3) a decrease component (s 5 to 11), and 4) a late increase component (s 12 to 22) (c.f. Montoro et al., 2015 for details). Mean values during these periods were obtained for each participant. At an exploratory level, associations between measured self-reported variables and CBF responses were quantified using Pearson correlations. In a subsequent step, associations were subjected to multiple stepwise regression analysis. Neuroticism, extraversion, psychoticism, catastrophizing, alexithymia, depression and insomnia were entered as predictors, and CBF components in each of the four insonated vessels were taken as dependent variables (in separate analyses). These regression analyses provided an adjusted (by degrees of freedom) r^2, used to index the predictive capacity of the model, and

standardized β coefficients, representing the slope of the regression line. The significance level was set at $p \leq .05$.

Figure 1. Grand averages of the cerebral blood flow response to pain averaged for the four arteries. Above: equal pain pressure (2.4 kg) condition; Bottom: equal subjective pain (6 VAS) condition.



Results

Results of correlation analysis

Associations between personality traits and CBF responses

While a pattern of positive associations arose between the Neuroticism scale and CBF responses in the right ACA and MCA, correlations only reached significance in the right ACA during the 2.4 kg condition for the anticipatory and decrease components (c.f. Table 2). Regarding the Extraversion scale, negative correlations were obtained for the early and decrease components in the left and right MCA during the fixed pressure (2.4 kg) condition. Concerning the equal subjective intensity (6 VAS) condition, Extraversion correlated negatively with the anticipatory component in the left MCA. The Psychoticism scale correlated positively with the anticipatory component in the left MCA under the 2.4 kg condition.

Table 2. Pearson correlations between the EPQR-A scales Neuroticism, Extraversion and Psychoticism and CBF responses in the anterior (ACA) and middle (MCA) cerebral arteries of the right and left hemispheres under the fixed pressure (2.4 kg) and equal subjective intensity (6 VAS) conditions for the anticipatory (1), early increase (2), decrease (3) and late increase components (4).

	Neuroticism		Extraversion		Psychoticism	
	ACA	MCA	ACA	MCA	ACA	MCA
Right, 2.4 kg, 1	**.400***	.217	-.038	-.132	.117	.292
Right, 2.4 kg, 2	.046	.192	.124	**-.522****	.157	.344
Right, 2.4 kg, 3	**.448***	.090	.160	**-.446***	-.081	.116
Right, 2.4 kg, 4	.341	-.044	.288	-.107	-.073	.344
Left, 2.4 kg, 1	-.134	.096	.209	-.062	-.125	**.394***
Left, 2.4 kg, 2	-.048	.052	.018	**-.444***	.122	.393
Left, 2.4 kg, 3	-.114	.182	.076	**-.512****	.005	.094
Left, 2.4 kg, 4	.375	-.025	-.044	-.080	.279	.299
Right, 6 VAS, 1	.121	.130	-.139	-.394	.319	.168
Right, 6 VAS, 2	.034	.252	-.246	-.106	.338	.110
Right, 6 VAS, 3	-.211	.042	-.355	.076	.328	-.126
Right, 6 VAS, 4	.015	-.151	.104	-.016	.083	.062
Left, 6 VAS, 1	.243	.032	-.184	**-.396***	.322	.229
Left, 6 VAS, 2	.180	.140	-.303	-.248	.345	.172
Left, 6 VAS, 3	-.324	-.060	-.345	-.014	.292	.036
Left, 6 VAS, 3	.197	-.365	-.221	-.026	.390	.080

*p<.05, **p<.01

Associations between catastrophizing and CBF responses

The Catastrophizing scale from the CSQ was positively associated with right MCA responses under the 2.4 kg condition for the early increase and decrease components. Negative associations arose under the 6 VAS condition for the decrease and late increase components (c.f. Table 3).

Table 3. Pearson correlations between the CSQ scale Catastrophizing and CBF responses in the anterior (ACA) and middle (MCA) cerebral arteries of the right and left hemispheres under the fixed pressure (2.4 kg) and equal subjective intensity (6 VAS) conditions for the anticipatory (1), early increase (2), decrease (3) and late increase components (4).

	Catastrophizing	
	ACA	MCA
Right, 2.4 kg, 1	.016	.045
Right, 2.4 kg, 2	-.232	.281
Right, 2.4 kg, 3	-.113	.303
Right, 2.4 kg, 4	-.219	-.005
Left, 2.4 kg, 1	.002	.149
Left, 2.4 kg, 2	-.111	**.458***
Left, 2.4 kg, 3	-.091	**.420***
Left, 2.4 kg, 4	-.157	.004
Right, 6 VAS, 1	-.006	-.098
Right, 6 VAS, 2	-.058	-.233
Right, 6 VAS, 3	-.048	**-.551****
Right, 6 VAS, 4	-.360	**-.489***
Left, 6 VAS, 1	.068	-.037
Left, 6 VAS, 2	-.114	-.107
Left, 6 VAS, 3	-.274	-.158
Left, 6 VAS, 4	-.279	-.358

*p<.05, **p<.01

Associations between alexithymia and CBF responses

No significant correlations arose for the Difficulty Identifying Feelings scale of the TAS-20 (Table 4). Regarding the Externally-Oriented Thinking scale, overall positive associations were obtained for all CBF components in the ACA under the 6 VAS condition, which were significant for the anticipatory, early increase and decrease components in the right, and the early and late increase components in the left, hemisphere. In the case of the MCA and the 6 VAS condition, significant positive associations were found between Externally-Oriented Thinking scores and right and left hemispherical CBF during the anticipatory component (see Table 4).

Table 4. Pearson correlations between the TAS-20 scales Difficulty Identifying Feelings and Externally-Oriented Thinking and CBF responses in the anterior (ACA) and middle (MCA) cerebral arteries of the right and left hemispheres under the fixed pressure (2.4 kg) and equal subjective intensity (6 VAS) conditions for the anticipatory (1), early increase (2), decrease (3) and late increase components (4).

	Difficulty Identifying Feelings		Externally-Oriented Thinking	
	ACA	MCA	ACA	MCA
Right, 2.4 kg, 1	-.029	.039	.283	.181
Right, 2.4 kg, 2	-.059	.140	-.005	.220
Right, 2.4 kg, 3	.162	.231	-.054	.034
Right, 2.4 kg, 4	.107	.149	-.169	.067
Left, 2.4 kg, 1	.093	-.063	-.234	.293
Left, 2.4 kg, 2	.167	-.073	-.055	.282
Left, 2.4 kg, 3	.108	.133	-.237	.141
Left, 2.4 kg, 4	-.078	.163	.383	.151
Right, 6 VAS, 1	-.149	-.347	**.485***	**.440***
Right, 6 VAS, 2	-.323	-.043	**.578****	.172
Right, 6 VAS, 3	-.361	.061	**.496***	.036
Right, 6 VAS, 4	-.328	-.111	.117	.148
Left, 6 VAS, 1	-.038	-.282	.395	**.421***
Left, 6 VAS, 2	-.175	-.010	**.481***	.182
Left, 6 VAS, 3	-.314	.083	.139	-.203
Left, 6 VAS, 4	-.175	-.210	**.413***	-.029

*p<.05, **p<.01

Associations between depression and CBF responses

The BDI score was positively associated with right and left MCA responses under the 2.4 kg condition for the early and decrease components. Under the 6 VAS condition, correlations were lower and tended to be negative, being significant only for the right late increase component (c.f. Table 5).

Table 5. Pearson correlations between BDI scores and CBF responses in the anterior (ACA) and middle (MCA) cerebral arteries of the right and left hemispheres under the fixed pressure (2.4 kg) and equal subjective intensity (6 VAS) conditions for the anticipatory (1), early increase (2), decrease (3) and late increase components (4).

	Depression	
	ACA	MCA
Right, 2.4 kg, 1	.040	.245
Right, 2.4 kg, 2	-.226	**.492***
Right, 2.4 kg, 3	.003	**.399***
Right, 2.4 kg, 4	-.008	-.042
Left, 2.4 kg, 1	.050	.250
Left, 2.4 kg, 2	.204	**.527****
Left, 2.4 kg, 3	**-.430***	**.528****
Left, 2.4 kg, 4	-.146	.046
Right, 6 VAS, 1	-.030	-.076
Right, 6 VAS, 2	-.208	-.043
Right, 6 VAS, 3	-.247	-.337
Right, 6 VAS, 4	-.063	**-.404***
Left, 6 VAS, 1	.100	-.084
Left, 6 VAS, 2	-.011	.017
Left, 6 VAS, 3	-.240	.096
Left, 6 VAS, 4	-.149	-.239

*p<.05, **p<.01

Associations between insomnia and CBF responses

Concerning the Insomnia scale of the COS, a general tendency towards negative associations was revealed for the 2.4 kg condition. However, only the correlation for the right ACA and the anticipatory component reached significance (c.f. Table 6). No significant correlations were found for the 6 VAS condition.

Table 6. Pearson correlations between the COS scale Insomnia and CBF responses in the anterior (ACA) and middle (MCA) cerebral arteries of the right and left hemispheres under the fixed pressure (2.4 kg) and equal subjective intensity (6 VAS) conditions for the anticipatory (1), early increase (2), decrease (3) and late increase components (4).

	Insomnia	
	ACA	MCA
Right, 2.4 kg, 1	**-.477***	-.215
Right, 2.4 kg, 2	.163	-.132
Right, 2.4 kg, 3	-.266	-.175
Right, 2.4 kg, 4	-.374	-.003
Left, 2.4 kg, 1	-.098	-.342
Left, 2.4 kg, 2	.029	-.226
Left, 2.4 kg, 3	.275	-.168
Left, 2.4 kg, 4	-.381	-.015

*p<.05, **p<.01

Results of multiple regression analysis

Significant results of the multiple regression analyses for the prediction of CBF responses by the questionnaire scales are summarized in Tables 7 and 8 for the ACA and MCA, respectively. Concerning the right ACA and the 2.4 kg condition, the Insomnia scale was the main negative predictor of the anticipatory component, while Neuroticism positively predicted the decrease and late increase components. No significant predictors arose for the left ACA response components. Regarding the 6 VAS condition, Externally-Oriented Thinking was the main positive predictor of the anticipatory (right hemisphere), early increase (both hemispheres) and decrease (right hemisphere) components in the ACA. Concerning the MCA and the 2.4 kg condition, the Extraversion scale negatively predicted the early (right hemisphere) and decrease (left hemisphere) response components. Depression and Psychoticism (in a second model) positively predicted the early component (left hemisphere). No significant predictors were observed under this condition for the anticipatory and late components. For the 6 VAS condition, Externally-Oriented Thinking was the main positive predictor for the anticipatory component (right hemisphere), while Catastrophizing negatively predicted the decrease and late increase components in the right hemisphere. No significant predictors were observed for the left hemisphere under the 6 VAS condition.

Table 7. Results of multiple regression analysis for the prediction of CBF responses in the ACA of the right and left hemisphere under the fixed pressure (2.4 kg) and equal subjective intensity (6 VAS) conditions for the anticipatory (1), early increase (2), decrease (3) and late increase components (4).

Dependent Variable	**Predictor**	stand. β	adj. r^2	t	p
Right, 2.4 kg, 1	Insomnia	-.49	.20	-2.51	.021
Right, 2.4 kg, 3	Neuroticism	.48	.19	2.46	.023
Right, 2.4 kg, 4	Neuroticism	.42	.14	2.10	.049
Right, 6 VAS, 1	Externally-Oriented Thinking	.49	.20	2.48	.022
Right, 6 VAS, 2	Externally-Oriented Thinking	.48	.19	2.45	.024
Right, 6 VAS, 3	Externally-Oriented Thinking	.50	.21	2.56	.019
Left, 6 VAS, 2	Externally-Oriented Thinking	.58	.30	3.17	.050

Table 8. Results of multiple regression analysis for the prediction of CBF responses in the MCA of the right and left hemisphere under the fixed pressure (2.4 kg) and equal subjective intensity (6 VAS) conditions for the anticipatory (1), early increase (2), decrease (3) and late increase components (4).

Dependent Variable	**Predictor**	stand. β	adj. r^2	*t*	*P*
Right, 2.4 kg, 2	Extraversion	-.49	.20	-2.56	.018
Left, 2.4 kg, 2	Depression	.45	.17	2.33	.030
	Depression	.46	.32	2.61	.017
	Psychoticism	.42	.32	2.42	.025
Left, 2.4 kg, 3	Extraversion	-.46	.18	-2.40	.026
Right, 6 VAS, 1	Externally-Oriented Thinking	.44	.15	2.4	.036
Right, 6 VAS, 3	Catastrophizing	-.61	.35	-3.55	.002
Right, 6 VAS, 4	Catastrophizing	-.49	.21	-2.59	.017

Discussion

The study revealed associations between amplitudes of CBF responses to painful stimulation and personality traits, emotional variables and insomnia in patients diagnosed with FMS. According to the correlation analysis, neuroticism was positively associated with CBF modulation in the right ACA under the fixed pressure condition, specifically for the anticipatory and decrease components of the response. Regression analysis revealed positive associations for the decrease and late increase components in this vessel. In contrast, no significant correlations arose for the MCA. The neuromatrix of nociception is commonly subdivided according to specific features of pain processing (Apkarian, Bushnell, Treede & Zubieta, 2005; Burgmer et al., 2009): a lateral subsystem including the somatosensory cortex, inferior parietal cortex and posterior insula is specifically related to the sensory pain component, i.e., stimulus localization as well as quality and intensity evaluation. Brain structures such as the anterior cingulate, medial prefrontal cortex and supplementary motor area constitute a medial pain system, which is linked to affective and cognitive pain processing. While the ACA supplies the area of the medial pain matrix, the perfusion territory of the MCA covers the lateral matrix (Duschek, Hellmann et al., 2012). Therefore, it may be concluded that neuroticism specifically modulates processing of the affective and cognitive pain component, which is ascribed to the medial part of the pain neuromatrix. This is in line with an observation by Harkins, Price & Braith (1989) suggesting that neuroticism does not affect sensory pain processing, but instead exerts its influence on cognitive and emotional processes related to the interpretation of pain. The finding concerning the anticipatory CBF component may be of particular relevance. Pain anticipation encompasses a negative emotional state occurring together with a rise in attentional arousal that, on a central nervous level, is ascribed to right anterior dominance (Montoro et al., 2015; Posner & Petersen, 1990). This finding suggests that neuroticism may potentiate these psychophysiological processes, where pain anticipation in turn is believed to play a relevant role in central nervous sensitization and pain chronification (Burgmer et al., 2009).

In the correlation analysis, extraversion was inversely associated with CBF responses in the MCA, both during the fixed pressure (early and decrease components in both hemispheres) and equal subjective pain intensity (anticipatory component in the right

hemisphere) conditions. Regression analysis revealed inverse associations for the fixed pressure condition (early component in the right hemisphere, decrease component in the left hemisphere). In contrast, no significant associations were obtained for the ACA. Considering the reasoning presented above, it would appear that the influence of extraversion on pain-related CBF modulations primarily concerns the lateral pain neuromatrix, representing the sensory pain component. The negative correlations suggest that greater extraversion is accompanied by reduced sensory processing of nociceptive input. This is consistent with Eysenck´s assumptions regarding the biological basis of extraversion, according to which lower activity in the ascending reticular activating system leads to lower cortical representation of afferent stimuli in extrovert individuals (Eysenck, 1967). This in turn accords with the notion of a protective role of extraversion in the sense that it may prevent cortical hyperarousal and limit pain experience (Eysenck, 1967; Montoro & Reyes del Paso, 2015). Correlations between psychoticism and CBF responses were overall low and less systematic, where only the positive association with the anticipatory response in the left MCA under the fixed pressure condition reached significance. In regression analysis, psychoticism positively predicted the early increase component in the MCA under the same condition. This finding may suggest a more pronounced increase of attentional arousal during pain anticipation and the initial processing phase in individuals with high psychoticism, probably due to greater activity of the dorsolateral frontal and inferior parietal lobes, which are part of the MCA perfusion territory (Duschek, Schuepbach & Schandry, 2008; Duschek, Heiss, Schmidt, Werner & Schuepbach, 2010). However, the extent of the linkage between neuroticism and CBF modulation is certainly too low to draw any firm conclusion.

According to the correlation analysis, the alexithymia dimension of externally-oriented thinking was positively associated with CBF responses in the ACA (anticipatory, early increase and decrease components in the right hemisphere, early and late increase components in the left hemisphere) and MCA (anticipatory component in the right and left hemispheres) under the equal subjective intensity condition. Regression analysis revealed a similar pattern of associations. Alexithymia has been related to aberrant activity in various brain structures that also form part of the medial (insula, anterior cingulate) or lateral (somatosensory cortex) neuromatrix of pain (Karlsson et al., 2008; Lane et al., 1998). This overlap may be relevant to the observed interaction. Externally-

oriented thinking, in terms of the tendency to focus on external events rather than inner (emotional) experience, has been suggested to interfere with successful emotional regulation leading to a sustained aversive affect. In turn, negative emotional states are well known to amplify pain in clinical conditions including FMS (Davis & Zautra & Reich, 2001; Huber et al., 2009; Montoya et al., 2005). Externally-oriented thinking is connected to the concepts of suppression and dissociation, which are also regarded as inefficient coping styles enhancing negative affect due to the intention to exclude negative experiences from conscious awareness (Andersen & Green, 2001; Grabe, Rainermann, Spitzer, Gänsicke & Freyberger, 2000; Lipsanen, Saarijärvi & Lauerma, 2004).

Catastrophizing was also more closely associated with MCA than ACA blood flow responses. This finding is in contrast to our expectation of a particular impact of catastrophizing on cognitive and affective pain processing in the medial part of the neuromatrix. However, it is consistent with an fMRI study by Burgmer et al. (2011), which revealed enhanced activity of the dorsolateral prefrontal and posterior parietal cortices during pain anticipation in FMS patients, but no effects for structures of the medial neuromatrix. Moreover, the direction of the presently observed correlations varied subject to stimulation conditions. While under the less intense fixed pressure condition (2.4 kg) catastrophizing was positively associated with the CBF response (early and decrease components in the left hemisphere), under the more intense equal subjective intensity condition (average, 3.5 kg) the correlations were negative (decrease and late increase components in the right hemisphere). The latter associations were also confirmed by regression analysis. The dependence of the association on stimulus intensity suggests that different psychophysiological mechanisms may be involved therein. The positive correlation during less intense stimulation is likely to reflect enhanced nociceptive processing in high levels of catastrophizing, which was previously observed in FMS patients (Graceley et al., 2004; Gracely & Ambrose, 2011). In contrast, the negative associations between the CBF response and catastrophizing during stronger stimulation may be interpreted in the context of the defense reflex (Sokolov, 1963). The defense reflex is assumed to limit neural activation during acute painful stimulation, restricting sensorial processing of aversive stimuli; it only occurs if stimulus intensity exceeds a critical intensity (Cook & Turpin, 1997; Sokolov, 1963; Turpin, 1986). This is illustrated by the finding of a lower late CBF response in FMS

patients vs. healthy controls, which was observed during average pressure stimulation of 3.5 kg, but not 2.4 kg (Montoro et al., 2015). The present result supports the view that catastrophizing modulates the occurrence of the defense reflex, where greater catastrophizing is accompanied by stronger inhibition of the neural pain response during relatively strong painful stimulation. The pattern of association between depression and blood flow modulations may be interpreted in the same manner. Under the less intense fixed pressure, depression correlated positively with the MCA response (early increase and decrease components in the left hemisphere), whereas correlations were negative under the stronger equal subjective pain condition (late increase component in the right hemisphere). The positive association for the fixed pressure condition (early increase in the left hemisphere) also arose in the regression analysis. While during lower stimulus intensity, patients with higher levels of depression exhibited enhanced nociceptive processing, during more intense stimulation higher depression is accompanied by stronger antinociceptive effects, presumably due to activation of the defense reflex.

The finding regarding insomnia did not meet our expectations. Instead of the predicted positive correlation between insomnia and CBF responses, correlation and regression analyses revealed an inverse association between insomnia and the anticipatory ACA response component under the fixed pressure condition. As a potential explanation, we should take into account that insomnia and associated symptoms like fatigue, tiredness and loss of vigor may decrease attentional capacity, also including the ability to raise attentional tone during pain anticipation. It has been shown, for example, that sleep deprivation decreases executive attention via a reduction of prefrontal cortex activation (Kane & Engle, 2002). However, it should not be overlooked that the correlation was restricted to the right ACA. While the brain network supporting phasic modulations of attentional tone is ascribed right hemispherical dominance, it is supplied by both the ACA (e.g., anterior cingulate) and MCA (dorsolateral frontal and inferior parietal lobes) (Duschek et al., 2008, 2010; Posner & Petersen, 1990).

As a matter of course, the exploratory design of this study had weaknesses. The main limitation concerns the small sample size, which can compromise statistical power and increases the risk of both type I and type II errors. Furthermore, we computed a high number of correlations, which also increases both type I and II error probability.

Consequently, our results should be considered as preliminary and need to be replicated using larger samples of patients.

In summation, this study lends credence to the notion that alterations in central nervous pain processing in FMS depend on psychological factors. Eysenck´s personality dimensions, and catastrophizing, alexithymia and depression, intuitively appear to be potentially relevant variables. In contrast to our expectations, the effects of these variables were not restricted to the processing of the affective and cognitive pain components in the medial neuromatrix, but in several cases they were even more evident for sensory pain processing in the lateral neuromatrix. Moreover, the direction of the associations varied according to stimulation intensity, where the defense reflex may be implicated in mediating these associations in addition to linear increases in nociceptive processing commensurate with the magnitude of negative cognitive and emotional states.

References

Affleck, G., Tennen, H., Urrows, S., & Higgins, P. (1992). Neuroticism and the pain mood relation in rheumatoid arthritis: Insights from a prospective daily study. *Journal of Consulting and Clinical Psychology, 60,* 119-126.

Affleck, G., Urrows, S., Tennen, H., Higgins, P., & Abeles, M. (1996). Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia. *Pain, 68,* 363-368.

Andersen, M.C., & Green, C. (2001). Suppressing unwanted memories by executive control. *Nature, 410,* 366–369.

Apkarian, A.V., Bushnell, M.C., Treede, R.D., & Zubieta, J.K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain,* 9, 463-484.

Asghari, A., & Nicholas, M.K. (2006). Personality and pain-related beliefs/coping strategies: a prospective study. *Clinical Journal of Pain, 22,* 10-18.

Bagby, R.M., Parker, J.D.A., & Taylor, G.L. (1994). The twenty-item Toronto Alexithymia Scale: I. Item selection and cross-validation of the factor structure. *Journal of Psychosomatic Research, 38,* 23-32

Ballina, G.F.J., Martín, L.P., Iglesias, G.A., Hernández, M.R., & Cueto, E.A. (1995). La fibromialgia. Revisión clínica. *Revista Clínica Española, 195,* 326-334.

Beales, D.L., & Dolton, R. (2000). Eating disordered patients: Personality, alexithymia, and implications for primary care. *British Journal of General Practice, 50,* 21–26

Beck, A.T., Ward, C., & Mendelson, M. (1961). Beck depression inventory (BDI). *Archives General Psychiatry, 4,* 561-571.

Besteiro, J., Álvarez, M., Lemos, S., Muñiz, J., Costas, C., & Weruaga, A. (2008). Dimensiones de personalidad, sentido de coherencia y salud percibida en pacientes con un Síndrome Fibromiálgico. *International Journal of Clinical and Health Psychology, 8*, 411-427.

Bigatti, S.M., Hernandez, A.M., Cronan, T.A., & Rand, K.L. (2008). Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. *Arthritis Care & Research, 59*, 961-967.

Bobes, J., González, M.P., Sáiz, P.A., Bascarán, M.T., Iglesias, C., & Fernández, J.M. (2000). Propiedades psicométricas del cuestionario Oviedo de Sueño. *Psicothema, 1*, 107-112.

Burgmer, M.., Petzke, F., Giesecke, T, Gaubitz, M., Heuft, G., & Pfleiderer, B. (2011). Cerebral activation and catastrophizing during pain Anticipation in patients with fibromyalgia. *Psychosomatic Medicine, 73*, 751-759.

Burgmer, M., Pogatzki-Zahn, E., Gaubitz, M., Wessoleck, E., Heuft, G., & Pfleiderer, B. (2009). Altered brain activity during pain processing in fibromyalgia. *NeuroImage, 44*, 502-508.

Carrillo, J.M., Collado, S., & Rojo, N. (2005). Personality and pain tolerance. *Clínica y Salud, 16*, 223-236.

Castelli, L., Tesio, V., Colonna, F., Molinaro, S., Leombruni, P., Bruzzone, M., ... & Torta, R. (2012). Alexithymia and psychological distress in fibromyalgia: prevalence and relation with quality of life. *Clinical and Experimental Rheumatology, 30*, 70-77.

Clauw, D. J. (2014). Fibromyalgia: a clinical review. *Jama*, *311*, 1547-1555.

Clauw, D., & Crofford. (2003). Chronic widespread pain and fibromyalgia: what we know, and what we need to know. *Research Clinical Rheumatology*, *4*, 685-701.

Cook, E.III., & Turpin, G. (1997). Differentiating orienting, startle, and defense responses: The role of affect and its implications for psychopathology. In P J Lang, R F Simons, & M Balaban, Attention and orienting: Sensory and motivational processes. New York: Psychology Press.

Davis, M.C., Zautra, A.J., & Reich, J.W. (2001). Vulnerability to stress among women in chronic pain from fibromyalgia and osteoarthritis. *Annals of Behavioral Medicine, 23*, 215-226.

De Souza, J.B., Potvin, S., Goffaux, P., Charest, J., & Marchand, S. (2009) The deficit of pain inhibition in fibromyalgia is more pronounced in patients with comorbid depressive symptoms. *Clinical Journal of Pain, 25*, 123–127.

Deary, I.J., Scott, S., & Wilson, J.A. (1997). Neuroticism, alexithymia and medically unexplained symptoms. *Personality and Individual Differences*, *22*, 551-564.

Devinsky, O., Morrell, M.J., & Vogt, B.A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain, 118*, 279–306.

Duschek, S., Schuepbach, D. & Schandry, R. (2008). Time-locked association between rapid cerebral blood flow modulation and attentional performance. *Clinical Neurophysiology, 119*, 1292-1299.

Duschek, S., Heiss, H., Schmidt, F.H., Werner, N. & Schuepbach, D. (2010). Interactions between systemic hemodynamics and cerebral blood flow during attentional processing. *Psychophysiology, 47*, 1159-1166.

Duschek, S., Hellmann, N., Merzoug, K., Reyes del Paso, G.A., & Werner, N.S. (2012). Cerebral blood flow dynamics during pain processing investigated by functional transcranial Doppler sonography. *Pain Medicine, 13*, 419-426.

Duschek, S., Mannhart, T., Winkelmann, A., Merzoug, K., Werner, N.S., Schuepbach, D., & Montoya, P. (2012). Cerebral blood flow dynamics during pain processing in patients with fibromyalgia syndrome. *Psychosomatic Medicine, 74*, 802-809.

Duschek, S., & Schandry, R. (2003). Functional transcranial Doppler sonography as a tool in psychophysiological research. *Psychophysiology, 40,* 436-454.

Duschek, S., Werner, N.S., Limbert, N. Winkelmann A. & Montoya, P. (2014). Attentional bias towards negative information in patients with fibromyalgia syndrome. *Pain Medicine, 15,* 603-612.

Edwards, R.R., Bingham, C.O. III., Bathon, J., & Haythornthwaite, J.A. (2006). Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. *Arthritis & Rheumatology, 55,* 325-332.

Eisenberger, N.I. (2012). The neural bases of social pain: evidence for shared representations with physical pain. *Psychosomatic Medicine, 74,* 126–135.

Eisenberger, N.I, & Lieberman, M.D. (2004). Why rejection hurts: a common neural alarm system for physical and social pain. *Trends in Cognitive Science, 8,* 294–300

Epstein, S.A., Kay, G., Clauw, D., Heaton, R., Klein, D., Krupp, L., Kuck, J., Leslie, V., Masur, D., Wagner., M., Waid, R., & Zisook. (1999). Psychiatric disorders in patients with Fibromyalgia: a multicenter investigation. *Psychosomatics, 1*, 57–63.

Eysenck, H.J. (1967). The Biological Basis of Personality. Springfield, Ill, Charles C Thomas.

Eysenck, H.J. (1995). *Genius: The natural history of creativity* (Vol. 12). Cambridge University Press.

Eysenck, H. J. (2013). Neuroticism and Psychoticism. *Individual Differences and Psychopathology: Physiological Correlates of Human Behaviour*, *3*, 13.

Francis, L.J., Brown, L.B., & Philipchalk, R. (1992). The development of an abbreviated form of the Revised Eysenck Personality Questionnaire (EPQR-A):

Its use among students in England, Ganada, the U.S.A and Australia. *Personality and Individual Differences, 13*, 443-449.

Geisser, M.E., Casey, K.L., Brucksch, C.B., Ribbens, C.M., Appleton, B.B., & Crofford, L.J. (2003). Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia: association with mood, somatic focus, and catastrophizing. *Pain, 102*, 243-250.

Geisser, M.E., & Roth, R.S. (1998). Knowledge of and agreement with pain diagnosis: relation to pain beliefs, pain severity, disability, and psychological distress. *Journal of Occupational Rehabilitation, 8*, 73-88.

Giesecke, T., Gracely, R.H., Williams, D.A., Geisser, M.E., Petzke, F.W., & Clauw, D.J. *(2005).* The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. *Arthritis Rheumatology, 52,* 1577–*158*4

Godinho, F., Magnin, M., Frot, M., Perchet, C., & Garcia-Larrea, L. (2006). Emotional modulation of pain: is it the sensation or what we recall? *Journal of Neuroscience, 26*, 11454–11461.

Grabe, H.J., Rainermann, S., Spitzer, C., Gänsicke, M., & Freyberger, H.J. (2000). The relationship between dimensions of alexithymia and dissociation. *Psychotherapy and Psychosomatics, 69*, 128-131.

Gracely, R.H., & Ambrose, K.R. (2011). Neuroimaging of fibromyalgia. *Best practice & research Clinical rheumatology, 25,* 271-284.

Gracely, R.H., Geisser, M.E., Giesecke, T., Grant, M.A.B., Petzke, F., Williams, D.A., & Clauw, D.J. (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain, 127*, 835-843.

Gracely, R.H., Petzke, F., Wolf, J.M., & Clauw, D.J. (2002) Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheumatology 46*, 1333-1343

Gray, J.A. (1970). The psychophysiological basis of introversion-extraversion. *Behavior Research and Therapy, 8*, 249–266

Gupta, A., Silman, A.J., Ray, D., Morriss, R., Dickens, C., MacFarlane, G.J., ... & McBeth, J. (2007). The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. *Rheumatology, 46*, 666-671.

Harkins, S.W., Price, D.D., & Braith, J. (1989). Effects of extraversion and neuroticism on experimental pain, clinical pain, and illness behavior. *Pain, 36*, 209-18.

Hosoi, M., Molton, I., Jensen, M., Ehde, D., Amtmann, S., O'Brien, S., Arimura, T., & Kubo, C. (2010). Relationships among alexithymia and pain intensity, pain interference, and vitality in persons with neuromuscular disease: Considering the effect of negative affectivity. *Pain, 149*, 273-277.

Huber, A., Suman, A.L., Biasi, G., & Carli, G. (2009). Alexithymia in fibromyalgia syndrome: associations with ongoing pain, experimental pain sensitivity and illness behavior. *Journal of Psychosomatic Research, 66*, 425-433.

Jensen, K.B., Kosek, E., Petzke, F., Carville, S., Fransson, P., Marcus, H., Williams, S.C., Choy, E., Giesecke, T., Mainguy, Y., Gracely, R., & Ingvar, M. (2009). Evidence of dysfunctional pain inhibition in fibromyalgia reflected in rACC during provoked pain. *Pain, 144*, 95-100.

Jensen, K.B., Petzke, F., Carville, S., Fransson, P., Marcus, H., Williams, S.C., ... & Kosek, E. (2010). Anxiety and depressive symptoms in fibromyalgia are related to poor perception of health but not to pain sensitivity or cerebral processing of pain. *Arthritis & Rheumatism*, *62*, 3488-3495.

Johnson, D., Wiebe, D., Gold, S., Andreasen, N.C., Hichwa, R., Watkins, L., & Boles-Ponto, L. (1999) Cerebral Blood Flow and Personality: A Positron Emission Tomography Study. *American Psychiatric Association*, *156*, 252-257

Kane, M.J., & Engle, R.W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. *Psychonomic Bulletin & Review*, *9*, 637-671.

Karlsson, H., Näätänen, P., & Stenman, H. (2008). Cortical activation in alexithymia as a response to emotional stimuli. *The British Journal of Psychiatry, 192*, 32-38.

Karsdorp, P.A., & Vlaeyen, J.W. (2009). Active avoidance but not activity pacing is associated with disability in fibromyalgia. *Pain, 147*, 29-35.

Keefe, F.J., Brown, G.K., Wallston, K.A., & Caldwell, D.S. (1989). Coping with rheumatoid arthritis pain: catastrophizing as a maladaptive strategy. *Pain, 37*, 51-56.

Kooiman, C.G., Spinhoven, P., & Trijsburg, R.W. (2002). The assessment of alexithymia – a critical review of the literature and a psychometric study of the Toronto Alexithymia Scale-20. *Journal of Psychosomatic Research, 53*, 1083–1090.

Lane, R.D. (2000). *Neural Correlates of Conscious Emotional Experience*. In: Cognitive Neuroscience of Emotion (eds: RD Lane & L Nadel). New York, Oxford: Oxford University Press, 359–360.

Lane, R.D., Reiman, E.M., Axelrod, B., Yun, L. S., Holmes, A., & Schwartz, G.E. (1998). Neural correlates of levels of emotional awareness: Evidence of an interaction between emotion and attention in the anterior cingulate cortex. *Journal of Cognitive Neuroscience*, *10*, 525-535.

Lipsanen, T., Saarijärvi, S., & Lauerma, H. (2004). Exploring the relations between depression, somatization, dissociation and alexithymia–overlapping or independent constructs?. *Psychopathology*, *37*, 200-206.

Lumley, M.A., Stettner, L., & Wehmer, F. (1996). How are alexithymia and physical illness linked? A review and critique of pathways. *Journal of Psychosomatic Research, 41*, 505–518

Lynn, R., & Eysenck, H.J. (1961). Tolerance for pain, extraversion and neuroticism. *Perceptual and Motor Skills*, *12*, 161-162

Malin, K., & Littlejohn, G. (2012). Neuroticism in young women with Fibromyalgia links to key clinical features. *Pain Research and Treatment, 2012,* 730-741.

Martínez-Sánchez, F. (1996). The Spanish version of the Toronto Alexithymia Scale (TAS-20). *Clínica y Salud, 7,* 19-32

Martínez, M.P., Sánchez, A.I., Miró, E., Lami, M.J., Prados, J., & Morales, A. (2015). Relationships between physical symptoms, emotional distress, and pain appraisal in Fibromyalgia: the moderator effect of alexithymia. *The Journal of Psychology: Interdisciplinary and Applied*, *149*, 115-140.

Martínez, M.P., Sánchez, A.I, Miró, E., Medina, A., & Lami, A. (2011). The relationship between the fear-avoidance model of pain and personality traits in Fibromyalgia patients. *Journal of Clinical Psychology in Medical Settings, 4*, 380-391.

Meerwijk, E.L., Ford, J.M., & Weiss, S.J. (2013). Brain regions associated with psychological pain: implications for a neural network and its relationship to physical pain. *Brain Imaging and Behavior, 7*, 1–14.

Melzack, R., & Loeser, J.D. (1978). Phantom body pain in paraplegics: evidence for a central “pattern generating mechanism” for pain. *Pain, 4*, 195–210

Montoro, C.I., Duschek, S., Muñoz, C., & Reyes del Paso, G. (2015). Patterns of cerebral blood flow modulation during painful stimulation in fibromyalgia: a transcranial Doppler sonography study. *Submitted.*

Montoro, C.I., & Reyes del Paso. (2015). Personality and fibromyalgia: Relationships with clinical, emotional, and functional variables. *Personality and Individual Differences, 85*, 236-244.

Montoya, P., Sitges, C., Garcia-Herrera, M., Izquierdo, R., Truyols, M., Blay, N., & Collado, D. (2005). Abnormal affective modulation of somatosensory brain processing among patients with fibromyalgia. *Psychosomatic Medicine, 67*, 957-963.

Nemiah, J.C., Sifneos, P.E., & Apfel-Savitz, R. (1977). A comparison of the oxygen consumption of normal and alexithymic subjects in response to affect provoking thoughts. *Psychotherapy and Psychosomatics, 28*, 167–171.

Ormel, J., Bastiaansen, A., Riese, H., Bos, E., Servaas, M., Ellenbogen, M., Rosmalen, J., & Aleman, E. (2013). The biological and psychological basis of neuroticism: Current status and future directions. *Neuroscience & Biobehavioral Reviews, 37*, 59-72.

Pilowsky, I., & Katsikitis, M. (1994). A classification of illness behavior in pain clinic patients. *Pain, 57*, 91–94.

Ploghaus, A., Narain, C., Beckmann, C.F., Clare, S., Bantick, S., Wise, R., ... & Tracey, I. (2001). Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *The Journal of Neuroscience, 21*, 9896-9903.

Posner, M.I, & Petersen, S.E. (1990). The attention system of the human brain. *Annual Review Neuroscience, 13*, 25-42

Pujol, J., López-Solà, M., & Ortiz, H. (2009). Mapping brain response to pain in fibromyalgia using temporal analysis of fMRI. *PLoS ONE, 4*, e5224.

Ramírez, C., Esteve, R., & López, A.E. (2001). Neuroticismo, afrontamiento y dolor crónico. *Anales de psicología, 17*, 129-137.

Rodríguez, L., Cano, E.J., & Blanco, A. (2004). Evaluación de las estrategias de afrontamiento de dolor crónico. *Actas Españolas de Psiquiatría, 32*, 82-91.

Rosenstiel, A.K., & Keefe, F. J. (1983). The use of coping strategies in chronic low back pain patients: Relationship to patient characteristics and current adjustment. *Pain, 17*, 33-44

Sandín, B., Valiente, R.M., Olmedo, M., Chorot, P. & Santed, M.A. (2002). Versión Española del EPQR-A (I). Análisis exploratorio de la estructura factorial. *Revista de Psicopatología y Psicología Clínica, 7*, 195-205.

Sanz, J., Navarro, M.E., & Vázquez, C. (2003). Adaptación española del Inventario para la Depresión de Beck-II (BDI-II): I. Propiedades psicométricas en estudiantes universitarios. *Análisis y Modificación de Conducta, 29*, 239-288.

Sifneos, P.E. (1973). The prevalence of ‘‘alexithymic’’ characteristic mechanisms in psychosomatic patients. *Psychotherapy and Psychosomatics, 21*, 133-136.

Sokolov, E.N. (1963). *Perception and the conditioned reflex*. Oxfrod: Pergamon.

Steinweg, D.L., Dallas, A.P., & Rea, W.S. (2011). Fibromyalgia: unspeakable suffering, a prevalence study of alexithymia. *Psychosomatics, 52*, 255-262.

Stenberg, G., Risberg, J., & Warkentin, S. (1990). Rosen I: Regional patterns of cortical blood flow distinguish extraverts from introverts. *Personality and Individual Differences, 11*, 663–673

Sullivan, M.J., Thorn, B., Haythornthwaite, J.A., Keefe, F., Martin, M., Bradley, L.A., & Lefebvre, J.C. (2001). Theoretical perspectives on the relation between catastrophizing and pain. *The Clinical Journal of Pain*, *17*, 52-64.

Taylor, G., & Bagby, M. (1997). *Affect dysregulation and alexithymia*. In: Taylor G, Bagby RM, Parker JDA, eds. Disorders of affect regulation. Cambridge University Press; 1997:26.

Taylor, G.J., Parker, J.D.A., Bagby, M.A., & Acklin, M.W. (1992). Alexithymia and somatic complaints in psychiatric outpatients. *Journal of Psychosomatic Research, 36*, 417–424.

Turpin, G. (1986). Effects of stimulus intensity on autonomic responding: the problem of differentiating orienting and defense reflexes. *Psychophysiology, 23*, 1-14.

Van Middendorp, H., Lumley, M.A., Jacobs, J.W., van Doornen, L.J., Bijlsma, J.W., & Geenen, R. (2008). Emotions and emotional approach and avoidance strategies in fibromyalgia. *Journal of Psychosomatic Research, 64*, 159-167.

Van Wilgen, C.P., van Ittersum, M.W., Kaptein, A.A., & van Wijhe, M. (2008). Illness perceptions in patients with fibromyalgia and their relationship to quality of life and catastrophizing. *Arthritis Rheumatology, 58*, 3618-3626.

Weiß, S. Winkelmann, A. & Duschek, S. (2013). Recognition of facially expressed emotions in patients with fibromyalgia syndrome. *Behavioral Medicine, 39*, 146-154.

Wise, T.N., & Mann, L.S. (1994). The relationship between somatosensory amplification, alexithymia and neuroticism. *Journal of Psychosomatic Research, 38*, 515-521.

Wolfe, F., Clauw, D.J., Fitzcharles, M.A., Goldenberg, D.L., Katz, R.S., Mease, P., …& Yunus, M.B. (2010). The American College of Rheumatology preliminary diagnostic criteria for Fibromyalgia and measurement of symptom severity. *Arthritis Care & Research, 62*, 600–610.

Wolfe, F., Ross, K., Anderson, J., Russell, I.J., & Hebert L. (1995). The prevalence and characteristics of fibromyalgia in the general population. *Arthritis and Rheumatism, 38,* 19-28.

Wolfe, F., Smythe, H.A., Yunus, M.B., Bennett, R.M., Bombardier, C., Goldenberg, D.L., …& Sheon, R.P. (1990). The American College of Rheumatology 1990 criteria for the classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis and Rheumatism, 33,* 160-172.

Woody, E., & Clarige, G. (2011). Psychoticism and thinking. *British Journal of Social and Clinical Psychology, 16,* 241–248.

Yunus, M.B. (2007). Fibromyalgia and overlapping disorders: The unifying concept of central sensitivity syndromes. *Seminars in Arthritis and Rheumatism, 36,* 339-356.

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Personality and fibromyalgia: Relationships with clinical, emotional, and functional variables

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ABSTRACT

This study evaluates H.J. Eysenck's three personality dimensions (neuroticism, extraversion, and psychoticism) in patients with fibromyalgia (FMS) compared with healthy controls (HC), and analyzes their association with clinical, emotional and functional variables and pain coping strategies. Ninety-two FMS patients and 65 HC completed the abbreviated EPQR, in addition to instruments measuring clinical pain, fatigue, sleep, anxiety, depression, health related quality of live (HRQL) and pain coping strategies. Results showed: (1) FMS patients exhibited greater levels of neuroticism and psychoticism but not extroversion, in comparison with HC; (2) group differences in all measured variables remained when the three personality dimensions were entered as covariates; (3) while in HC neuroticism was positively associated with pain, anxiety, depression, catastrophizing strategy scores, and lower HRQL, in FMS patients associations were sparse and lower in magnitude; (4) in FMS patients extroversion was associated with lower pain, anxiety, and depression, and higher mental HRQL; and (5) psychoticism was associated with lower anxiety in the FMS group and greater catastrophizing in HC. Data suggest that neuroticism only plays a minor role in clinical manifestations of FMS. However, extraversion appears to exert a protective influence in FMS, as it is associated with better health outcomes in several domains.

1. Introduction

Fibromyalgia syndrome (FMS), a chronic disorder characterized by persistent and widespread musculoskeletal pain, affects 2–4% of the general population (Wolfe, Ross, Anderson, Russell, & Hebert, 1995; Wolfe et al., 1990). FMS occurs predominately in females, affecting approximately 3.4% of women and 0.5% of men (Wolfe et al., 1990). In addition to pain, FMS is characterized by a heterogeneous range of symptoms such as fatigue, insomnia, morning stiffness, mild cognitive impairment, migraine and irritable bowel syndrome, among others (Wolfe et al., 2010; Yunus, 2007). FMS is also associated with a high prevalence of anxiety and mood disorders (e.g. Fietta, Fietta, & Manganelli, 2007; Reyes del Paso, Pulgar, Duschek, & Garrido, 2012; Van Middendorp et al., 2008). The etiology and pathophysiology of FMS are currently unknown and there are no specific somatic signs of disease, which appears to involve abnormal central pain processing and inhibition of central anti-nociceptive inhibitory mechanisms (i.e. central pain sensitization), resulting in diffuse hyperalgesia and allodynia (Loggia et al., 2014).

Pain is a multidimensional phenomenon affected by attentional, emotional and cognitive factors, in addition to prior experience (McMahon & Wall, 2006). Psychological factors (depression, anxiety, coping, self-efficacy, social support, etc.) can play a significant role in the development and maintenance of chronic pain, as well as in the severity of reported symptoms and complaints (Martínez, Sánchez, Miró, Medina, & Lami, 2011; McMahon & Wall, 2006). Affective measures are associated with clinical pain reports (Petzke, Gracely, Park, Ambrose, & Clauw, 2003). Pain increases negative emotional states and psychological distress, which in turn may engender subsequent increases in pain (Loggia, Mogil, & Bushnell, 2008; Martínez et al., 2011). Cognitive variables, such as catastrophizing, are relevant to the development and maintenance of this vicious circle of chronic pain (Keefe, Rumble, Scipio, Giordano, & Perri, 2004). For example, greater catastrophizing is associated with increased pain and pain-related disability in FMS (Geisser & Roth, 1998; Geisser et al., 2003) as well with increased activation of brain areas associated with pain processing (Gracely et al., 2004). Lower self-esteem levels in FMS patients also appear to modulate the use of non-adaptive pain and stress copying strategies (Dysvik, Natvig, Eikeland, & Lindstrom, 2005).

One variable that may modulate psychosocial factors affecting pain experience is personality. Through several mediating mechanisms (propensity of specific emotional states, sensitivity–

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reactivity, coping strategies, life style, interpersonal and social relationships, etc.), personality can significantly influence how pain is experienced and evaluated, how we react to and experience it, the adjustment process to a chronic illness, the use of medication and medical services, adherence and compliance with professional prescriptions, etc. (Affleck, Tennen, Urrows, & Higgins, 1992; Asghari & Nicholas, 2006; Ramírez, Esteve, & López, 2001). FMS has been associated with extreme personality traits (Anderberg, Forsgren, Ekselius, Marteinsdottir, & Hallman, 1999; Kendall, Elert, Ekselius, & Gerdle, 2002; Pérez-Pareja, Sesé, González-Ordi, & Palmer, 2010), with patients described as perfectionists (Ayats, Martín, & Soler, 2006; Herken, Gursoy, Yetkin, Virit, & Esgi, 2001), exhibiting emotional dependence (Cerón, Centelles, Abellana, & García, 2010), unrealistically high expectations of themselves and people around them (Gursoy, Erdal, Herken, Madenci, & Alasehirli, 2001; Herken et al., 2001), tendencies toward somatization (Gursoy et al., 2001), introspection, pessimism regarding the future (Kendall et al., 2002), high levels of demanding behavior (Amir et al., 2000), exasperating (Asbring & Narvanen, 2003), harm avoidance (Glazer, Buskila, Cohen, Ebstein, & Neumann, 2010), etc. Overall, it appears that the FMS-type personality is associated with greater psychological vulnerability (Hallberg & Carlsson, 1998; Hassett, Cone, Patella, & Sigal, 2000).

One of the most well-known and empirically supported personality theories is that of H. J. Eysenck (Eysenck & Eysenck, 1985), which includes three broad dimensions of personality, namely neuroticism (N), extraversion (E) and psychoticism (P), measured with the Eysenck Personality Questionnaire (EPQ). N (a stable tendency toward the experience of negative emotions, physiological hyperreactivity, greater physical and mental fatigability, higher distress in response to environmental stressors, etc.) represents a personality trait of great public health significance, because it is associated with numerous comorbid mental and physical disorders, in addition to increased use of mental and general health services, and impaired life quality and longevity among other outcomes (Lahey, 2009). Chronic pain patients who score high on N tend to experience more intensely and catastrophically their symptoms and negative emotions (Affleck et al., 1992; Montoya, Pauli, Batra, & Wiederman, 2005), and showed a reduced ability to tolerate discomfort (Costa, 1987; Harkins, Price, & Braith, 1989). High levels of N may also be associated with pain catastrophizing and a more passive-oriented stress and pain coping strategies (Asghari & Nicholas, 2006; Martínez et al., 2011; Ramírez et al., 2001). In turn, passive coping strategies predict higher perceived pain intensity (Affleck et al., 1992; Bolger, 1990). High N is also associated with lower scores for health-related quality of life (HRQL) (McCain, 1996). Furthermore, N, along with E, is associated with autonomic nervous system responses to pain (Paine, Kishor, Worthen, Gregory, & Aziz, 2009).

High N has been widely implicated as a potential mechanism underlying chronic pain diseases, including FMS. High N scores in FMS patients, in comparison to healthy controls, have been reported previously (Asghari & Nicholas, 1999; Besteiro et al., 2008; Netter & Hennig, 1998; Malt, Olafsson, Lund, & UrsIn, 2002). However, the relationship between N and FMS symptoms is not clear. Some studies have found associations between N and pain anxiety and severity, depression, stress, anxiety, sleep disturbance, fatigue and confusion in FMS patients (Malin & Littlejohn, 2012a; Martínez et al., 2011), although other studies reported no such associations (e.g. Albertsen, Olafsson, Lund, & Ursin, 2002; Zautra et al., 2005).

Regarding E (higher activity, dynamism, positive emotionality, interest in the outside world, sociability, etc.), chronic pain patients scoring highly on this dimension have higher pain thresholds and tolerance compared with introverts (Eysenck, 1967). Therefore, E might represent a protective factor against pain (Ramírez & Valdivia, 2003) and may also affect selective attention toward it (Eysenck, 1967). Reduced levels of E have been reported in FMS patients (Ayats et al., 2006; Besteiro et al., 2008; Glazer et al., 2010; Kersh et al., 2001; Malin & Littlejohn, 2012b; Zautra et al., 2005). N and E are considered as the two most salient factors differentiating FMS and healthy control patient personality types (see Malin & Littlejohn, 2012b for a review).

Finally, regarding P (tough mindedness, impulsivity, aggressiveness, egocentrism, irresponsibility, emotional detachment or low empathy, anti-sociability, impersonality, and creativity; Eysenck & Eysenck, 1985), to the best of our knowledge, no studies have specifically assessed this dimension in the context of FMS, although some reports suggests higher levels of P in FMS patients relative to healthy controls (e.g. Banic et al., 2004).

The study of personality traits in FMS may currently be of heightened relevance due to newly proposed criteria for FMS diagnosis, based on the use of two self-report scales measuring widespread pain (Widespread Pain Index Scale) and symptom severity (Symptom Severity Scale) (Wolfe et al., 2010). Self-reported scales can be affected by a negative affectivity component that may artificially inflate the reportage of somatic symptoms (Watson & Pennebaker, 1989), such that individuals with high negative affectivity or N usually report greater levels of somatic symptoms (Lahey, 2009; Watson & Pennebaker, 1989).

In this study we evaluate differences in H. J. Eysenck's three personality dimensions between FMS patients and a healthy control group, and assess each dimension's association with (a) clinical (pain, fatigue, sleep), (b) emotional (anxiety and depression), (c) and functional (HRQL and impact of disease) variables, in addition to (d) pain-coping strategies. Finally, we also evaluate the association between personality, comorbid emotional disorders (depression and anxiety) and medication use. In accordance with the studies reviewed above we anticipate that: (1) FMS will exhibit higher levels of N and lower levels of E compared to healthy participants; (2) high N will be associated with more severe clinical symptoms, anxiety, and depression, a greater impact of illness on HRQL and the use of passive, non-adaptive coping strategies; and (3) high E will be associated with less clinical symptoms, lower anxiety and depression levels, higher scores on HRQL and a lower impact of illness, and the use of more active-adaptive coping strategies. We have no clear expectations regarding P, although given the observations of Banic et al. (2004), higher scores on this dimension may occur in FMS patients. Finally, the relative magnitude of associations between personality dimensions and measured outcomes in each group will be additionally compared. In analyzing the association between personality (especially N) and clinical outcomes in FMS, it is necessary to take into account the fact that the disability and clinical manifestations associated with a debilitating illness such as FMS may also negatively affect certain clinical outcomes, and probably surpass the modifying influence of personality characteristics. Given the relevance of the negative influence of the disability associated with FMS, we expected that associations (especially concerning N due to its expected negative influence) would be of lower magnitude in FMS patients than in healthy participants.

2. Method

2.1. Participants

Eighty-nine women and three men diagnosed with FMS, recruited via the Fibromyalgia Association of Jaén, participated in the study. All patients were examined by a rheumatologist and met the American College of Rheumatology criteria for FMS

(Wolfe et al., 1990). Exclusionary criteria comprised cardiovascular diseases of any kind, metabolic abnormalities, inflammatory causes of pain, neurological disorders, and severe somatic (e.g., cancer) or psychiatric (e.g. psychotic or bipolar) diseases. The control group included 63 healthy women and 2 men, who were recruited via women's associations and family relatives. Controls were matched to patients according to age, body mass index and educational level. In addition to not having any kind of pain disorder, the control group was subject to the same exclusionary criteria as were the patients. Table 1 displays the demographic and clinical data of both groups.

2.2. Psychological measures

In addition to a semi-structured interview assessing clinical history and demographic data, participants were evaluated with the Structured Clinical Interview for Axis I Disorders of the Diagnostic and Statistical Manual for Mental Disorders (SCID, First, Spitzer, Gibbon, & Williams, 1999), in order to detect possible mental disorders. Self-reported questionnaires are delineated below:

- *Spanish Adaptation of the Eysenck Personality Questionnaire Revised-Abbreviated (EPQR-A) Questionnaire:* This scale was developed by Francis, Brown, and Philipchalk (1992), and translated into Spanish by Sandín, Valiente, Chorot, Olmedo, and Santed (2002). It consists of 24 items spread among four subscales (6 items each): N, E, P and social desirability (sincerity). Scores range between 0 and 6 on all subscales (answer format = YES/NO). Due to its relative brevity, this questionnaire is particularly suited for use in clinical settings and correlates adequately with its predecessor, the EPQ. Internal consistency (Cronbach's α) is 0.74 for N, 0.78 for E, 0.63 for P and 0.54 for the sincerity scale.
- *State-Trait Anxiety Inventory (STAI):* It consists of 40 items scored using Likert scales of four response alternatives (score range: 0–60, for both state and trait anxiety). The internal consistency of the Spanish version ranges between 0.90 and 0.93 for state anxiety and between 0.84 and 0.87 for trait anxiety (Spielberger, Gorsuch, & Lushene, 1982).
- *Beck Depression Inventory (BDI):* Spanish adaptation by Sanz, Navarro, and Vázquez (2003). The BDI consists of 21 items rated on 4-point Likert scales according to symptom severity (score range: 0–63). The internal consistency of the Spanish version ranges between 0.76 and 0.95.
- *Fisk Fatigue Severity Score (FFSS):* Developed by Krupp, LaRocca, Muir-Nash, and Steinberg (1989) and adapted to Spanish samples by Bulbena, Berrios, and Fernández de Larrinoa (2000). It consists of nine items, the summation of which provides an overall fatigue score (score range: 9–63). The internal consistency of the FFSS is 0.88.
- *Short-From Health Survey (SF-36) (Ware & Sherbourne, 1992):* Spanish adaptation by Alonso, Prieto, and Antó (1995): The SF-36 is widely used to measure HRQL and consists of 36 items spread among eight domains of functioning (physical functioning, physical role, body pain, general health, vitality, social functioning, emotional role and mental health). Higher scores indicate higher well-being and less interference by the illness. The Cronbach's α values of the different scales range between 0.7 and 0.94. Using the above subscales, two general HRQL indices were obtained: a physical (score range: 25–99) and mental (score range: 10–46) component.
- *Coping Strategies Questionnaire (Rosenstiel & Keefe, 1983)*: Spanish adaptation by Rodriguez, Cano, and Blanco (2004). This is a 39-item, self-administered questionnaire that consists of eight scales that measure the frequency of use of both adaptive (auto-instructions, cognitive distraction, diversion of attention, reinterpreting pain sensations, ignoring pain sensations, and hope) and maladaptive pain coping strategies (catastrophizing and faith). Cronbach's α values range between 0.68 (ignoring pain) to 0.89 (catastrophizing). In order to simplify the presentation of results, only the scales in which significant results were observed will be reported: catastrophizing (score range: 0–36), cognitive distraction (score range: 0–36), and ignoring pain sensations (score range: 0–42).
- *McGill Pain Questionnaire:* Spanish adaptation by Lázaro, Bosch, Torrubia, and Baños (1994). This instrument reliably measures sensory, affective and evaluative characteristics of pain. The following parameters were obtained: total pain index (TPI), given by the sum of sensory, affective and evaluative pain descriptors (score range: 19–66); and the current pain intensity index (CPI), which represents an indicator of current pain intensity (score range: 0–5). Cronbach's α internal consistency values ranged between 0.56 (affective pain descriptor) and 0.74 (TPI).
- *Fibromyalgia Impact Questionnaire (FIQ)*: Spanish adaptation by Esteve-Vives, Rivera, Salvat, de Gracia, and Alegre (2007). The FIQ is a multidimensional, self-administered questionnaire that evaluates functional domains affected in FMS patients. It consists of 10 items (the first of which is further divided into several sub-items) with total scores ranging between 0 and 100; lower scores indicate greater functional capacity and quality of life. The internal consistency of the overall score is 0.82.
- *Oviedo Quality of Sleep Questionnaire (OQSQ, Bobes et al., 2000):* Completed during interview, the OQSQ possesses 15 items scored on a 5-point Likert scale (except for item 1, [subjective sleep satisfaction], which is rated according to a 7-point scale). The internal consistency of the questionnaire is 0.77. Sleep satisfaction (score range: 1–7), insomnia (score range: 9–45), and hypersomnia (score range: 3–15) indices were taken from the OQSQ.

Table 1
Demographic and clinical data (mean ± SD) and medications use (number of participants and percentage in brackets) in the FMS and control groups. Results of group comparisons were also reported (Student's *t*-test or χ^2).

Demographic and clinical data	Fibromyalgia	Control group	*t* or χ^2	*p*
Age	51.55 ± 8.12	49.92 ± 8.61	1.46	.228
Body mass index	28.03 ± 4.68	26.78 ± 5.44	2.37	.126
Years of education	9.12 ± 4.60	10.25 ± 4.79	2.21	.139
Depression (%)	42 (47.2)	5 (7.9)	26.61	<.0001
Anxiety disorders (%)	37 (41.6)	9 (14.3)	13.02	<.0001
Antidepressant use (%)	49 (53.8)	2 (3.1)	44.41	<.0001
Anxiolytic use (%)	56 (61.5)	13 (20)	26.52	<.0001
Analgesic use (%)	66 (72.5)	6 (9.2)	61.13	<.0001
Opiate use (%)	36 (39.6)	0 (0)	33.43	<.0001

2.3. Procedure

The study was conducted across two sessions. In the first session a clinical psychologist recorded patients' clinical histories, medication use, and socio-demographic data, and confirmed that there were no violations of the exclusionary criteria. The SCID, McGill Pain Questionnaire, BDI and OQSQ questionnaires were subsequently administered via individual interviews. During administration of the McGill Questionnaire to the control group, participants were asked to refer to possible sporadic pains, or the corporal area in which they usually felt some discomfort. In the second session the remaining standardized self-report questionnaires (EPQR-A, CSQ, FFSS, STAI, SF-36, and FIQ-completed only

by FMS patients) were administered during group sessions. All participants provided informed consent. The study protocol was approved by the Bioethics Committee of the University of Jaén. None of the participants were excluded on the basis of low sincerity values on the EPQR-A.

2.4. Statistical analysis

The groups were compared on all measured variables by multivariate analysis of variance (MANOVA). In a second MANOVA model, the three personality dimensions were included as covariates. Comparisons within the FMS group, between patients taking or not taking each medication type, and patients suffering or not suffering from depression or anxiety disorders, were performed using ANOVAs. Adjusted squared theta (η^2) was used as effect size indicator. Analysis of the relationship between personality and the remaining variables was performed in the first instance using Pearson correlations, followed by multiple regression analysis. The three personality dimensions were entered simultaneously as predictors; clinical, emotional, functional, and coping features of FMS (in a separate analysis), were the dependent variables. Group differences in correlation coefficients were tested for significance using Fisher's Z statistic. N was asymmetrically (negatively) distributed; in order to avoid possible ceiling effects in the associative analyses it was subjected to an x^2 transformation. To avoid spurious effect arising from large expected group differences in the measured variables, analyses were performed separately for each group. Significance was set at $p \leqslant .05$.

3. Results

3.1. Group differences

The results of MANOVA revealed a main effect of Group ($F(23,133) = 28.19$, $p < .0001$, $\eta^2 = .830$). Table 2 displays means (±SD) and statistics for group comparisons of each variable. N and P scores were greater in FMS patients than in controls (with greater effect size for N than for P). No group difference was found in E. Regarding coping strategies, catastrophizing was greater in patients than in controls, while "ignoring pain sensations" scores were higher in controls. As expected, state-trait anxiety, fatigue, depression, insomnia, hypersomnia and pain scores were higher in FMS patients than in healthy controls. Finally, FMS patients exhibited lower levels of HRQL compared with healthy participants in the two SF-36 indexes. When N, E, and P were entered into the analysis as covariates, all of these group differences remained (at $p < .001$).

Table 2
Means (±SD) of the measured variables as a function of group. The results of group comparisons are also displayed.

		Fibromyalgia	Healthy group	F	p	η^2
EPQR-A	N	4.72 ± 1.33	2.65 ± 1.71	72.96	<.001	.320
	E	3.52 ± 1.66	3.82 ± 1.40	1.49	.224	.010
	P	2.34 ± .99	1.94 ± 1.18	5.26	.023	.033
McGill	TPI	52.92 ± 23.98	16.11 ± 12.30	129.03	<.001	.454
	CPI	3.44 ± .97	1.28 ± .97	187.24	<.001	.547
FFSS		51.26 ± 12.15	25.21 ± 12.99	165.51	<.001	.516
COS	S	2.69 ± 1.44	4.37 ± 1.45	51.51	<.001	.249
	I	30.51 ± 7.54	17.02 ± 7.23	126.25	<.001	.449
	H	8.67 ± 4.82	4.27 ± 1.87	49.03	<.001	.240
STAI	STAI-T	39.01 ± 10.25	21.04 ± 10.16	118.35	<.001	.433
	STAI-S	30.02 ± 11.39	18.91 ± 8.24	45.09	<.001	.225
BDI		22.37 ± 10.56	6.94 ± 6.29	110.92	<.001	.417
SF-36	MC	32.71 ± 9.21	54.41 ± 9.25	210.45	<.001	.576
	PC	35.96 ± 8.18	63.41 ± 7.47	460.42	<.001	.748
CSQ	CAT	17.89 ± 5.20	7.41 ± 4.38	175.45	<.001	.531
	CD	17.49 ± 5.36	18.14 ± 5.52	.54	.464	.003
	IPS	21.75 ± 4.96	24.98 ± 5.34	15.14	.000	.089

Note: *Eysenck Personality Questionnaire Revised-Abbreviated* (EPQR-A): N = Neuroticism, E = Extraversion, P = Psychoticism; *McGill Pain Questionnaire (McGill):* TPI = Total Pain Index, CPI = Current Pain intensity; *Fisk Fatigue Severity Score (FFSS):* Fatigue; *Oviedo Quality of Sleep Questionnaire (COS):* S = Satisfaction, I = Insomnia, H = Hypersomnia; *State-Trait Anxiety Inventory (STAI):* STAI-T = Trait, STAI-S = State; *Beck Depression Inventory (BDI):* Depression; *Short-From Health Survey (SF-36)*: MC = Mental Component, PC = Physical Component; *Coping Strategies Questionnaire (CSQ):* CAT = catastrophizing, CD = cognitive distraction, IPS = ignoring pain sensations.

3.2. Associations between personality dimensions and clinical indicators

N was positively associated with TPI scores in the control group, but not in FMS patients (see Table 3); the difference between the two correlation coefficients was significant ($Z = -2.11$, $p < .05$). E was negatively associated with CPI scores in FMS patients but not in healthy participants, with significant differences between the two correlation coefficients ($Z = -2.86$, $p < .01$). The results of multiple regression analysis showed a significant effect of E on CPI in FMS patients (see Table 4). However the association between N and TPI in the control group remain marginal ($p = .065$) when tested simultaneously with the other personality dimensions in the regression analysis. No associations between personality and fatigue or sleep indices were found in any group.

3.3. Associations between personality dimensions and anxiety-depression

N was positively associated with trait anxiety in both groups. Although this correlation was greater in healthy controls than in FMS patients, differences between the two correlation coefficients remained only marginally significant ($Z = -1.49$, $p = .065$). N was also positively associated with state anxiety, but only in the control group. E was negatively associated with trait anxiety in FMS patients; the association did not reach significance in the control group. The results of the regression analysis showed that N (positively) and E (negatively) were significant predictors of trait anxiety in both groups. P was negatively associated with trait anxiety

Table 3
Correlations between personality dimensions and measured outcomes in fibromyalgia (FMS) patients and healthy participants.

Measured outcomes		Neuroticism		Extraversion		Psychoticism	
		FMS	Healthy	FMS	Healthy	FMS	Healthy
McGill	TPI	−.062	.280*	−.144	.226	.061	.147
	CPI	−.153	.137	−.295**	.167	−.065	.069
FFSS		.130	.115	−.124	−.020	−.114	−.061
COS	S	.013	−.180	.103	−.081	.006	−.219
	I	.076	.232	−.010	−.062	.014	.226
	H	−.092	.124	−.040	.011	−.154	.196
STAI	STAI-T	.428**	.607**	−.350**	−.233	−.194	.111
	STAI-S	.084	.308*	−.156	−.127	.093	.214
BDI		.259*	.417**	−.268**	−.147	−.051	.192
SF-36	MC	−.208*	−.514**	.388**	−.137	.027	−.061
	PC	−.154	−.256*	.070	−.235	.014	.076
CSQ	CAT	.179	.396**	−.093	−.015	.032	.374**
	CD	−.248*	.041	.034	−.048	−.130	.185
	IPS	−.154	−.054	.081	−.038	−.020	−.021

Note: Identical abbreviations are used to those of Table 2.
* $p < .05$.
** $p < .01$.

Table 4
Results of multiple regression analysis of the prediction of measured outcomes from personality dimensions in fibromyalgia (FMS) patients and healthy controls (HC). β = unstandardized beta.

	Dependent variable	Group	B			r^{2} adjusted
			N	E	P	
McGill	TPI	FMS	−.188	−.188	.100	.030
		HC	.235	.225	.112	.091*
	CPI	FMS	−.108	−.310**	−.012	.068*
		HC	.109	.168	.061	.000
FSS		FMS	.123	−.089	−.108	.007
		HC	.148	−.044	−.107	−.024
COS	S	FMS	.030	.110	−.012	−.022
		HC	−.118	−.099	−.200	.027
	I	FMS	.075	−.000	.010	−.028
		HC	.189	−.053	.167	.040
	H	FMS	−.088	−.032	−.144	−.002
		HC	.073	.029	.179	−.002
STAI	STAI-T	FMS	.399**	−.262**	−.182*	.274**
		HC	.655**	−.290**	−.107	.426**
	STAI-S	FMS	.051	−.166	.115	.008
		HC	.284*	−.131	.119	.087*
BDI		FMS	.226*	−.229*	−.031	.092**
		HC	.413**	−.167	.057	.169**
SF36	MC	FMS	−.151	.368**	−.019	.146**
		HC	−.528**	−.093	.072	.244**
	PC	FMS	−.148	.044	.017	−.007
		HC	−.277*	−.200	.126	.085*
FIQ		FMS	−.082	−.118	.110	−.029
		HC	–	–	–	–
CSQ	CAT	FMS	.166	−.073	.033	−.005
		HC	.317**	.001	.287*	.196**
	CD	FMS	−.238*	.015	−.118	.043
		HC	−.008	−.024	.184	−.013
	IPS	FMS	−.144	.062	−.020	−.006
		HC	−.048	−.037	−.013	−.045

Note: Identical abbreviations are used to those of Table 2.
* $p < .05$.
** $p < .01$.

in the FMS group. N positively predicted state anxiety but only in the control group.

N was positively associated with depression scores in both groups. Although the correlation was greater in control participants than in FMS patients, the difference between the two coefficients did not reach significance ($Z = -1.08$, $p > .1$). In the FMS group only, E was negatively associated with depression scores. The results of the regression analysis showed that N (positively) and E (negatively) were significant predictors of depression scores in the FMS group, while in the control group only N negatively predicted depression levels.

3.4. Associations between personality, quality of life and impact of fibromyalgia

N was negatively associated with the mental HRQL component in both groups, but the relationship was stronger in the control vs. FMS group ($Z = 2.16$, $p < .05$). N also was negatively associated with the physical HRQL component, but only in the control group. E was positively associated with the mental HRQL component in the FMS group but not in healthy participants (see Table 3), with significant differences observed between the two correlation coefficients ($Z = 3.31$, $p < .01$). The results of the regression analysis (Table 4) showed that N negatively predicted, in the control group, both the physical and mental HRQL components. In the FMS group E positively predicted the mental HRQL component. No significant associations were found between personality and impact of fibromyalgia (FIQ).

3.5. Associations between personality and pain coping strategies

Correlation and regression analysis showed that both N and P were associated with greater use of the catastrophizing strategy, but only in the control group. The group difference between the two correlation coefficients for P was significant ($Z = -2.18$, $p < .05$). In FMS patients, N was associated with significantly less use of the "cognitive distraction" coping strategy compared with the healthy group ($Z = -1.78$, $p < .05$).

3.6. Differences in personality as a function of medication use and emotional comorbidity in the FMS group

FMS patients taking antidepressants, relative to patients not taking this medication, exhibited lower scores on E (3.03 ± 1.81 vs. 4.07 ± 1.29; $F(3,88) = 9.77$; $p = .002$; $\eta^2 = .098$). FMS patients taking anxiolytics, relative to those who were not, exhibited higher scores on N (4.97 ± 1.07 vs. 4.33 ± 1.59; $F(3,88) = 5.26$; $p = .024$; $\eta^2 = .055$), and lower scores on E (3.22 ± 1.69 vs. 3.97 ± 1.54; $F(3,88) = 4.63$; $p = .034$; $\eta^2 = .049$). Concerning opioids, FMS patients using this medication, relative to those who were not, exhibited lower scores on E (2.87 ± 1.86 vs. 3.93 ± 1.40; $F(3,88) = 9.60$, $p = .003$; $\eta^2 = .096$). Finally, lower scores on E were observed in FMS patients with comorbid depression (3.11 ± 1.83 vs. 3.86 ± 1.44; $F(3,88) = 4.86$; $p = .030$; $\eta^2 = .051$) as well as comorbid anxiety (2.96 ± 1.53 vs. 3.89 ± 1.66; $F(3,88) = 7.41$; $p = .008$; $\eta^2 = .076$).

4. Discussion

As expected, FMS patients exhibited greater levels of N compared with healthy controls. This result corroborates previous reports (Asghari & Nicholas, 1999; Besteiro et al., 2008; Netter & Hennig, 1998; Malt et al., 2002) and was expected in light of the high co-morbidity between FMS and affective and anxiety disorders (e.g. Fietta et al., 2007; Reyes del Paso et al., 2012; Van Middendorp et al., 2008; Wolfe et al., 1990). This high level of N is consistent with descriptions of FMS patients as individuals characterized by a highly negative emotional state, strong tendency toward excessive concern about future and past events, a high level of anticipatory anxiety and avoidance of both emotional and physical damage (Anderberg et al., 1999; Van Middendorp et al., 2008). FMS patients also exhibit higher levels of P compared with healthy controls, confirming the observation of Banic et al. (2004). Given the features included in the P trait, this difference may be difficult to understand at first glance. One possible explanation concerns the suggested relationship between antisocial and somatization disorders, where it has been postulated that both disorders represent sex-differentiated manifestations of the same underlying predisposition (Lilienfeld, 1992). In support of this interpretation, H.J. Eysenck's P trait includes antisocial characteristics (impulsivity, aggressiveness, egocentrism, irresponsibility, anti-sociability, etc.). Another explanation is that increased P may represent a secondary adaptation to adjustments made in response to the chronic disabilities that characterize FMS (see below). Contrary to our expectations, no group difference in E was found. This result does not supports previous studies that reported low E in FMS patients (Ayats et al., 2006; Besteiro et al., 2008; Glazer et al., 2010; Kersh et al., 2001; Malin & Littlejohn, 2012b; Zautra et al., 2005). However, it does accord with a recent study in which there were also no differences in E between FMS patients and healthy controls (Malin & Littlejohn, 2012a).

As expected, and in accordance with pre-existing knowledge (Malin & Littlejohn, 2012a; Wolfe et al., 2010), our FMS sample exhibited greater levels of anxiety, depression, fatigue, sleep

problems, and clinical pain, in addition to lower levels of HRQL, and increased prevalence of both depression and anxiety disorders compared with our healthy participants. Regarding pain coping strategies, FMS patients scored more highly for "catastrophizing" and lower for "ignoring pain sensations" compared with healthy controls. Greater use of the "catastrophizing" strategy by FMS patients accords with studies showing greater use of poor coping strategies in response to stressors in FMS (Herken et al., 2001; Houdenhove & Luyten, 2006), and a higher degree of pain catastrophizing among FMS patients compared with patients suffering from other rheumatologic conditions (Börsbo, Gerdle, & Peolsson, 2010; Hassett et al., 2000). Elevated pain catastrophization in FMS would lead to fear-avoidance behaviors that often result in physical inactivity (Hassett et al., 2000), which in turn frequently leads to further complications such as weakening of the musculoskeletal system, increased pain, fatigue and functional disability (Kelley, Kelley, Hootman, & Jones, 2010). The coping strategy of "ignoring pain sensations", related to superior psychological functioning in the context of chronic pain (Jensen & Karoly, 1991), is used less by FMS patients. It should be noted that all of the above group differences remained when the three personality dimensions were entered into the analysis as covariates.

As expected, the associations found between N and the variables measured were in general of lesser magnitude in the FMS vs. healthy group. In FMS patients no relationship between N and clinical pain parameters was observed, contrary to several previous studies reporting, for example, that higher levels of N are associated with lower pain thresholds and greater pain sensitivity in FMS (Netter & Hennig, 1998), and further that N predicts a substantial amount of the variance in FMS pain (Albertsen et al., 2002), etc. Eysenck (1994) also found that higher scores on N, in patients with chronic pain, were associated with more disability, somatization and pain intensity. However, our result accords with recent reports in which there were no associations between N and pain in FMS (Kersh et al., 2001; Malin & Littlejohn, 2012a; Wade, Dougherty, Hart, Rafii, & Price, 1992). In healthy controls, however, N was associated with higher Total Pain Index values, thereby confirming the association between N and pain responses observed in the general population (Paine et al., 2009).

Moreover, N, in both FMS patients and healthy controls, was positively associated with trait anxiety. In healthy controls, N furthermore was associated with greater levels of state-anxiety. Also for both groups, higher scores on N were associated with higher depression levels. These associations have been repeatedly reported in the literature in patients with chronic pain disorders (e.g. Affleck et al., 1992; Kentle, 1989; Malin & Littlejohn, 2012a) and are compatible with the increased levels of negative affect that characterize both depression and anxiety (Clark & Watson, 1991). However, it is of relevance to specify that the influence of N, and in general the three personality dimensions, on both anxiety and depression levels, is greater in healthy controls (in whom the three dimensions explained 42.6% of the variance in trait-anxiety and 16.9% in depression) than in FMS patients (27.4% and 9.2% of the variance in trait-anxiety and depression explained, respectively).

Concerning functional features, in the FMS group N negatively predicted the mental HRQL component, which accords with a previous study in which N was associated with lower satisfaction indices of HRQL in FMS (McCain, 1996). In healthy controls, N negatively predicted both the mental and physical HRQL components. Furthermore, the magnitude of the association between N and the mental HRQL component was greater in healthy controls than in FMS patients.

Higher N in FMS patients is associated with less use of the "cognitive distraction" coping strategy. This strategy is adaptive as it tends to confer reduced interference from pain, such that its disuse in FMS patients with higher N may lead to an impaired ability to adjust and adapt to the illness (Jensen, Turner, & Romano, 1992). Contrary to our expectations, we detected no relationship between N and the use of non-effective strategies, such as "catastrophism", in contrast to previous FMS studies (Affleck et al., 1992; Asghari & Nicholas, 2006; Jensen, Turner, Romano, & Lawler, 1994; Martínez et al., 2011; Ramírez et al., 2001). However, in healthy controls, N was associated with greater use of "catastrophizing", which accords with previous evidence of a relationship between high levels of N and the use of such maladaptive stress-coping strategies in general populations (Bolger, 1990; Gunthert, Cohen, & Armeli, 1999).

The associations between N and total McGill score, SF-36 components and catastrophizing observed in healthy controls accord with the symptom perception hypothesis (Watson & Pennebaker, 1989). Individuals with high negative affectivity (i.e. neuroticism) attend more to physical symptoms, complain more about, magnify, exaggerate and overreact to them, are more hypervigilant (i.e. scan the world for signs of trouble), ruminative and introspective (internally focused), exhibit higher somatic sensitivity, and are biased toward interpreting somatic symptoms as negative or threatening, etc. (Watson & Pennebaker, 1989). In principle, all of these dispositional features may be increased in our FMS patients, given that they exhibit higher N values. However, according to our analyses, the associations between N and health outcomes were few in the FMS group, and markedly scarcer than in the healthy controls. This group difference in the magnitude of associations was expected from the point of view that the interfering effect of disability from a debilitating illness such as FMS, and its clinical manifestations, would be more relevant than the negative effects of N.

Regarding E, our expectations were only confirmed in part. In the FMS group, E was associated with lower present pain intensity. This result is consistent with Eysenck (1967), where patients with chronic pain and high scores on E exhibited a higher pain tolerance than did introverted patients. The protective role of E on pain accords with its assumed biological basis, as lower activity in the ascending reticular activating system would lead to lower cortical representation of afferent stimuli (Eysenck, 1967).

In both FMS patients and healthy controls, E was negatively associated with trait anxiety. Specifically in the FMS group, extroversion was also negatively associated with depression levels. These associations were expected in light of affective-based models of emotional disorders, and the positive affect component included in the E trait (Clark & Watson, 1991; Watson & Pennebaker, 1989). E was positively associated with the mental HRQL component in FMS patients. The higher scores on E in FMS patients were associated with fewer functional problems in daily life pertaining to social, emotional, energy-vitality and mental domains.

These results suggest a protective role of E in present pain perception, anxiety, depression, functional disabilities induced by the disorder, and certain pain coping strategies, but only in the FMS group. This protective effect may be related to several features associated with the E trait, including greater levels of positive affect, optimism, social support and interpersonal relationships, lower tendency toward internal focus, etc. (Clark & Watson, 1991; Eysenck, 1967). The negative association between E and depression in our FMS sample accords with the affective basis of depression (i.e. lower positive affectivity, Clark & Watson, 1991).

The relevance and protective role of E in FMS was also apparent when differences in personality were analyzed as a function of comorbid emotional disorders and medication use. FMS patients suffering from depression or anxiety disorders exhibited lower E levels. Similarly, FMS patients taking antidepressants, anxiolytics, and opiates also displayed lower E levels. The greater N levels observed in patients taking anxiolytics accords with the presence of an anxiety component in N.

Regarding P, in the regression analysis a negative association with trait anxiety in the FMS group was observed. Greater P in FMS patients might decrease trait anxiety through components such as tough-mindedness, egocentrism, emotional detachment, impersonality or low empathy (Eysenck & Eysenck, 1985). Furthermore, a moderate level of P appears to be associated with greater objectivity, realism and hardiness in daily life, including situation involving pain (Carrillo, Collado, & Rojo, 2005). However, in the control group a higher P was associated with greater use of the catastrophism strategy. This result appears with the above interpretation and suggests differential roles of the P trait in both groups.

Fatigue and sleep complaints were unrelated to personality, in contrast to the study of Malin and Littlejohn (2012a) in which there was a positive association between N and fatigue. Sleep disturbances appear to be related to the presence of somatic symptoms, but not to personality (Kolar, Hartz, Roumm, Ryan, & Jones, 1989). The impact of the disease on daily life, as measured by the FIQ, was unrelated to personality in our study. This accords with a study by Zautra, Hamilton, and Burke (1999), in which N did not affect FIQ scores in an FMS sample, but is contrary to a more-recent study in which extroversion predicted fibromyalgia's impact on everyday life (Starowicz-Filip, Borcz, & Prochwicz, 2014). In our study personality was associated with functional disability measured by the SF-36 but not the FQI. These results are particularly striking because the FQI is an instrument specifically adapted for use with FMS patients, whereas the SF-36 is more general in scope.

One important question concerns the origin of the personality differences observed. Are they present before the disease onsets, perhaps even conferring heightened vulnerability, or are they secondary to, or concomitant with, the development of FMS? The cross-sectional nature of our study does not allow us to address this question directly, such that possible interpretations are necessarily speculative. A chronic pain disorder characterized by the types of disabilities associated with FMS may be considered as a relevant negative stressful life event. During the adjustment to chronic suffering and disability personality may change toward greater expression of negative affect and N levels. Therefore, coping strategies are essential for managing adaptation and reducing discomfort, distress and helplessness (Goldenberg, Mossey, & Schmid, 1995). In this context, one means of coping with chronic circumstances may be by developing more "tough-mindedness", egocentrism, emotional detachment or impersonality (i.e. P), such that negative circumstances confer less burden. The negative association we found between P and trait anxiety in our FMS participants accords with this interpretation. These two explanations are not incompatible because certain previous personality predispositions may be present that develop further as a consequence of disease. Furthermore, the direction of associations between personality and FMS manifestations can be bidirectional and interactive, such that the personality can modulate FMS symptoms, and these symptoms can in turn influence personality, all the while interacting with other relevant factors (Charles, Gatz, Kato, & Pedersen, 2008; Herken et al., 2001).

One limitation of our study concerns the instrument used to measure personality, i.e. a short version (only 6 items per dimension) of the original Eysenck questionnaire. However, this abbreviated version exhibits good concurrent validity with the EPQ in addition to appropriate psychometric indices (Francis et al., 1992; Sandín et al., 2002). A strength of our study concerns the sample size, which is larger than that of many other studies in this area, in which samples comprising fewer than 40 participants per group are typical (see Malin & Littlejohn, 2012b for a review).

In conclusion, FMS patients displayed greater N and P levels, but not E scores, compared to healthy controls. It is possible that the high N that characterized the FMS group might serve to artificially inflate self-reported clinical and functional disabilities. However, in the FMS group N was weakly associated with health outcomes and the magnitudes of certain such associations were lower than they were in the control group. Furthermore, when the three personality dimensions were entered into the analysis as covariates, all previously observed group differences remained, and at similar magnitudes. Therefore, we conclude that N only plays a minor role in the clinical manifestations of FMS. These results are contrary to the widely held belief that FMS is a disorder rooted in, and dependent on, its accompanying affective-emotional alterations. N, which represents the common underlying trait of anxiety and depression (Clark & Watson, 1991), plays an even less important role in FMS patients than it does in healthy controls with respect to associations with the dependent variables measured herein. In contrast, E appears to play a protective role specifically in FMS patients, in whom it was associated with superior health outcomes across several domains.

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References

Affleck, G., Tennen, H., Urrows, S., & Higgins, P. (1992). Neuroticism and the pain mood relation in rheumatoid arthritis: Insights from a prospective daily study. *Journal of Consulting and Clinical Psychology, 60*, 119–126.

Albertsen, E., Olafsson, S., Lund, A., & Ursin, H. (2002). Factors explaining variance in perceived pain in women with fibromyalgia. *BMC Musculoskeletal Disorders, 3*, 12.

Alonso, J., Prieto, L., & Antó, J. M. (1995). La versión española del SF-36 Health Survey (Cuestionario de Salud SF-36): Un instrumento para la medida de los resultados clínicos. *Medicina clínica, 104*, 771–776.

Amir, M., Neuman, L., Bor, O., Shir, Y., Rubinow, A., & Buskila, D. (2000). Coping styles, anger, social support, and suicide risk of women with Fibromyalgia. *Journal of Musculoskeletal Pain, 8*, 7–20.

Anderberg, U. M., Forsgren, T., Ekselius, L., Marteinsdottir, H., & Hallman, J. (1999). Personality traits on the basis of the Temperament and Character Inventory in female Fibromyalgia Syndrome patients. *Nordic Journal of Psychiatry, 5*, 353–359.

Asbring, P., & Narvanen, A. L. (2003). Ideal versus reality: Physicians perspectives on patients with Chronic Fatigue Syndrome (CFS) and Fibromyalgia. *Social Science and Medicine, 57*, 711–720.

Asghari, M. A., & Nicholas, M. K. (1999). Personality and adjustment to chronic pain. *Pain Reviews, 6*, 85–97.

Asghari, M. A., & Nicholas, M. K. (2006). Personality and pain-related beliefs/coping strategies: A prospective study. *Clinical Journal of Pain, 22*, 10–18.

Ayats, M., Martín, M. J., & Soler, P. A. (2006). Fibromialgia y estilo de funcionamiento. *Psiquiatría Biológica, 13*, 193–197.

Banic, B., Petersen, S., Andersen, O., Radanov, B., Villiger, P. M., Arendt-Nielsen, L., et al. (2004). Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in Fibromyalgia. *Pain, 107*, 7–15.

Besteiro, J., Álvarez, M., Lemos, S., Muñiz, J., Costas, C., & Weruaga, A. (2008). Dimensiones de personalidad, sentido de coherencia y salud percibida en pacientes con un Síndrome Fibromiálgico. *International Journal of Clinical and Health Psychology, 8*, 411–427.

Bobes, J., González, M. P., Sáiz, P. A., Bascarán, M. T., Iglesias, C., & Fernández, J. M. (2000). Propiedades psicométricas del cuestionario Oviedo de Sueño. *Psicothema, 1*, 107–112.

Bolger, N. (1990). Coping as a personality process: A prospective study. *Journal of Personality and Social Psychology, 59*, 525–537.

Börsbo, B., Gerdle, B., & Peolsson, M. (2010). Impact of the interaction between self-efficacy, symptoms and catastrophising on disability, quality of life and health in chronic pain patients. *Disability and Rehabilitation, 32*, 1387–1396.

Bulbena, A., Berrios, G. E., & Fernández de Larrinoa, P. (2000). *Medición clínica en psiquiatría y psicología*. Madrid: Masson.

Carrillo, J. M., Collado, S., & Rojo, N. (2005). Personality and pain tolerance. *Clínica y Salud, 16*, 223–236.

Cerón, A. M., Centelles, F., Abellana, M., & García, S. (2010). Fibromialgia y trastornos de personalidad. *Semergen, 9*, 501–506.

Charles, S. T., Gatz, M., Kato, K., & Pedersen, N. L. (2008). Physical health 25 years later: The predictive ability of neuroticism. *Health Psychology, 3*, 369–378.

Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology, 100*, 316–336.

Costa, P. T. Jr., (1987). Influence of the normal personality dimension of neuroticism on chest pain symptoms and coronary artery disease. *American Journal of Cardiology, 60*, 20J–26J.

Dysvik, E., Natvig, G. K., Eikeland, O., & Lindstrom, T. C. (2005). Coping with chronic pain. *International Journal of Nursing Studies, 42*, 297–305.

Esteve-Vives, J., Rivera, J., Salvat, I., de Gracia, M., & Alegre, C. (2007). Propuesta de una versión de consenso del Fibromyalgia Impact Questionnaire (FIQ) para la población española. *Reumatología Clínica, 3*, 21–24.

Eysenck, H. J. (1967). *The biological basis of personality*. Springfield, IL: Charles C. Thomas.

Eysenck, H. J. (1994). Neuroticism and the illusion of mental health. *American Psychologist, 49*, 971–972.

Eysenck, H. J., & Eysenck, M. W. (1985). *Personality and individual differences: A natural science approach*. New York: Plenum.

Fietta, P., Fietta, P., & Manganelli, P. (2007). Fibromyalgia and psychiatric disorders. *Acta Biomedica, 78*, 88–95.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1999). *Entrevista clínica estructurada para los trastornos de eje I del DSM-IV (versión clínica) SCID-I*. Barcelona: Masson.

Francis, L. J., Brown, L. B., & Philipchalk, R. (1992). The development of an abbreviated form of the Revised Eysenck Personality Questionnaire (EPQR-A): Its use among students in England, Ganada, the U.S.A and Australia. *Personality and Individual Differences, 13*, 443–449.

Geisser, M. E., Casey, K. L., Brucksch, C. B., Ribbens, C. M., Appleton, B. B., & Crofford, L. J. (2003). Perception of noxious and innocuous heat stimulation among healthy women and women with Fibromyalgia: Association with mood, somatic focus, and catastrophizing. *Pain, 102*, 243–250.

Geisser, M. E., & Roth, R. S. (1998). Knowledge of and agreement with pain diagnosis: Relation to pain beliefs, pain severity, disability, and psychological distress. *Journal of Occupational Rehabilitation, 8*, 73–88.

Glazer, D., Buskila, H., Cohen, R. P., Ebstein, L., & Neumann (2010). Differences in the personality profile of Fibromyalgia patients and their relatives with and without Fibromyalgia. *Clinical and Experimental Rheumatology, 28*, S27–S32.

Goldenberg, D. L., Mossey, C. J., & Schmid, C. H. (1995). A model to assess severity and impact of Fibromyalgia. *The Journal of Rheumatology, 22*, 2313–2318.

Gracely, R. H., Geisser, M. E., Giesecke, T., Grant, M. A. B., Petzke, F., Williams, D. A., et al. (2004). Pain catastrophizing and neural responses to pain among persons with Fibromyalgia. *Brain, 127*, 835–843.

Gunthert, K. C., Cohen, L. H., & Armeli, S. (1999). The role of neuroticism in daily stress and coping. *Journal of Personality and Social Psychology, 77*, 1087–1100.

Gursoy, S., Erdal, E., Herken, H., Madenci, E., & Alasehirli, B. (2001). Association of T102C polymorphism of the 5-HT2A receptor gene with psychiatric status in fibromyalgia syndrome. *Rheumatology International, 21*, 58–61.

Hallberg, L. R. M., & Carlsson, S. G. (1998). Psychosocial vulnerability and maintaining forces related to Fibromyalgia. *Scandinavian Journal of Caring Science, 12*, 95–103.

Harkins, S. W., Price, D. D., & Braith, J. (1989). Effects of extraversion and neuroticism on experimental pain, clinical pain, and illness behavior. *Pain, 36*, 209–218.

Hassett, A. L., Cone, J. D., Patella, S. J., & Sigal, L. H. (2000). The role of catastrophizing in the pain and depression of women with Fibromyalgia Síndrome. *Arthritis and Rheumatism, 43*, 2493–2500.

Herken, H., Gursoy, S., Yetkin, O., Virit, O., & Esgi, K. (2001). Personality characteristics and depression levels in female patients with Fibromyalgia Syndrome. *Internal Medicine Journal, 8*, 41–44.

Houdenhove, B. V., & Luyten, P. (2006). Stress, depression and fibromyalgia. *Acta Neurologica Belgica, 106*, 149–156.

Jensen, M. P., & Karoly, P. (1991). Control beliefs, coping efforts, and adjustment to chronic pain. *Journal of Consulting and Clinical Psychology, 59*(3), 431–438.

Jensen, M. P., Turner, J. A., & Romano, J. M. (1992). Chronic pain coping measures: Individual vs. composite scores. *Pain, 51*, 273–280.

Jensen, M. P., Turner, J. A., Romano, J. M., & Lawler, B. K. (1994). Relationship of pain specific beliefs to chronic pain adjustment. *Pain, 57*, 301–309.

Keefe, F. J., Rumble, M. E., Scipio, C. D., Giordano, L. A., & Perri, L. M. (2004). Psychological aspects of persistent pain: Current state of the science. *The Journal of Pain, 5*, 195–211.

Kelley, G., Kelley, G., Hootman, J., & Jones, D. (2010). Exercise and global well-being in community-dwelling adults with Fibromyalgia: A systematic review with meta-analysis. *BMC Public Health, 10*, 198.

Kendall, S. A., Elert, J., Ekselius, L., & Gerdle, B. (2002). Are perceived muscle tension, electromyographic hyperactivity and personality traits correlated in the Fibromyalgia Syndrome? *Journal of Rehabilitation Medicine, 34*, 73–79.

Kentle, R. L. (1989). Headache symptomatology and neuroticism in a college sample. *Psychological Reports, 65*, 976–978.

Kersh, B. C., Bradley, L. A., Alarcon, G. S., Alberts, K. R., Sotolongo, A., Martin, M. Y., et al. (2001). Psychosocial and health status variables independently predict health care seeking in Fibromyalgia. *Arthritis Care & Research, 45*, 362–371.

Kolar, A., Hartz, A., Roumm, L., Ryan, R., & Jones, E. (1989). Factors associated with severity of symptoms in patients with chronic unexplained muscular aching. *Annals of the Rheumatic Diseases, 48*, 317–321.

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology, 46*, 1121–1123.

Lahey, B. B. (2009). Public health significance of neuroticism. *American Psychologist, 64*, 241–256.

Lázaro, C., Bosch, F., Torrubia, R., & Baños, J. E. (1994). The development of a Spanish Questionnaire for assessing pain: Preliminary data concerning reliability and validity. *European Journal Psychological Assessment, 10*, 145–151.

Lilienfeld, S. O. (1992). The association between antisocial personality and somatization disorders: A review and integration of theoretical models. *Clinical Psychology Review, 12*, 641–662.

Loggia, M. L., Berna, C., Kim, J., Cahalan, C. M., Gollub, R. L., Wasan, A. D., et al. (2014). Disrupted brain circuitry for pain related reward/punishment in Fibromyalgia. *Arthritis & Rheumatology, 66*, 203–212.

Loggia, M. L., Mogil, J. S., & Bushnell, M. C. (2008). Experimentally induced mood changes preferentially affect pain unpleasantness. *The Journal of Pain, 9*, 784–791.

Malin, K., & Littlejohn, G. (2012a). Neuroticism in young women with Fibromyalgia links to key clinical features. *Pain Research and Treatment, 2012*, 730–741.

Malin, K., & Littlejohn, G. (2012b). Personality and Fibromyalgia Syndrome. *The Open Rheumatology Journal, 6*, 273–285.

Malt, E. A., Olafsson, S., Lund, A., & Ursln, H. (2002). Fac tors explaining variance in perceived pain in women with Fibromyalgia. *BMC Musculoskeletal Disorders, 3*, 2–8.

Martínez, M. P., Sánchez, A. I., Miró, E., Medina, A., & Lami, A. (2011). The relationship between the fear-avoidance model of pain and personality traits in Fibromyalgia patients. *Journal of Clinical Psychology in Medical Settings, 4*, 380–391.

McCain, G. A. (1996). A cost-effective approach to the diagnosis and treatment of Fibromyalgia. *Rheumatic Disease Clinics of North America, 22*, 323–349.

McMahon, S. B., & Wall, K. M. (2006). *Melzack's textbook of pain*. Philadelphia (PA): Elsevier.

Montoya, P., Pauli, P., Batra, A., & Wiederman, G. (2005). Altered processing of pain-related information in patients with Fibromyalgia. *European Journal of Pain, 9*, 293–303.

Netter, P., & Hennig, J. (1998). The Fibromyalgia Syndrome as a manifestation of neuroticism? *Zeitschrift für Rheumatologie, 57*, 105–108.

Paine, P., Kishor, J., Worthen, S. F., Gregory, L. J., & Aziz, Q. (2009). Exploring relationships for visceral and somatic pain with autonomic control and personality. *Pain, 3*, 236–244.

Pérez-Pareja, J., Sesé, A., González-Ordi, H., & Palmer, A. (2010). Fibromyalgia and chronic pain: Are there discriminating patterns by using the Minnesota Multiphasic Personality Inventory-2 (MMPI-2)? *International Journal of Clinical and Health Psychology, 10*, 41–56.

Petzke, F., Gracely, R. H., Park, K. M., Ambrose, K., & Clauw, D. J. (2003). What do tender points measure? Influence of distress on 4 measures of tenderness *The Journal of Rheumatology, 30*, 567–574.

Ramírez, C., Esteve, R., & López, A. E. (2001). Neuroticismo, afrontamiento y dolor crónico. *Anales de Psicología, 17*, 129–137.

Ramírez, C., & Valdivia, I. (2003). Evaluación del funcionamiento diario de pacientes con dolor crónico. *Psicología Conductual, 11*, 283–291.

Reyes del Paso, G. A., Pulgar, A., Duschek, S., & Garrido, S. (2012). Cognitive impairment in Fibromyalgia Syndrome: The impact of cardiovascular regulation, pain, emotional disorders and medication. *European Journal of Pain, 16*, 421–429.

Rodriguez, L., Cano, E. J., & Blanco, A. (2004). Evaluación de las estrategias de afrontamiento de dolor crónico. *Actas Españolas de Psiquiatría, 32*, 82–91.

Rosenstiel, A. K., & Keefe, F. J. (1983). The use of coping strategies in chronic low back pain patients: Relationship to patient characteristics and current adjustment. *Pain, 17*, 33–44.

Sandín, B., Valiente, R. M., Chorot, P., Olmedo, M., & Santed, M. A. (2002). Versión española del cuestionario EPQR-Abreviado (EPQR-A) (I): Análisis exploratorio de la estructura factorial. *Revista de Psicopatología y Psicología Clínica, 7*, 195–205.

Sanz, J., Navarro, M. E., & Vázquez, C. (2003). Adaptación española del Inventario para la Depresión de Beck-II (BDI-II): I. Propiedades psicométricas en estudiantes universitarios. *Análisis y Modificación de Conducta, 29*, 239–288.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1982). *Manual del Cuestionario de Ansiedad Estado/Rasgo (STAI)*. Madrid, España: TEA Ediciones.

Starowicz-Filip, A., Borcz, J., & Prochwicz, K. (2014). EPA-0518-Psychological predictors of adaptation to Fibromyalgia. *European Psychiatry, 29*, 1.

Van Middendorp, H., Lumley, M., Jacobs, J., Van Doornen, L., Bijlsma, J., & Geenen, R. (2008). Emotions and emotional approach and avoidance strategies in Fibromyalgia. *Journal of Psychosomatic Research, 64*, 159–167.

Wade, J. B., Dougherty, L. M., Hart, R. P., Rafii, A., & Price, D. D. (1992). A canonical correlation analysis of the influence of neuroticism and extraversion on chronic pain, suffering, and pain behaviour. *Pain, 51*, 67–73.

Ware, J. E., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care, 30*, 473–483.

Watson, D., & Pennebaker, J. W. (1989). Health complaints, stress and distress: Exploring the central role of negative affectivity. *Psychological Review, 96*, 234–254.

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P., et al. (2010). The American College of Rheumatology preliminary diagnostic criteria for Fibromyalgia and measurement of symptom severity. *Arthritis Care & Research, 62*, 600–610.

Wolfe, F., Ross, K., Anderson, J., Russell, I. J., & Hebert, L. (1995). The prevalence and characteristics of Fibromyalgia in the general population. *Arthritis and Rheumatism, 38*, 19–28.

Wolfe, F., Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., et al. (1990). The American College of Rheumatology 1990 criteria for the classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis and Rheumatism, 33*, 160–172.

Yunus, M. B. (2007). Fibromyalgia and overlapping disorders: The unifying concept of central sensitivity syndromes. *Seminars in Arthritis and Rheumatism, 36*, 339–356.

Zautra, A. J., Fasman, R., Reich, J. W., Harakas, P., Johnson, L. M., Olmsted, M. E., et al. (2005). Fibromyalgia: Evidence for deficits in positive affect regulation. *Psychosomatic Medicine, 67*, 147–155.

Zautra, A. J., Hamilton, N. A., & Burke, H. M. (1999). Comparison of stress responses in women with two types of chronic pain: Fibromyalgia and osteoarthritis. *Cognitive Therapy and Research, 23*, 209–230.

ESTUDIO 6. ALEXITHYMIA IN FIBROMYALGIA SYNDROME

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(Submitted)

Alexithymia in Fibromyalgia Syndrome

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Abstract

The study compared facets of alexithymia in fibromyalgia syndrome (FMS) patients and healthy individuals, and analyzed their association with clinical, emotional and functional variables, as well as pain coping strategies. Forty-five FMS patients and 31 healthy individuals completed the Toronto Alexithymia Scale (TAS-20), which includes the following dimensions: Difficulty Identifying Feelings, Difficulty Describing Feelings, and Externally-Oriented Thinking. The participants also completed instruments assessing Eysenck´s personality dimensions (neuroticism, psychoticism, extraversion), clinical pain, fatigue, sleep, anxiety, depression, health-related quality of life (HRQL) and ability to cope with pain. FMS patients exhibited higher scores in the Difficulty Identifying Feelings and Difficulty Describing Feelings domains than healthy individuals; group differences were markedly lower when depression and anxiety were statistically controlled. Patients furthermore displayed greater depression, anxiety, fatigue, sleep problems and neuroticism, lower HRQL and more frequent use of the catastrophizing and ignoring pain sensations coping strategies. According to a regression analysis, in FMS patients Difficulty Identifying Feelings positively predicted anxiety and depression and negatively predicted HRQL and use of the adaptive coping strategies (i.e. distraction, and ignoring and reinterpreting pain sensations). The data corroborate the high prevalence of alexithymia in FMS; enhancement was strongest in the Difficulty Identifying Feelings dimension, which was also most closely associated with the patients´ affective symptoms, functional disabilities and maladaptive coping styles. Together with the interaction observed between alexithymia and anxiety and depression, the results support an association between deficient affective processing and the symptoms and functional status of affected patients.

Keywords: Fibromyalgia; chronic pain; alexithymia; neuroticism; extroversion; psychoticism; quality of life; anxiety; depression; coping

Introduction

Fibromyalgia Syndrome (FMS) is a chronic condition characterized by persistent and widespread musculoskeletal pain, which affects 2–4% of the general population (Wolfe et al., 1990; Wolfe, Ross, Anderson, Russell & Hebert, 1995) and approximately 15% of rheumatological samples gathered across different countries (Neumann & Buskila, 2003). Frequent comorbid conditions include fatigue, insomnia, mild cognitive impairment, depression and anxiety disorders (Reyes del Paso, Pulgar, Duschek & Garrido, 2012; Van Middendorp et al., 2008; Wolfe et al., 2010). Despite intensive research, the etiology and pathophysiology of FMS are still widely unknown; furthermore, the disease has no specific somatic signs, and is considered to be on the spectrum of medically unexplained syndromes (Jackson & Kroenke, 2008**)**. Nevertheless, FMS most likely involves abnormal central nervous pain processing and the inhibition of anti-nociceptive inhibitory mechanisms (i.e. central pain sensitization), thereby resulting in diffuse hyperalgesia and allodynia (Loggia et al., 2014; Sumpton & Moulin, 2014).

Psychological vulnerability to stress and negative affect have been proposed as relevant factors in CNS nociceptive sensitization (Duschek et al., 2012; Gracely, Petzke, Wolf & Clauw, 2002; Montoya, Pauli, Batra & Wiedemann., 2005). Interindividual differences in emotional and stress responses may also be relevant in the modulation of psychosocial adaptation and health outcomes in FMS (Crofford & Demitrack, 1996; Goldenberg, 1996), where vulnerability may partly result from the maladaptive ways in which FMS patients regulate their emotions and respond to aversive stimuli (Bartley, Rhudy & Williams., 2009; Duschek, Werner, Limbert, Winkelmann & Montoya, 2014). In this context, alexithymia is considered a relevant factor (Brosschot & Aarsse, 2001; van Middendorp et al., 2008). Alexithymia has been traditionally conceptualized as a personality trait involving a lack of emotional awareness, difficulties in identifying and communicating feelings and an externally oriented cognitive thinking style (Bagby, Parker, & Taylor, 1994a; Sifneos, 1973). However, it has been pointed out that alexithymia can also manifest as a transient state that varies in severity in accordance with stress levels and the presence of psychopathological conditions, including depression and anxiety disorders (Honkalampi, Hintikka, Saarinen, Lehtonen & Viinamäki, 2000; Sifneos, 1988). The most frequently used self-report measure of

alexithymia is the 20-item Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994a; Bagby, Taylor & Parker, 1994b). This questionnaire comprises three subscales pertaining to dimensions of alexithymia: Difficulty Identifying Feelings, Difficulty Describing Feelings, and Externally-Oriented Thinking. The fact that this instrument has been used extensively, together with its good psychometric properties, support its utility (Parker, Bagby, Taylor, Endler & Schmitz, 1993).

Alexithymia has been proposed as factor a mediating the relationship between maladaptive coping and pain chronification. It has also been associated with clinical pain and other factors related to FMS, such as general distress, depression, anxiety, somatosensory amplification, neuroticism and psychoticism (Deary, Scott & Wilson, 1997; Hosoi et al., 2010; Luminet, Bagby, Wagner, Taylor & Parker, 1999; Sandín, Chorot, Santed & Jiménez, 1996; Wise & Mann, 1994). A negative impact of alexithymia on vitality (Hosoi et al., 2010) and extraversion (Parker, Taylor & Bagby, 1989; Luminet et al., 1999) has also been postulated. A large body of research documents increased alexithymia in FMS (e.g. Castelli et al., 2012; Huber, Suman, Biasi & Carli, 2009; Steinweg, Dallas, & Rea, 2011), suggesting that affected patients are more likely than healthy individuals to exhibit deficits in emotional awareness, and difficulties distinguishing emotions from physical sensations and verbally expressing their feelings. Concerning the specific components of alexithymia affected by FMS, recent research points towards a particular enhancement of the Difficulty Identifying Feelings and Difficulty Describing Feelings dimensions (Huber et al., 2009; Martínez et al., 2015).

However, the precise role of alexithymia in FMS pathology is still poorly understood (Taylor, 2000; Huber et al., 2009). It has been proposed that alexithymia interferes with the successful self-regulation of negative emotions, where the resulting sustained aversive affective state may contribute to the onset and exacerbation of psychic and somatic symptoms (Huber et al., 2009). High alexithymic individuals may furthermore tend to misinterpret emotional arousal as symptoms of physical illness, which, by extension, may reinforce maladaptive illness-related behaviors and pain chronification (Pilowsky & Katsikitis, 1994; Lumley, Stettner & Wehmer, 1996). The first studies on the association between alexithymia and specific features of FMS and related symptoms revealed correlations with affective pain experience, depression, anxiety, neuroticism

and health-related quality of life (HRQL; Castelli et al., 2012; Malt, Olafsson, Lund & Ursin., 2002; Tuzer et al., 2011). While the Difficulty Describing Feelings factor appears related to insomnia, anxiety, depression, fear of pain, pain catastrophizing and vigilance to pain (Martínez et al., 2015; Tuzer et al., 2011), the Difficulty Identifying Feelings factor exhibited associations with increased affective pain and experimental pain sensitivity (Huber et al., 2009). However, it should be noted that equivocal results have also been reported that in particular challenge the notion that alexithymia is involved in FMS pain (Evren, Evren & Guler, 2006; Castelli et al., 2012; Sayar, Gulec & Topbas, 2004).

Building on these observations, the present study aimed to further evaluate alexithymia in patients with FMS, in comparison with a healthy control group, and to explore its role in the following, associated clinical features and personality characteristics: (a) clinical symptoms (pain, fatigue, sleep), (b) emotional alterations (anxiety and depression), (c) functional variables (HRQL and functional restrictions) (d) strategies to cope with pain, and (e) H.J. Eysenck´s personality dimensions (neuroticism, psychoticism, extraversion). The main hypotheses were as follows: (1) FMS patients will exhibit more pronounced alexithymia than healthy individuals, specifically in the Difficulty Identifying Feelings and Difficulty Describing Feelings dimensions; and (2) greater levels of alexithymia will be associated with higher levels of clinical pain, anxiety and depression, lower HRQL, more frequent use of maladaptive pain coping strategies, and higher levels of neuroticism and lower levels of extraversion. Given the connection between alexithymia and negative affective states (Hoffart, 1994; Lumley, 2000; Marchesi, Ossola, Tonna & de Panfilis, 2014), and the high prevalence of mood disturbances in FMS patients, depression and anxiety were statistically controlled during the comparison between patients and healthy participants with respect to alexithymia indices. The possible effects of medication use and comorbid psychiatric disorders on alexithymia were also assessed.

Methods

Participants

Fifty-five women with FMS, recruited via the Fibromyalgia Association of Jaén, participated in the study. All patients had been examined by a rheumatologist and met

the American College of Rheumatology criteria for FMS (Wolfe et al., 1990). The exclusionary criteria were as follows: cardiovascular diseases of any kind, metabolic abnormalities, inflammatory causes of pain, neurological disorders, and severe somatic (e.g., cancer) or psychiatric (e.g. psychotic or bipolar) diseases. The control group included 34 healthy women recruited from women's associations in Jaén. They were matched to the patients with respect to age, body mass index and educational level. In addition to having no type of pain disorder, the control group was subject to the same exclusionary criteria as were the patients. Table 1 displays the demographic and clinical characteristics of both study groups.

Table 1

Psychological measures

In addition to a semi-structured interview that assessed clinical history and demographic data, participants were evaluated with the Structured Clinical Interview for Axis I Disorders of the Diagnostic and Statistical Manual for Mental Disorders (SCID, First, Spitzer, Gibbon & Williams, 1999) in order to diagnose possible mental disorders. The self-reported questionnaires used are described below:

Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994a; Spanish adaptation by Martínez-Sánchez, 1996). This instrument measures alexithymia using the following three subscales and 5-point Likert scales ranging from 1 (*strongly disagree*) to 5 (*strongly agree*): Difficulty Identifying Feelings, i.e. the inability to distinguish between specific emotions or between emotions and bodily sensations; Difficulty Describing Feelings, i.e. the inability to verbalize one's emotions; Externally-Oriented Thinking, i.e. an individual´s tendency to focus attention externally rather than on their inner emotional experience. In addition, scores on each subscale are summed to provide a total score, for which the internal consistency (Cronbach´s Alpha) was reported as .76 (Bagby et al., 1994b).

Eysenck Personality Questionnaire Revised-Abbreviated (EPQR-A) (Francis, Brown & Philipchalk, 1992; Spanish adaptation by Sandín, Valiente, Olmedo, Chorot & Santed, 2002a). The EPQR-A comprises three scales (6 items each): Neuroticism,

Extraversion, and Psychoticism. Scores for all scales range from 0 to 6 (answer format: YES / NO). According to Sandín et al. (2002b) the internal consistency values are .74 for Neuroticism, .78 for Extraversion, and .63 for Psychoticism.

State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch & Lushene, 1970; Spanish adaptation by TEA, 1988). This questionnaire consists of 40 items and employs a Likert format with four response alternatives. There are 20 items each for State and Trait Anxiety. The internal consistency of the Spanish version ranges between .90 and .93 for State Anxiety, and between .84 and .87 for Trait Anxiety (Spielberger, Gorsuch & Lushene, 1982).

Beck Depression lnventory (BDI) (Beck, Ward & Mendelson, 1961; Spanish adaptation by Sanz, Navarro & Vázquez, 2003). This scale comprises 21 items, each of which is rated on a 4-point Likert scale ranging from 0 to 3. The internal consistency of the Spanish version ranges from .76 to .95 (Vázquez & Sanz, 1999).

Fisk Fatigue Severity Score (FFSS) (Krupp, LaRocca, Muir-Nash & Steinberg, 1989; Spanish addaption by Bulbena, Berrios & Fernández de Larrinoa, 2000). This scale consists of nine items rated on a 7-point Likert scale ranging from 1 to 7. The scores on each subscale are summed to provide an overall fatigue score. This instrument has an internal consistency value of .88 (Bulbena et al., 2000).

Short-Form Health Survey (SF-36) (Ware & Sherbourne, 1992; Spanish adaptation by Alonso, Prieto & Anto, 1995). This instrument is widely used to measure HRQL; it consists of 36 items covering eight functional domains (Physical Functioning, Physical Role, Bodily Pain, General Health, Vitality, Social Functioning, Emotional Role and Mental Health). Higher scores indicate a higher degree of well-being and less interference from the illness. The internal consistency values of the different scales range from .70 to .94. Three more general indices may be derived from the above subscales: the Physical Component, the Mental Component and a Global Index of HRQL.

Coping Strategies Questionnaire (CSQ) (Rosenstiel & Keefe, 1983; Spanish adaptation by Rodriguez, Cano & Blanco (2004). This self-report questionnaire

comprises eight scales that assess the frequency of use of adaptive (Auto-Instructions, Cognitive Distraction, Diverting Attention, Reinterpreting Pain Sensations, Ignoring Pain Sensations, Hope) and maladaptive (Catastrophizing, Faith-Prayers) pain coping strategies. Internal consistencies values for these scales range between .68 (Ignoring Pain) and .89 (Catastrophizing).

McGill Pain Questionnaire (MPQ) (Melzack, 1975; Spanish adaptation by Lázaro, Bosch, Torrubia & Banos, 1994). This instrument measures sensory, affective and evaluative characteristics of pain. The following parameters were obtained: Total Pain Rating Index (PRI-T; given by the sum of sensory, affective and evaluative pain descriptors), Sensory Pain Rating Index (PRI-S), Emotional Pain Rating Index (PRI-E) and Current Pain Intensity Index (CPI). Internal consistency values range from .56 (PRI-E) to .74 (PRI-T) (Masedo & Esteve, 2000).

Fibromyalgia Impact Questionnaire (FIQ); Spanish adaptation by Esteve-Vives, Rivera, Salvat, de Gracia & Alegre (2007). This questionnaire evaluates aspects of HRQL that tend to be affected in patients suffering from FMS. It consists of 10 items (the first of which also has several sub-items) and total scores range between 0 and 100 (lower scores indicate greater functional capacity and HRQL). According to Rivera & Gonzalez (2004), the internal consistency value for the test is .82.

Oviedo Quality of Sleep Questionnaire (COS, Bobes et al., 2000). The Sleep Satisfaction, Insomnia and Hypersomnia scales were derived from this instrument. Completed under interview, this questionnaire comprises 15 items, each of which is scored on Likert scale ranging from 1 to 5 (aside from item 1, which refers to subjective sleep satisfaction and is scored on a 7-point Likert scale). Bobes et al. (2000) reported a global internal consistency value of .77 for this scale.

Procedure

To avoid overloading the subjects (given the large size of the questionnaire battery), and to ensure that the data was reliable, the study was conducted across two sessions. In the first session, a clinical psychologist recorded the patients' clinical history, medication use and socio-demographic data, assessed the inclusionary and exclusionary criteria and

conducted the SCID interview; the MPQ, BDI and COS were then completed. In the second session, participants completed the remaining questionnaires, i.e. the TAS-20, EPQR-A, CSQ, FFSS, STAI, SF-36, FIQ (FMS patients only). All subjects provided informed consent prior to their participation. The study protocol was approved by the Bioethics Committee of the University of Jaén.

Statistical Analysis

Groups were compared on all questionnaire scales using multivariate analysis of variance (MANOVA). ANOVA models, for the TAS-20 subscales and Anxiety (STAI) and Depression (BDI) scores, were also applied as covariates. Finally, comparisons of the TAS-20 scores, of patients taking and not taking antidepressants, anxiolytics, analgesics and opiates, and of patients who were and were not suffering from depression or anxiety disorders, were performed using ANOVA models. Eta squared (η^2), adjusted for degrees of freedom, was taken as an effect size indicator. Relationships between TAS-20 scores and the remaining scales were examined using step-wise multiple regression analyses. Given the high correlations between total TAS-20 scores and scores on the three individual TAS-20 subscales, and in order to avoid collinearity, only the three TAS-20 subscales were used as predictors (all tolerance values > .60). Separate models were conducted for each of the questionnaire scales. The regression analyses provided an adjusted (for degrees of freedom) r^2 value – which provided an index of the predictive capacity of the model – and standardized β coefficients that represented the slopes of the regression lines. To avoid spurious effects of the expected differences between FMS patients and healthy participants, for each measured variable, regression analyses were performed separately for each group. The significance level was set at $p < .05$.

Results

Group Differences in Questionnaire Scales

MANOVA revealed a multivariate group effect ($F(29, 59) = 12.20$, $p < .0001$, $\eta^2 = .86$). Table 2 displays means (± SD) values, and the statistical results of univariate group comparisons for each variable. For alexithymia, TAS-20 Difficulty Identifying Feelings

and Difficulty Describing Feelings scores, as well as the sum score, were higher in FMS patients vs. controls. The groups did not differ in their scores on the Externally-Oriented Thinking scale. Although Neuroticism was higher in FMS patients vs. controls, no group differences were found in Psychoticism or Extraversion (EPQR-A). Regarding coping strategies (CSQ), Catastrophizing was greater in patients vs. controls, whereas Ignoring Pain Sensations was greater in controls. State and Trait Anxiety (STAI), Depression (BDI), Fatigue (FFSS), Sleep Satisfaction, Insomnia and Hypersomnia (COS), and all McGill Pain Questionnaire scale values, were greater in patients vs. healthy participants. Finally, FMS patients showed lower levels of HRQL than healthy participants according to the three SF-36 indices.

Table 2

Effect of Anxiety and Depression in the TAS-20 Scale Group Comparison

Group differences, in TAS-20 Difficulty Identifying Feelings, Difficulty Describing Feelings and sum scores, remained significant when Anxiety and Depression were entered as covariates. However, a significant effect was revealed for the covariate Trait Anxiety in Difficulty Describing Feelings ($F [1, 88] = 4.24$, $p = .043$, $\eta^2 = .048$); Depression also exhibited a significant effect on Difficulty Identifying Feelings ($F [1, 88] = 9.31$, $p = .003$, $\eta^2 = .100$). In this ANOVA, effect sizes for the group comparisons were lower ($F [1, 88] = 11.09$, $p = .001$, $\eta^2 = .117$ for Difficulty Identifying Feelings; and $F [1, 88] = 4.31$, $p = .041$, $\eta^2 = .049$ for Difficulty Describing Feelings) compared to those in which Anxiety and Depression were not controlled ($F [1, 88] = 58.81$, $p = .000$, $\eta^2 = .403$ for Difficulty Identifying Feeling; $F [1, 88] = 28.08$, $p = .000$, $\eta^2 = .244$ for Difficulty Describing Feelings).

Association between Alexithymia and Personality

TAS-20 Difficulty Describing Feelings was positively associated with EPQR-A Neuroticism in FMS patients ($\beta = .30$, $r^2 = .07$, $t (54) = 2.30$, $p = .025$). In healthy individuals, Externally-Oriented Thinking was correlated positively with both Neuroticism ($\beta = .40$, $r^2 = .13$, $t (33) = 2.47$, $p = .019$) and Psychoticism ($\beta = .37$, $r^2 = .11$, $t (33) = 2.26$, $p = .031$).

Associations between Alexithymia and Clinical Parameters

No significant regression models were obtained for the associations between TAS-20 scale scores and clinical indicators (MPQ, FFSS, COS) in FMS patients. In the healthy group, Difficulty Identifying Feelings was positively associated with the MPQ scales PRI-S (β = .37, r^2 = .11, t (33) = 2.29, p = .029) and PRI-E (β = .35, r^2 = .09, t (33) = 2.20, p = .043), while Difficulty Identifying Feelings was correlated negatively with the COS Sleep Satisfaction scale (β = -.44, r^2 = .17, t (33) = -2.81, p = .008), and positively with Insomnia (β = .44, r^2 = .17, t (33) = 2.80, p = .009); Difficulty Describing Feelings was positively associated with Hypersomnia (β = .42, r^2 = .16, t (33) = 2.65, p = .012).

Associations between Alexithymia, Anxiety and Depression

Difficulty Identifying Feelings correlated positively with STAI Trait Anxiety in both FMS patients (β = .35, r^2 = .11, t (54) = 2.71, p = .009) and healthy participants (β = .34, r^2 = .09, t (33) = 2.07, p = .047). In the healthy group, Difficulty Describing Feelings was positively associated with State Anxiety (β = .42, r^2 = .15, t (33) = 2.62, p = .013). Finally, Difficulty Identifying Feelings showed a positive association with the BDI scores of FMS patients (β = .46, r^2 = .19, t (54) = 3.72, p < .0001).

Associations between Alexithymia and HRQL

In FMS patients, Difficulty Identifying Feelings was inversely associated with the Physical (β = -.35, r^2 = .11, t (54) = -2.75, p = .008) and Global (β = -.37, r^2 = .12, t (54) = -2.93, p = .005) SF-36 components. In healthy participants, Difficulty Identifying Feelings was negatively associated with the Global SF-36 component (β = -.40, r^2 = .13, t (33) = -2.45, p = .020). In a second regression model, Externally-Oriented Thinking was also included as a predictor (β = -.40, t (54) = -2.57, p = .015 for Difficulty Identifying Feelings and β = -.33, t (54) = -2.17, p = .038 for Externally-Oriented Thinking, r^2 = .22). In the healthy group, Difficulty Identifying Feelings was also negatively associated with the Physical SF-36 component (β = -.58, r^2 = .32, t (33) = -4.03, p < .0001), and Externally-Oriented Thinking correlated negatively with the Mental SF-36 scale (β = -.41, r^2 = .14, t = -2.54, p = .016). There were no significant associations between the TAS-20 and the FIQ scales.

Associations between Alexithymia and Pain Coping Strategies

In FMS patients, Difficulty Identifying Feelings correlated negatively with the CSQ scales Cognitive Distraction (β = -.32, r^2 = .08, t (54) = -2.44, p = .018), Ignoring Pain Sensations (β = -.27, r^2 = .05, t (54) = -2.00, p = .050) and Reinterpreting Pain Sensations (β = -.27, r^2 = .05, t (54) = -2.09, p = .042). In healthy participants, Difficulty Describing Feelings was inversely associated with Cognitive Distraction (β = -.48, r^2 = .20, t (33) = -3.08, p = .004), and Externally-Oriented Thinking correlated positively with scores on the Hope scale (β = .64, r^2 = .39, t (33) = 4.71, p < .0001).

Differences in Alexithymia as a Function of Medication Use and Psychiatric Co-morbidity

Stratified comparisons of TAS-20 scale scores, between patients taking and not taking antidepressants, anxiolytics, analgesics and opiates, revealed no significant effects (all p > .05). This was also the case for the comparisons between patients suffering and not suffering from co-morbid depression and anxiety disorders.

Discussion

As expected based on previous evidence, patients diagnosed with FMS exhibited markedly greater levels of alexithymia compared to healthy controls (Castelli et al., 2012; Gil et al., 2008; Huber et al., 2009; Sayar et al., 2004; Steinweg et al., 2011; Tuzer et al., 2011; Van Middendorp et al., 2008). Specifically, patients had significantly higher TAS-20 Difficulty Identifying Feelings, Difficulty Describing Feelings and sum scores. Based on the two major components of the alexithymia construct (Herbert, Herbert, & Pollatos, 2011), the present finding suggests a particular enhancement of the affective dimension in FMS, whereas the cognitive dimension may remain largely unaffected. While Difficulty Identifying Feelings and Difficulty Describing Feelings are commonly viewed as affective traits, External-Oriented Thinking represents operatory thinking i.e. a specific cognitive style that focuses on external events rather than inner experiences (Lane, Sechrest, Riedel, Shapiro & Kaszniak, 2000; Zackheim, 2007). As previously observed, the largest effect size in alexithymia components was revealed for Difficulty Identifying Feelings (Castelli et al., 2012; Huber et al., 2009; Steinweg et al.,

2011). According to Taylor, Bagby & Parker (1997), poor accuracy in perceiving physical symptoms is mainly represented by the component Difficulty Identifying Feelings and to a lesser extent by Difficulty Describing Feelings; the Externally-Oriented Thinking dimension (Deary et al., 1997; Martínez-Sánchez., 1996) contributes only minimally.

Additionally, as one might expect given the well-known comorbidity between FMS and affective and anxiety disorders (e.g. Reyes del Paso et al., 2012; Van Middendorp et al., 2008; Wolfe et al., 1990), the presently investigated patients exhibited higher levels of neuroticism than did healthy participants (Besteiro et a., 2008; Malt et al., 2002; Montoro & Reyes del Paso, 2015; Ortet, Ibanez, llerena & Torrubia, 2002). While the lack of a group difference in psychoticism contrasts with an earlier observation (Montoro & Reyes del Paso, 2015), the lack of an effect of extraversion is in line with previous reports (Malin & Littlejohn, 2012; Montoro & Reyes del Paso, 2015). Our FMS sample furthermore showed increased levels of anxiety, depression, fatigue and sleep problems, as well as lower HRQL than healthy participants, which also accords with the current literature (Malin & Littlejohn, 2012; Montoro & Reyes del Paso, 2015; Wolfe et al., 2010). Regarding strategies to cope with pain, patients scored higher on Catastrophizing, and lower on the CSQ scale Ignoring Pain Sensations, supporting the notion of suboptimal coping in FMS (Herken, Gursoy, Yetkin, Virit & Esgi., 2001; Houdenhove & Luyten, 2006).

In the present context, the differentiation between "primary" or “trait” alexithymia (i.e. a stable personality characteristic) and "secondary" or “state” alexithymia (i.e. a transient stress response) may also be of interest (Honkalampi et al., 2000, 2001; Sifneos, 1988). State alexithymia has been related to the experience of childhood trauma (Frewen et al., 2008; Lumley, Smith & Longo, 2002); patients with FMS frequently report a history of psychological trauma before the onset of the illness (Cohen et al., 2002; Greenfield, Fitzcharles & Esdaile, 1992), including high rates of childhood trauma (Imbierowicz & Egle, 2003; Goldberg, Pachas & Keith, 1999; Walker et al., 1997). Posttraumatic stress may give rise to maladaptive cognitive and affective information-processing (Heaton, Davis & Happe, 2008) and sustained psychological distress (Alexander et al., 1998; McBeth, Macfarlane, Benjamin, Morris & Silman, 1999). It has been recently suggested that the TAS-20 primarily assesses alexithymia in

terms of a state-dependent syndrome, which varies according to stress levels, negative affect and clinical depression and anxiety (Marchesi et al., 2014). Various studies have demonstrated a decrease in TAS-20 scores during the remission of depressive symptoms (Honkalampi et al., 2000; Marchesi, Bertoni & Maggini, 2009; Saarijärvi, Salminen & Toikka, 2001). To examine the role of negative affect in TAS-20 scale group differences, depression and anxiety were entered into the analysis as covariates. This led to a decrease in effect sizes for both Difficulty Identifying Feelings (η^2 = .40 vs. .12) and Difficulty Describing Feelings (η^2 = .24 vs. .05). In light of the reasoning delineated above, it may be speculated that these TAS-20 scales do indeed, at least partly, represent negative stress and affect-related states rather than personality traits (Hoffart, 1994; Lumley, 2000; Marchesi et al., 2014).

Regarding personality factors, Difficulty Describing Feelings was positively associated with neuroticism in FMS patients (c.f. Malt et al., 2002). This accords with the notion of a mutual influence of deficient emotional processing and emotional instability (Taylor et al., 1997). In healthy individuals, the Externally-Oriented Thinking scale was positively associated with psychoticism. Alexithymia has been related to different aspects that can be involved in interpersonal problems, such as assertiveness, sociability, intimacy and responsibility (Nicoló et al., 2011; Zarei & Besharat., 2010). This may account for the relationship with psychoticism, conceptualized as a tendency towards tough mindedness, impulsivity, aggressiveness, egocentrism, irresponsibility, emotional detachment and low empathy (Eysenck & Eysenck, 1985).

Interestingly, no significant relationship was found between alexithymia and clinical pain in the patient group. While several previous studies in patients with FMS (Huber et al., 2009; Martínez et al., 2015) and other chronic pain diseases (Hosoi et al., 2010; Kano, Hamaguchi, Itoh, Yanai & Fukudo, 2007) revealed positive correlations between alexithymia and pain severity, other studies reported no such associations (e.g. Evren et al., 2006); some authors regard pain and alexithymia to be independent phenomena in FMS (Castelli et al., 2012; Sayar et al., 2004). In contrast, Difficulty Identifying Feelings correlated positively with both sensorial and affective pain in the control group, which may point towards an association between this facet of alexithymia and sporadic pain in healthy individuals (c.f. Shibata et al., 2014 for a similar finding in a population-based sample).

In accordance with pre-existing knowledge, and the affective nature of alexithymia, Difficulty Identifying Feelings was associated with higher levels of anxiety and depression in FMS patients (Malt et al., 2002). In both study groups, Difficulty Identifying Feelings also correlated positive with trait anxiety. In addition, the Difficulty Describing Feelings scale was positively associated with state anxiety in healthy subjects. These observations reflect the known connections between alexithymia and pathological and non-pathological anxiety and depressiveness (Hendryx, Haviland & Shaw, 1991). Concerning functional features, Difficulty Identifying Feelings was inversely associated with global HRQL (indexed by scores on the SF-36) in both study groups (c.f. Castelli et al., 2012 and Honkalampi, Hintikka, Tanskanen, Lehtonen & Viinamäki., 2000, for similar results). In FMS patients, Difficulty Identifying Feelings also correlated negative with the physical SF-36 component. In contrast, FIQ scores were unrelated to alexithymia, which is surprising because the FIQ is an instrument specifically adapted for use with FMS patients, whereas the SF-36 is more general in scope (for further discussion of this issue c.f. Montoro & Reyes del Paso, 2015). Finally, in the FMS sample the Difficulty Identifying Feelings score was inversely associated with the CSQ Cognitive Distraction, Ignoring Pain Sensations and Reinterpreting Pain Sensations scales, which supports the notion that high alexithymic patients are less able to adaptively cope with pain (Acklin & Bernat, 1987; Martínez et al., 2015).

In summary, this study corroborates the notion that alexithymia prevalence is high in FMS patients, where the enhancement appears to be greatest in the affective dimension, particularly the Difficulty Identifying Feelings component. While our results challenge the assumption of an involvement of alexithymia in primary pain symptoms, they support its contribution to the patients´ self-reported affective symptoms, functional disabilities and maladaptive coping with pain. Among the TAS-20 scales, Difficulty Identifying Feeling explained the largest proportion of the variance in all of these features, which again underlines the relevance of this dimension in FMS-related pathology. However, the fact that, in certain cases, relationships between alexithymia and psychological variables were even closer in the healthy control group than in FMS patients, should not be overlooked. It would therefore not be justified to regard altered affective processing as a cause of primary and secondary disease symptoms. Future research in this field should take into consideration the overlap between alexithymia and depression, anxiety and general emotional distress. Furthermore, it may be worthwhile

to explicitly differentiate between alexithymia as a personality trait and a state-dependent stress response, and to consider possible dissociations between these two facets.

References

Acklin, M.W., & Bernat, E. (1987). Depression, alexithymia and pain prone disorder: A Rorschach study. *Journal of Assessment, 51*, 462-479.

Alexander, R.W., Aaron, L.A., Alberts, K.R., Martin, M.Y., Stewart, K.E., Bradley, L. A., ... & Triana-Alexander, M. (1998). Sexual and physical abuse in women with fibromyalgia: association with outpatient health care utilization and pain medication usage. *Arthritis & Rheumatism*, *11*, 102-115.

Alonso, J., Prieto, L., & Antó, J.M. (1995). La versión española del SF-36 Health Survey (Cuestionario de Salud SF-36): Un instrumento para la medida de los resultados clínicos. *Medicina clínica, 104*, 771-776.

Bagby, R.M., Parker, J.D.A., & Taylor, G.L. (1994a). The twenty-item Toronto Alexithymia Scale: I. Item selection and cross-validation of the factor structure. *Journal of Psychosomatic Research, 38 (1),* 23-32

Bagby, R.M., Taylor G.J., & Parker J.D. (1994b). The twenty item Toronto Alexithymia Scale-II: Convergent, discriminant, and concurrent validity. *Journal of Psychosomatic Research, 38(1),* 33-40.

Bartley, E., Rhudy, J., & Williams, A. (2009). Experimental Assessment of Affective Processing in Fibromyalgia. *The Journal of Pain, 10*, 1151–1160

Beck, A.T., Ward, C.H., & Mendelson, M. (1961). Inventory for measuring depression. *Archives of general Psychiatry, 4*, 561-571.

Besteiro, J., Álvarez, M., Lemos, S., Muñiz, J., Costas, C., & Weruaga, A. (2008). Dimensiones de personalidad, sentido de coherencia y salud percibida en pacientes con un Síndrome Fibromiálgico. *International Journal of Clinical and Health Psychology, 8*, 411-427.

Bobes, J., González, M.P., Sáiz, P.A., Bascarán, M.T., Iglesias, C., & Fernández, J.M. (2000). Propiedades psicométricas del cuestionario Oviedo de Sueño. *Psicothema, 1*, 107-112.

Brosschot, J.F., & Aarsse, H.R. (2001). Restricted emotional processing and somatic attribution in fibromyalgia. *The International Journal of Psychiatry in Medicine, 31*, 127-146.

Bulbena, A., Berrios, G.E. & Fernández de Larrinoa, P. (2000). *Medición clínica en psiquiatría y psicología.* Madrid: Masson.

Castelli, L., Tesio, V., Colonna, F., Molinaro, S., Leombruni, P., Bruzzone, M., ... & Torta, R. (2012). Alexithymia and psychological distress in fibromyalgia: prevalence and relation with quality of life. *Clinical and Experimental Rheumatology, 30 (6 Suppl 74)*, 70-7.

Cohen, H., Neumann, L., Haiman, Y., Matar, M.A., Press, J., & Buskila, D. (2002). Prevalence of posttraumatic stress disorder in fibromyalgia patients: overlapping syndromes or post-traumatic fibromyalgia syndrome? *Seminars in Arthritis and Rheumatism, 32*, 38-50.

Crofford, L.J., & Demitrack, M.A. (1996). Evidence that abnormalities of central neurohormonal systems are key to understanding fibromyalgia and chronic fatigue. *Rheumatic Disease Clinics of North America, 2*, 267–284.

Deary, I.J., Scott, S., & Wilson, J.A. (1997). Neuroticism, alexithymia and medically unexplained symptoms. *Personality and Individual Differences*, 22, 551-564.

Duschek, S., Mannhart, T., Winkelmann, A., Merzoug, K., Werner, N.S., Schuepbach, D., & Montoya, P. (2012). Cerebral blood flow dynamics during pain processing in patients with fibromyalgia syndrome. *Psychosomatic Medicine, 74*, 802-809.

Duschek, S., Werner, N.S., Limbert, N. Winkelmann A., & Montoya, P. (2014). Attentional bias towards negative information in patients with fibromyalgia syndrome. *Pain Medicine, 15*, 603-612.

Esteve-Vives, J., Rivera, J., Salvat, I., de Gracia, M., & Alegre, C. (2007). Propuesta de una versión de consenso del Fibromyalgia Impact Questionnaire (FIQ) para la población española. *Reumatología Clínica, 3*, 21-24.

Evren, B., Evren, C., & Guler, M.H. (2006). Clinical correlates of alexithymia in patients with fibromyalgia. *Pain Clinic, 18*:1-9

Eysenck, H.J., & Eysenck, M.W. (1985). *Personality and individual differences: a natural science approach*. New York: Plenum.

First, M.B., Spitzer, R.L., Gibbon, M., & Williams, J.B.W. (1999). Entrevista clínica estructurada para los trastornos de eje I del DSM-IV (versión clínica) SCID-I.

Francis, L.J., Brown, L.B., & Philipchalk, R. (1992). The development of an abbreviated form of the Revised Eysenck Personality Questionnaire (EPQR-A): Its use among students in England, Ganada, the U.S.A and Australia. *Personality and Individual Differences, 13*, 443-449.

Frewen, P.A., Lanius, R.A., Dozois, D.J., Neufeld, R.W., Pain, C., Hopper, J.W., ... & Stevens, T.K. (2008). Clinical and neural correlates of alexithymia in posttraumatic stress disorder. *Journal of Abnormal Psychology, 117*, 171-81.

Gil, F., Pedrosa, M.D., Weigl, M., Wessels, T., Irnich, D., Baumüller, E., & Winkelmann, A. (2008). Parental Bonding and Alexithymia in Adults with Fibromyalgia, *Psychosomatics, 49, 2*, 115-22.

Goldenberg, D.L (1996). Fibromyalgia, chronic fatigue syndrome, and myofacial pain. *Current Opinion in Rheumatology, 8*, 113–123.

Goldberg, R.T., Pachas, W.N., & Keith, D. (1999). Relationship between traumatic events in childhood and chronic pain. *Disability and Rehabilitation, 21*, 23-30.

Gracely, R.H., Petzke, F., Wolf, J.M., & Clauw, D.J. (2002) Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis & Rheumatism, 46*, 1333-1343

Greenfield, S., Fitzcharles, M., & Esdaile, J. (1992). Reactive fibromyalgia syndrome. *Arthritis & Rheumatism, 35*, 678-81.

Heaton, P., Davis, R.E., & Happe, F.G. (2008). Research note: exceptional absolute pitch perception for spoken words in an able adult with autism. *Neuropsychologia, 46*, 2095-8.

Hendryx, M.S., Haviland, M.G., & Shaw D.G. (1991). Dimensions of alexithymia and their relationships to anxiety and depression. *Journal of Personality Assessment, 56*, 227-237.

Herbert, B.M., Herbert, C., & Pollatos, O. (2011). On the relationship between interoceptive awareness and alexithymia: is interoceptive awareness related to emotional awareness? *Journal of personality*, *79*, 1149-1175.

Herken, H., Gursoy, S., Yetkin, O., Virit, O., & Esgi, K. (2001). Personality characteristics and depression levels in female patients with Fibromyalgia Syndrome. *International Medical Journal, 8*, 41-44.

Hoffart, A. (1994). State and personality in agoraphobic patients. *Journal of Personality Disorders, 8*, 333-41.

Honkalampi, K., Hintikka, J., Tanskanen, A., Lehtonen, J., & Viinamäki, H. (2000). Depression is strongly associated with alexithymia in the general population. *Journal of Psychosomatic Research, 48*, 99-104

Honkalampi, K., Hintikka, J., Saarinen, P., Lehtonen, J., & Viinamäki, H. (2000). Is alexithymia a permanent feature in depressed outpatients? Results from a 6-month follow-up study. *Psychotherapy and Psychosomatics, 69,* 303-8.

Honkalampi, K., Koivumaa-Honkanen, H., Tanskanen, A., Hintikka, J., Lehtonen, J., & Viinamaeki, H. (2001). Why do alexithymic features appear to be stable? *Psychotherapy and Psychosomatics, 70,* 247-253.

Hosoi, M., Molton, I., Jensen, M., Ehde, D., Amtmann, S., O'Brien, S., Arimura, T., & Kubo, C. (2010). Relationships among alexithymia and pain intensity, pain interference, and vitality in persons with neuromuscular disease: Considering the effect of negative affectivity. *Pain, 149,* 273-277.

Houdenhove B.V., & Luyten, P. (2006). Stress, depression and fibromyalgia. *Acta Neurologica Belgica, 106,* 149–156.

Huber, A., Suman, A.L., Biasi, G., & Carli, G. (2009). Alexithymia in fibromyalgia syndrome: associations with ongoing pain, experimental pain sensitivity and illness behavior. *Journal of Psychosomatic Research, 66,* 425-433.

Imbierowicz, K., & Egle, U.T. (2003). Childhood adversities in patients with fibromyalgia and somatoform pain disorder. *European Journal of Pain, 7,* 113-9.

Jackson, J.L., & Kroenke, K. (2008). *Prevalence, impact, and prognosis of multisomatoform disorder in primary care: a 5-year follow-up study. Psychosomatic Medicine, 70, 430–4.*

Kano, M., Hamaguchi T., Itoh M., Yanai K., & Fukudo S. (2007).Correlation between alexithymia and hypersensitivity to visceral stimulation in human. *Journal of Pain, 132,* 252-263.

Krupp, L.B., LaRocca, N.G., Muir-Nash, J., & Steinberg, A.D. (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology, 46,* 1121-1123.

Lane, R.D., Sechrest, L., Riedel, R., Shapiro, D.E., & Kaszniak, A.W. (2000). Pervasive emotion recognition deficit common to alexithymia and the repressive coping style. *Psychosomatic Medicine, 62,* 492-501.

Lázaro, C., Bosch, F., Torrubia, R., & Banos, J.E. (1994). The development of a Spanish Questionnaire for assessing pain: preliminary data concerning reliability and validity. *European Journal Psychological Assessment, 10,* 145–151.

Loggia, M.L., Berna, C., Kim, J., Cahalan, C.M., Gollub, R.L., Wasan, A.D., ... & Napadow, V. (2014). Disrupted brain circuitry for pain related reward/punishment in Fibromyalgia. *Arthritis Rheumatism, 66,* 203-212.

Luminet, O., Bagby, R.M., Wagne r, H., Taylor, G.J., & Parker, J.D. (1999). Relations between alexithymia and the five-factor model of personality: a facet-level analysis. *Journal of Personality Assessment, 73(3),* 345-358.

Lumley, M.A. (2000). Alexithymia and negative emotional conditions. *Journal of Psychosomatic Research, 49,* 51-4.

Lumley, M.A, Smith, J.A., & Longo, D.J. (2002). The relationship of alexithymia to pain severity and impairment among patients with chronic myofascial pain: comparisons with self-efficacy, catastrophizing, and depression. *Journal of Psychosomatic Research, 53,* 823-30.

Lumley, M.A., Stettner, L., & Wehmer, F. (1996). How are alexithymia and physical illness linked? A review and critique of pathways. *Journal of Psychosomatic Research 41,* 505–518

Malin, K. & Littlejohn, G. (2012). Neuroticism in young women with Fibromyalgia links to key clinical features. *Pain Research and Treatment, 2012,* 730-741.

Malt, E.A., Olafsson, S., Lund, A., & Ursin, H. (2002). Factors explaining variance in perceived pain in women with fibromyalgia. *BMC Musculoskeletal Disorders, 3,* 12.

Marchesi, C., Bertoni, S., & Maggini, C. (2009). Major and minor depression in pregnancy. *Obstetrics & Gynecology, 113,* 1292-8.

Marchesi, C., Ossola, P., Tonna, M., & de Panfilis, C. (2014). The TAS-20 more likely measures negative affects rather than alexithymia itself in patients with major depression, panic disorder, eating disorders and substance use disorders. *Comprehensive Psychiatry, 55,* 972-8.

Martínez-Sánchez, F. (1996). The Spanish version of the Toronto Alexithymia Scale (TAS-20). *Clínica y Salud, 7,* 19-32

Martínez, M.P., Sánchez, A.I., Miró, E., Lami, M.J., Prados, J., & Morales, A. (2015). Relationships between physical symptoms, emotional distress, and pain appraisal in Fibromyalgia: the moderator effect of alexithymia. *The Journal of Psychology: Interdisciplinary and Applied, 149,* 115-140.

Masedo, A.I., & Esteve, R. (2000). Some empirical evidence regarding the validity of the Spanish version of the McGill Pain Questionnaire (MPQ-SV). *Pain, 85,* 451-6.

McBeth, J., Macfarlane, G.J., Benjamin, S., Morris, S., & Silman, A.J. (1999). The association between tender points, psychological distress and adverse childhood experiences: a community-based study. *Arthritis and Rheumatism, 42,* 1397-404.

Melzack, R. (1975). The Mc Gill Pain questionnaire: major properties and scoring methods. *Pain, 1,* 277-299.

Montoro, C.I., & Reyes del Paso, G.A. (2015). Personality and fibromyalgia: relationships with clinical, emotional, and functional variables. *Personality and Individual Differences, 85,* 236-244.

Montoya, P., Pauli, P., Batra, A., & Wiedemann, G. (2005). Altered processing of pain-related information in patients with fibromyalgia. *European Journal of Pain, 9*, 293–303.

Neumann, L., & Buskila, D. (2003). Epidemiology of fibromyalgia. *Current Pain and Headache Reports, 7*, 362–368.

Nicoló, G., Semeri, A., Lysaker., Dimaggio, G., Conti., L., D´Angerio, S., Procacci, M., Popolo, R., & Carcione, A. (2011). Alexithymia in personality disorders: Correlations with symptoms and interpersonal functioning. *Psychiatry Research, 190*, 37-42.

Ortet, G., Ibanez, M., llerena, A., & Torrubia, R. (2002). The underlying traits of the Karolinska Scales of Personality (KSP). *European Journal of Psychological Assesstment, 18*, 139-48.

Parker, J.D., Bagby R.M., Taylor G.J., Endler N.S., & Schmitz P. (1993). Factorial validity of the 20-item Toronto Alexithymia Scale. *European Journal of Personality, 7*, 221-232.

Parker, J.D., Taylor, G.J., & Bagby, R.M. (1989). The alexithymia construct: relationship with sociodemographic variables and intelligence. *Comprehensive Psychiatry, 30*, 434-441.

Pilowsky, I., & Katsikitis, M. (1994). A classification of illness behavior in pain clinic patients. *Pain, 57*, 91–94.

Reyes del Paso, G.A., Pulgar, A., Duschek, S., & Garrido, S. (2012). Cognitive impairment in Fibromyalgia Syndrome: The impact of cardiovascular regulation, pain, emotional disorders and medication. *European Journal of Pain, 16*, 421–429.

Rivera, J., & González, T. (2004). The Fibromyalgia Impact Questionnaire: a validated Spanish version to assess the health status in women with Fibromyalgia. *Clinical and Experimental Rheumatology, 22,* 554-60.

Rodriguez, L., Cano, E.J., & Blanco, A. (2004). Evaluación de las estrategias de afrontamiento de dolor crónico. *Actas Españolas Psiquiatría, 32,* 82-91.

Rosenstiel, A.K., & Keefe, F.J. (1983). The use of coping strategies in chronic low back pain patients: Relationship to patient characteristics and current adjustment. *Pain, 17,* 33-44.

Sandin, B., Chorot, P., Santed, M.A., & Jiménez, P. (1996). Dimensiones de la alexitimia y estados emocionales de ansiedad, depresión e ira. *Psiquis: Revista de Psiquiatria, Psicologia y Psicosomatica, 17,* 37-45.

Sandín, B., Valiente, R.M., Olmedo, M., Chorot, P., & Santed, M.A. (2002a). Versión Española del EPQR-A (I). Análisis exploratorio de la estructura factorial. *Revista de Psicopatología y Psicología Clínica, 7,* 195-205.

Sandín, B., Valiente, R. M., Olmedo, M., Chorot, P., & Santed, M. A. (2002b). Versión Española del EPQR-Abreviado (EPQR-A) (III). Replicación factorial, fiabilidad y validez. *Revista de Psicopatología y Psicología Clínica, 3,* 207-216.

Sanz, J., Navarro, M.E., & Vázquez, C. (2003). Adaptación española del Inventario para la Depresión de Beck-II (BDI-II): I. Propiedades psicométricas en estudiantes universitarios. *Análisis y Modificación de Conducta, 29,* 239-288.

Saarijärvi, S., Salminen, J.K., & Toikka, T.B. (2001). Alexithymia and depression. A 1-year follow-up study in outpatients with major depression. *Journal of Psychosomatic Research, 51,* 729-33.

Sayar, K., Gulec, H., & Topbas, M. (2004). Alexithymia and anger in patients with fibromyalgia. *Clinical Rheumatology, 23,* 441-448

Shibata, M., Ninomiya, T., Jensen, M.P., Anno, K., Yonemoto, K., Makino, S., … & Hosoi, M. (2014). Alexithymia is associated with greater risk of chronic pain and negative affect and with lower life satisfaction in a general population: the Hisayama study. *PLoS ONE, 9 (3),* e90984. doi:10.1371/journal.pone.0090984.

Sifneos, P.E. (1973). The prevalence of ‘‘alexithymic’’ characteristic mechanisms in psychosomatic patients. *Psychotherapy and Psychosomatics, 21,* 133-136.

Sifneos, P.E. (1988). Alexithymia and its relationship to hemispheric specialization, affect, and creativity**.** *Psychiatric Clinic of North America, 3,* 287-92.

Spielberger, C.D., Gorsuch, R.C., & Lushene, R.E. (1970). *Manual for the State Trait Anxiety Inventory*. Palo Alto. California: Consulting Psychologists Press. (Adapt. Española, TEA, 1982).

Spielberger, C.D., Gorsuch, R.L., & Lushene, R.E. (1982). *Manual del Cuestionario de Ansiedad Estado/Rasgo (STAI).* Madrid, España: TEA Ediciones.

Spielberger, C.D., Gorsuch, R.L., & Lushene, R.E. (1988). *Cuestionario de ansiedad estado-rasgo.* Madrid: TEA.

Steinweg, D.L., Dallas, A.P., & Rea, W.S. (2011). Fibromyalgia: unspeakable suffering, a prevalence study of alexithymia. *Psychosomatics, 52,* 255-262.

Sumpton, J., & Moulin, D. (2014). Fibromyalgia. *Handbook of Clinical Neurology, 119,* 513-27.

Taylor, G.J. (2000). Recent development in alexithymia theory and research. The *Canadian Journal of Psychiatry, 45,* 134–142.

Taylor, G.J., Bagby, R.M., & Parker, J.D. (1997). *Disorders of affect regulation*. Cambridge, UK: Cambridge University Press.

Tuzer, V., Bulut, S.D., Bastug, B., Kayalar, G., Göka, E., & Bestepe, E. (2011).Causal attributions and alexithymia in female patients with fibromyalgia or chronic low back pain. *Nordic Journal of Psychiatry, 65,* 138–144.

Van Middendorp, H., Lumley, M., Jacobs, J., Van Doornen, L., Bijlsma, J., & Geenen, R. (2008). Emotions and emotional approach and avoidance strategies in fibromyalgia. *Journal of Psychosomatic Research, 64,* 159-167.

Vázquez, C., & Sanz, J. (1999). Fiabilidad y validez de la versión española del Inventario para la Depresión de Beck de 1978 en pacientes con trastornos psicológicos. Reliability and validity of the Spanish version of the Beck Depression Inventory (1978) in patients with psychological disorders. *Clínica y Salud, 1,* 59-81.

Walker, E.A., Keegan, D., Gardner, G., Sullivan, M., Bernstein, D., & Katon, W.J. (1997). Psychosocial factors in fibromyalgia compared with rheumatoid arthritis: II. Sexual, physical and emotional abuse and neglect. *Psychosomatic Medicine, 59,* 572-7.

Ware, J.E., & Sherbourne, C.D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care, 30,* 473–483.

Wise, T.N., & Mann, L.S. (1994). The relationship between somatosensory amplification, alexithymia and neuroticism. *Journal of Psychosomatic Research, 38,* 515-521.

Wolfe, F., Clauw, D.J., Fitzcharles, M.A., Goldenberg, D.L., Katz, R.S., Mease, P., …& Yunus, M.B (2010). "The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity". *Arthritis Care and Research, 5,* 600–610.

Wolfe, F., Ross, K., Anderson, J., Russell, I.J., & Hebert L. (1995). The prevalence and characteristics of fibromyalgia in the general population. *Arthritis and Rheumatism, 38,* 19-28.

Wolfe, F., Smythe, H.A., Yunus, M.B., Bennett, R.M., Bombardier, C., Goldenberg, D.L., …& Sheon, R.P. (1990). The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis and Rheumatism, 33,* 160-172.

Zackheim, L. (2007). Alexithymia: The expanding realm of research. *Journal of Psychosomatic Research, 63,* 345-347.

Zarei, J., & Besharat, M. (2010). Alexithymia and interpersonal problems. *Procedia-Social and Behavioral Sciencies, 5,* 619-622.

Table 1. Demographic and clinical data (mean ± SD) and medications use (number of participants, percentage in brackets) in both study groups; results of group comparisons (Student's *t*-test or χ^2-test).

	Fibromyalgia	**Control group**	***t or*** χ^2	***P***
Age	51.93±8.75	49.06±9.25	2.16	.15
Body Mass Index	28.06±4.52	26.31±5.44	2.67	.11
Years of education	10.07±4.14	11.41±4.62	2.01	.16
Depression (%)	21 (38.2)	4 (11.8)	7.18	.006
Anxiety disorders (%)	25 (45.5)	4 (11.8)	10.73	.001
Antidepressant use (%)	25 (45.5)	1 (2.9)	18.15	<.0001
Anxiolytic use (%)	31 (56.4)	12 (35.5)	3.69	.043
Analgesic use (%)	44 (80.0)	6 (17.6)	32.81	<.0001
Opiate use (%)	19 (34.5)	0 (0)	14.77	<.0001

Table 2. Questionnaire scales (mean ± SD) in both study groups; values of F, p and η^2 from the group comparisons.

		Fibromyalgia Patients	Control Group	F	p	η^2
TAS-20	DIF	19.98±6.83	10.36±3.31	58.81	<.001	.40
	DDF	15.04±4.63	10.18±3.39	28.08	<.001	.24
	EOT	22.42±3.89	21.75±3.75	0.65	.42	.007
	TAS	57.44±10.94	42.18±7.21	52.07	<.001	.37
EPQR-A	N	4.67±1.35	2.87±1.65	31.50	<.001	.27
	E	3.53±1.20	3.75±.89	0.87	.35	.010
	P	2.65±.89	2.62±1.07	0.02	.89	.00
CSQ	CAT	17.95±6.73	7.59±6.10	53.31	<.001	.38
	CD	17.35±6.91	18.34±7.64	0.40	.53	.005
	AUT	18.35±5.69	19.09±6.78	0.31	.58	.004
	IPS	21.76±6.43	25.09±7.37	5.04	.027	.055
	RPS	15.25±6.79	15.90±9.45	0.14	.71	.002
	HOP	9.78±4.37	10.41±4.81	0.40	.53	.005
	FP	8.31±5.53	6.47±5.45	2.35	.13	.026
	DA	10.56±3.91	11.47±4.06	1.09	.30	.012
FFSS		50.19±12.97	20.81±8.42	138.06	<.001	.61
STAI	STAI-S	30.98±11.61	20.87±8.94	18.85	<.001	.18
	STAI-T	35.74±8.95	19.34±9.67	66.35	<.001	.43
BDI		21.56±11.72	7.30±7.57	39.93	<.001	.32

COS	S	2.65±1.45	4.00±1.54	17.37	<.001	.17
	I	29.46±7.55	18.81±8.08	39.62	<.001	.31
	H	8.51±5.09	4.57±1.88	18.78	<.001	.18
MPQ	PRI-S	35.33±18.57	11.39±7.54	51.09	<.001	.37
	PRI-E	6.06±4.52	1.36±1.70	33.58	<.001	.28
	CPI	3.28±.95	1.39±.95	82.42	<.001	.49
	PRI-T	54.35±30.41	18.88±11.95	42.10	<.001	.33
SF-36	PC	37.72±9.16	65.43±4.89	263.79	<.001	.75
	MC	34.22±9.63	54.71±5.58	103.22	<.001	.54
	GQL	75.16±15.05	123.00±11.07	257.10	<.001	.75

Abbreviations: TAS-20 = Toronto Alexithymia Scale, 20 Item Version, DIF = Difficulty Identifying Feelings, DDF = Difficulty Describing Feelings, EOT = Externally-Oriented Thinking, TAS = TAS Total Score, *EPQR-A* = Eysenck Personality Questionnaire Revised-Abbreviated, *N = Neuroticism*, *E = Extraversion*, *P = Psychoticism*, CSQ = Coping Strategies Questionnaire, CAT = Catastrophizing, CD = Cognitive Distraction, AUT = Auto-Instructions, IPS = Ignoring Pain Sensations, RPS = Reinterpreting Pain Sensations, HOP = Hope, FP = Faith-Prayers, DA = Diverting Attention, FFSS = Fisk Fatigue Severity Score, STAI = State-Trait Anxiety Inventory, STAI-S = STAI-State, STAI-T = STAI-Trait, BDI = Beck Depression lnventory, COS = Oviedo Quality of Sleep Questionnaire, S = Sleep Satisfaction, I = Insomnia, H = Hypersomnia; MPQ = McGill Pain Questionnaire, Sensorial Pain Rating Index (PRI-S), Emotional Pain Rating Index (PRI-E), CPI= Current Pain intensity, PRI-T = Total Pain Index, SF-36 = Short-Form Health Survey, PC = Physical Component, MC = Mental Component, GQL = Global Quality of Life

4. DISCUSIÓN GENERAL Y PERSPECTIVAS FUTURAS

Hasta ahora, la práctica clínica ha centrado su atención en el manejo de las pacientes con fibromialgia y la veracidad de sus síntomas. Estudios como los que conforman el presente trabajo abogan por la confirmación de la realidad de mecanismos que explican los síntomas en la fibromialgia. Los resultados a obtenidos también pueden proporcionar pistas útiles para desarrollar una intervención eficaz en la fibromialgia (hoy en día no existe un tratamiento óptimo). El conocimiento más detallado de los posibles factores intervinientes en el proceso de Sensibilización Central al Dolor, junto con los mecanismos que puedan explicar los déficits cognitivos, podría ser útil para iniciar investigaciones tendentes a buscar tratamientos más efectivos para esta enfermedad.

Por ello, el objetivo de la presente Tesis Doctoral fue la aplicación de la técnica de *ultrasonografía Doppler transcraneal funcional* (fTCD) al estudio de la dinámica temporal de las respuestas de flujo sanguíneo cerebral en la fibromialgia ante estimulación nociceptiva y procesamiento cognitivo (aritmética mental y tiempo de reacción). Respecto al primer apartado, se analizó la existencia de Sensibilización Central al Dolor en la fibromialgia mediante el estudio de las respuestas de flujo sanguíneo cerebral ante estimulación dolorosa. Respecto al segundo apartado, dado que la capacidad para incrementar el flujo sanguíneo cerebral durante el procesamiento cognitivo se asocia a un mayor rendimiento, se analizaron estas respuestas de flujo durante la realización de tareas cognitivas en pacientes con fibromialgia en comparación con participantes sanos. A partir de los resultados obtenidos en el primer estudio que pusieron de manifiesto: 1) la existencia de un componente de anticipación específico para las pacientes con fibromialgia, el cual puede relacionarse con diversos mecanismos cognitivos, emocionales y conductuales implicados en la cronificación del dolor; 2) las mayores respuestas específicas para la ACA derecha durante el componente de aumento temprano en fibromialgia, que apoya la sugerencia de la existencia de una hiperactividad específica de la matriz del dolor medial en la fibromialgia; se llevó a cabo un reanálisis del este primer estudio para evaluar la influencia de factores psicológicos en las respuestas de flujo sanguíneo cerebral ante estimulación dolorosa. Para finalizar, se analizó la relación entre los rasgos de personalidad más fuertemente asociados a la fibromialgia y algunos de los síntomas de la fibromialgia.

En conjunto, los resultados de los diferentes estudios muestran que tanto el procesamiento del dolor como el rendimiento cognitivo están asociados a un patrón específico de cambios en flujo sanguíneo cerebral, lo que apoya la utilidad de la técnica de fTCD en el estudio de la dinámica temporal de la modulación hemodinámica asociada al procesamiento central nociceptivo y la cognición en la fibromialgia.

Durante el procesamiento nocioceptivo las pacientes con fibromialgia exhibieron alteraciones en el patrón del flujo sanguíneo cerebral durante todos los componentes de respuesta, lo que junto con las menores puntuaciones en umbral y tolerancia al dolor, apunta a la existencia de un procesamiento central anormal del dolor en la fibromialgia, apoyando así la presencia de hiperalgesia en la fibromialgia como consecuencia de la existencia de un proceso de Sensibilización Central al Dolor (Desmeules y cols., 2003; Duschek y cols, 2012; Granges y Littlejohn, 1993; Jensen y cols., 2009; Petzke y cols., 2003; Price y Staud., 2005; Reyes y cols., 2011). Además, el hecho de que exclusivamente se observa un componente de anticipación dolorosa en las pacientes y no en el grupo control pone de relieve, en concordancia con los resultados posteriores del reanálisis realizado, la influencia de los factores psicológicos y emocionales en las respuestas de flujo sanguíneo cerebral bajo estimulación dolorosa en la fibromialgia. Esta influencia, contrariamente a lo que se esperaba, no se redujo a las respuestas de flujo sanguíneo cerebral en la arteria cerebral anterior, cuyos territorios de perfusión abarcan áreas relacionadas con la elaboración emocional y cognitiva del dolor, sino que los factores psicológicos y emocionales en la fibromialgia también se asociaron a modulaciones de flujo en la arteria cerebral media, lo que sugiere también una asociación con el procesamiento sensorial del estímulo doloroso.

Por otra parte, corroborando estudios previos, los resultados referentes al procesamiento cognitivo durante la tarea de aritmética apuntaron hacia una reducción en la velocidad de procesamiento cognitivo, o lentitud mental, en la fibromialgia (Cherry y cols, 2012; Reyes del Paso y cols, 2012; Veldhuijzen, Sondaal y Oosterman, 2012). Además, se observó una reducción en flujo sanguíneo cerebral en los componentes de respuesta relacionados con la correcta resolución de este tipo de tareas; mientras que se producía un mayor incremento en flujo sanguíneo cerebral en áreas no relacionadas con el desempeño de esta tarea. Esto podría actuar como un mecanismo de interferencia, al reducir los recursos necesarios en otras áreas a fin de activar las áreas cerebrales

adecuadas para la resolución de la tarea. Igualmente, es oportuno resaltar el efecto disruptivo por parte del dolor y las variables clínicas en el rendimiento cognitivo, que parece estar mediado en parte por alteraciones en la regulación del flujo sanguíneo cerebral durante la realización de la tarea.

En cuanto a los resultados referentes al procesamiento cognitivo durante la tarea de tiempo de reacción, éstos revelaron la necesidad de un mayor tiempo de reacción para realizar la tarea por parte de las pacientes con fibromialgia, sugiriendo una menor activación atencional y capacidad para mejorar el estado de alerta durante la preparación de la respuesta ante la señal de aviso. De forma general, los aumentos en la respuesta de flujo sanguíneo cerebral, en los diferentes periodos, se asoció de forma negativa con el tiempo de reacción en la fibromialgia. De acuerdo con las bases de la teoría de la eficiencia neuronal de la inteligencia, se podría sugerir que para compensar la interferencia del procesamiento nociceptivo en la cognición, es posible que se activen mayores recursos neurales en los pacientes que experimentan dolor más intenso que en aquellos con niveles de dolor inferiores. Para concluir con los resultados obtenidos en este estudio, como se esperaba la respuesta de deceleración en la tasa cardíaca fue menor en los pacientes que en el grupo control sano. Los cambios en tasa cardiaca alrededor del estímulo imperativo se relacionaron de forma significativa en la muestra general con el tiempo de reacción (es decir, una mayor desaceleración de la tasa cardíaca se asoció con un mejor rendimiento). En tareas que miden tiempo de reacción la desaceleración en tasa cardíaca durante el período entre el estímulo de aviso y el estímulo imperativo se ha interpretado como indicativo de un aumento de la atención y la preparación para la acción (Jennings y van der Molen, 2005; Lacey y Lacey, 1970; Porges, 1992).

El quinto estudio pone de manifiesto, también de acuerdo con informes previos, mayores niveles de neuroticismo (Asghari y Nicolas, 1999; Besteiro et a., 2008; Malt, Olafsson, Lund y UrsIn., 2002; Netter y Hennig, 1998) y psicoticismo (Banic, 2004) en pacientes con fibromialgia en comparación con controles sanos, mientras que no se obtuvieron diferencias en extroversión entre ambos grupos, en contraste con algunos estudios previos (Ayats y cols., 2006; Besteiro y cols., 2008; Glazer y cols., 2010; Kersh y cols., 2001; Malin y Little John, 2012; Zautra y cols., 2005). No obstante, a pesar de las puntuaciones elevadas en neuroticismo en fibromialgia, las asociaciones entre éste y

los resultados de salud fueron escasas y de menor magnitud que las recogidas para el grupo control. Estos resultados podrían sugerir que el neuroticismo sólo juega un papel menor en las manifestaciones clínicas de la fibromialgia. En cuanto a la extroversión, ésta se asoció con mejores resultados de salud en varios dominios en las pacientes con fibromialgia, incluyendo un menor dolor, confirmando de esta manera la posible influencia protectora de la extroversión sobre el dolor y su repercusión clínica en la fibromialgia (Ballina y cols., 1995).

Finalmente, el sexto estudio corrobora la idea de una alta prevalencia de alexitimia en pacientes con fibromialgia (Castelli y cols., 2012; Huber y cols., 2009; Steinweg, Dallas y Rea, 2011), fundamentalmente en la dimensión afectiva "dificultad para identificar sentimientos", la cual a su vez se ha relacionado con la menor precisión en la percepción de los síntomas físicos (Deary y cols., 1997; Martínez-Sánchez, 1996). Esta dimensión, aunque no se asoció a las puntuaciones en dolor clínico, si se relacionó significativamente a la presencia de síntomas afectivos, y discapacidad funcional, poniendo de relieve la importancia de esta dimensión en la patología relacionada con la fibromialgia.

Tras los resultados encontrados en los diferentes estudios que componen esta Tesis Doctoral, y teniendo en cuenta las limitaciones de los mismos, se perfilan algunas perspectivas futuras de investigación y la necesidad de profundizar en los siguientes aspectos:

-Estudio de los mecanismos inhibitorios nociceptivos relacionados con el sistema cardiovascular y el reflejo barorreceptor en la fibromialgia. Se sugiere profundizar en su relación con la hiperalgesia y medidas de Sensibilización Central al Dolor como la sumación temporal del dolor. Esta línea de trabajo ya ha sido iniciada con la validación y puesta a punto de protocolos útiles en individuos sanos. En este sentido se adjuntan dos estudios en el apartado "Anexo", cuyo objetivo es la exploración de los sistemas periféricos inhibitorios del dolor, como el sistema barorreceptor, en estudiantes universitarios.

-Análisis en mayor profundidad el componente de respuesta anticipatorio al dolor, observado exclusivamente en pacientes con fibromialgia durante el registro de la arteria

cerebral anterior. Se propone la replicación de estos resultados mediante un protocolo con un mayor rigor experimental, que utilice la presentación de estímulos explícitos de aviso que den lugar a un proceso de aprendizaje por condicionamiento clásico del dolor.

-Replicación, estudio y explicación de los factores implicados en la gran reducción del flujo sanguíneo cerebral durante el componente temprano de respuesta en la arteria cerebral media en pacientes con fibromialgia durante la ejecución de la tarea aritmética. Se propone su replicación con la utilización de otras pruebas de tipo aritmético.

-Replicación y estudio del origen de la mayor activación de la arteria cerebral anterior derecha y del patrón aberrante de asimetría cerebral encontrado durante la realización de la tarea aritmética en pacientes con fibromialgia. Se propone también el estudio de la lateralización de otras funciones psicológicas en la fibromialgia (como el lenguaje, las emociones, etc.).

-Estudio y explicación de la gran disminución en flujo sanguíneo cerebral tras el componente de respuesta tardío, observada en pacientes con fibromialgia durante la realización de las tareas de aritmética y tiempo de reacción. Se propone la replicación de este efecto usando otro tipo de tareas y un análisis más profundo del mismo con la utilización de tiempos inter-estímulo más largos.

-Esta mayor contra-respuesta o efecto rebote tras los componentes tardíos de respuesta durante la realización de las dos pruebas cognitivas parece sugerir también la existencia de deficiencias en la regulación u homeostasis del flujo sanguíneo cerebral en la fibromialgia. La variabilidad espontánea en medidas fisiológicas se ha tomado tradicionalmente como un índice de auto-regulación fisiológica. Se propone profundizar en el estudio de esta regulación mediante el análisis de la variabilidad espontánea del flujo sanguíneo cerebral mediante análisis espectral y su relación con medidas de variabilidad cardiovasculares (variabilidad de la tasa cardiaca y de la presión sanguínea) y respiratorias (tasa respiratoria).

-Análisis del patrón de respuesta cardiovascular (tasa cardiaca y presión sanguínea) asociado al patrón de respuesta en flujo sanguíneo cerebral en respuesta al dolor y las tareas cognitivas; de modo parecido a lo realizado en el estudio de la tarea de tiempo de

reacción, pero con una metodología más fiable (electrocardiograma) y más completa (incluyendo medidas de presión sanguínea).

-Estudio y explicación del componente de decremento en flujo sanguíneo cerebral al dolor tras el componente de incremento temprano. Especialmente el estudio de su relación con el reflejo de defensa. Para ello se propone estudiar el patrón de respuesta del flujo sanguíneo cerebral ante el protocolo típico usado para elicitar defensa: estimulación auditiva intensa (110 db) inesperada. Este tipo de estimulación debería conllevar también un componente de decremento en flujo sanguíneo cerebral.

5. REFERENCIAS BIBLIOGRÁFICAS.

Aaslid, R. (1987). Visually evoked dynamic blood flow response of the human cerebral circulation. *Stroke, 18,* 771–775.

Aaslid, R., Markwalder, T.M., & Nornes, H. (1982). Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *Journal of Neurosurgery, 57,* 769-774.

Affleck, G., Tennen, H., Urrows, S., & Higgins, P. (1992). Neuroticism and the pain mood relation in rheumatoid arthritis: insights from a prospective daily study. *Journal of Consulting and Clinical Psychology, 60,* 119-26.

Al-Allaf, A.W., Dunbar, K.L., Hallum, N.S., Nosratzadeh, B., Templeton, K.D., & Pullar, T. (2002). A case–control study examining the role of physical trauma in the onset of fibromyalgia syndrome. *Rheumatology, 41,* 450-453.

Alfonso, J.L., Álvarez, B., y Alegre, J. (2000). Fibromialgia. *Medicina Familiar y Comunitaria, 1,* 199-211.

Amaro, T., Martín, M., Soler, P., y Granados, J. (2006). Fibromialgia: Estudio de la calidad de vida antes y después del tratamiento psicológico. *Cuadernos de Medicina Psicosomática, 79/80,* 47-52.

Andrianakos, A., Trontzas, P., Christoyannis, F., Dantis, P., Voudouris, C., Georgountzos, A., ... & Kontoyanni, A. (2003). Prevalence of rheumatic diseases in Greece: a cross-sectional population based epidemiological study. The ESORDIG Study. *The Journal of Rheumatology, 30,* 1589-1601.

Apkarian, A.V., Bushnell, M.C., Treede, R.D., & Zubieta, J.K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain, 9,* 463–484.

Arnold, L.M., Hudson, J.I., Hess, E.V., Ware, A.E., Fritz, D.A., Auchenbach, M.B., ... & Keck, P.E. (2004). Family study of fibromyalgia. *Arthritis & Rheumatism, 50,* 944-952.

Arnow, B.A., Hunkeler, E.M., Blasey, C.M., Lee, J., Constantino, M.J., Fireman, B., ... & Hayward, C. (2006). Comorbid depression, chronic pain, and disability in primary care. *Psychosomatic Medicine, 68,* 262-268.

Arnstein, P., Caudill, M., Lynn, C., Norris, A., & Beasley, R. (1999). Self-efficacy as a mediator of the relationship between pain Intensity, disability and depression in chronic pain patients. *Pain, 80,* 483-491

Asghari, M.A., & Nicholas, M.K. (1999). Personality and adjustment to chronic pain. *Pain Reviews, 6,* 85-97.

Asghari, M.A., & Nicholas, M.K. (2006). Personality and pain-related beliefs/coping strategies: a prospective study. *Clinical Journal of Pain, 22,* 10-18.

Ayats, M., Martín, M.J., & Soler, P.A. (2006). Fibromialgia y estilo de funcionamiento. *Psiquiatría Biológica, 13,* 193-7

Baillou, G. (1736). *Liber de Rheumatismo et pleuritide dorsali*. Thevart M J, ed. Paris.

Bagby, R.M., Parker, J.D.A., & Taylor, G.L. (1994). The twenty-item Toronto Alexithymia Scale: I. Item selection and cross-validation of the factor structure. *Journal of Psychosomatic Research, 38,* 23-32

Bair, M.J., Robinson, R.L., Katon, W., & Kroenke, K. (2003). Depression and pain comorbidity: a literature review. *Archives of Internal Medicine, 163,* 2433–2445

Baliki, M.N., Chialvo, D.R., Geha, P.Y., Levy, R.M., Harden, R.N., Parrish, T.B., & Apkarian, A.V. (2006). Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *The Journal of Neuroscience, 26,* 12165-12173.

Ballina, G.F.J., Martín, L.P., Iglesias, G.A., Hernández, M.R., & Cueto, E.A. (1995). La fibromialgia. Revisión clínica. *Revista Clínica Española, 195,* 326-334.

Banic, B., Petersen, S., Andersen, O., Radanov, B., Villiger, P.M., Arendt-Nielsen, L., & Curatoloa, M. (2004). Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in Fibromyalgia. *Pain, 107,* 7–15.

Bantick, S.J., Wise, R.G., Ploghaus, A., Clare, S., Smith, S.M., & Tracey, I. (2002). Imaging how attention modulates pain in humans using functional MRI. *Brain, 125,* 310-319

Baraniuk, J.N., Whalen, G., Cunningham, J., & Clauw, D.J. (2004). Cerebrospinal fluid levels of opioid peptides in fibromyalgia and chronic low back pain. *BMC Musculoskeletal Disordes,* 5, 48-54

Baron, R., Binder, A., & Wasner, G. (2010). Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurology, 9,* 807–19.

Barrera, M.I, Cortés, J.F., Guerrero, H., & Aguirre, A. (2005). La fibromialgia: ¿un síndrome somático funcional o una nueva conceptualización de la histeria? Análisis cuali-cuantitativo. *Salud Mental, 28,* 41-50.

Bartley, E., Rhudy, J., & Williams, A. (2009). Experimental Assessment of Affective Processing in Fibromyalgia. *The Journal of Pain, 10,* 1151–1160

Beard, G. (1869). Neurasthenia, or nervous exhaustion. *The Boston Medical and Surgical Journal, 80,* 217-221.

Bennett, G.J. (2000). Update on the neurophysiology of pain transmission and modulation: focus on the NMDA-receptor. *Journal of Pain and Symptom Management, 19,* S2-S6.

Bennett, R.M. (2002). Rational management of fibromyalgia. *Rheumatic Disease Clinics of North America, 28,* 13-15.

Bennett, R.M., Jones, J., Turk, D.C., Russell, I.J., & Matallana, L. (2007). An internet survey of 2,596 people with fibromyalgia. *BMC Musculoskeletal Disorders*, *8*:27.

Bergman, S. (2005). Psychosocial aspects of chronic widespread pain and fibromyalgia. *Disability and Rehabilitation, 27,* 675–83.

Besteiro, J., Álvarez, M., Lemos, S., Muñiz, J., Costas, C., & Weruaga, A. (2008). Dimensiones de personalidad, sentido de coherencia y salud percibida en pacientes con un síndrome fibromiálgico. *International Journal of Clinical and Health Psychology, 8,* 411-427.

Boland, E.W. (1947). Psychogenic rheumatism: the musculoskeletal expression of psychoneurosis. *Annals of the Rheumatic Diseases, 6,* 195.

Bolger, N. (1990). Coping as a personality process: A prospective study. *Journal of Personality and Social Psychology*, *59,* 525-537.

Borsbo, B., Peolsson, M., & Gerdle, B. (2009). The complex interplay between pain intensity, depression, anxiety and catastrophising with respect to quality of life and disability. *Disability and Rehabilitation, 31*, 1605–13

Boulware, D.W., Schmid, L.D., & Baron, M. (1990). The fibromyalgia síndrome. Could you recognize and treat it? *Postgrado Medicina, 87,* 211-214.

Breimhorst, M., Sandrock, S., Fechir, M., Hausenblas, N., Geber, C., & Birklein, F. (2011). Do intensity ratings and skin conductance responses reliably discriminate between different stimulus intensities in experimentally induced pain?. *The Journal of Pain, 12,* 61-70.

Brosschot, J.F., & Aarsse, H.R. (2001). Restricted emotional processing and somatic attribution in fibromyalgia. *The International Journal of Psychiatry in Medicine*, *31,* 127-146.

Brown, G.K., & Nicassio, P.M. (1987). The development of a questionnaire for the assessment of active and passive coping strategies in chronic pain patients. *Pain, 31,* 53-65.

Bruehl, S., & Chung, O.Y. (2004). Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain. *Neuroscience & Biobehavioral Reviews, 28,* 395-414.

Brummett, C.M., Janda, A.M., Schueller, C.M., Tsodikov, A., Morris, M., Williams, D.A., & Clauw, D.J. (2013). Survey Criteria for Fibromyalgia Independently Predict Increased Postoperative Opioid Consumption after Lower Extremity Joint Arthroplasty: A Prospective, Observational Cohort Study. *Anesthesiology, 119,* 1434-1443.

Buchwald, D. (1996). Fibromyalgia and chronic fatigue syndrome: similarities and differences. *Rheumatic Disease Clinics of North America, 22,* 219-243.

Buckelew, S.P., Shutty, M.S., Hewett, J., Landon, T., Morrow, K., & Frank, R.G. (1990). Health locus of control, gender differences and adjustment to persistent pain. *Pain, 42,* 287-294.

Burgmer, M., Petzke, F., Giesecke, T., Gaubitz, M., Heuft, G., & Pfleiderer, B. (2011). Cerebral activation and catastrophizing during pain anticipation in patients with fibromyalgia. *Psychosomatic Medicine, 73,* 751-759.

Burgmer, M., Pogatzki-Zahn, E., Gaubitz, M., Wessoleck, E., Heuft, G., & Pfleiderer, B. (2009). Altered brain activity during pain processing in fibromyalgia. *NeuroImage, 44,* 502-8.

Buskila, D., Neumann, L., Sibirski, D., & Shvartzman, P. (1997). Awareness of diagnostic and clinical features of fibromyalgia among family physicians. *Family Practice, 14,* 238–241.

Buskila, D., Neumann, L., Vaisgerg, G., Alkalay, D., & Wolfe, F. (1997). Increased rates of fibromyalgia following cervical spine injury. A controlled study of 161 cases of traumatic injury. *Arthritis and Rheumatism, 40,* 446-452.

Buskila, D., & Sarzi-Puttini, P. (2008). Fibromyalgia and autoimmune diseases: the pain behind autoimmunity. *The Israel Medical Association Journal, 10,* 77–78.

Camino, A., Jiménez, B., de Castro-Palomino, M., & Fábregas, M. (2009). Ira, fibromialgia y ansiedad: aproximación desde un CSM. *Revista de la Asociación Española de Neuropsiquiatría, 29,* 203-215.

Cannon, W.B. (1987). The James-Lange theory of emotions: a critical examination and an alternative theory. *The American Journal of Psychology, 100,* 567-586.

Caro, X.J. (1989). Is there an immunologic component to the fibrositis syndrome?. *Rheumatic Diseases Clinics of North America, 15,* 169-186.

Caro, X.J., & Winter, E.F. (2014). Evidence of abnormal epidermal nerve fiber density in fibromyalgia: clinical and immunologic implications. *Arthritis & Rheumatology, 66,* 1945-1954.

Caro, X.J., Winter, E.F., & Dumas, A. (2008). A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy (CIDP) and appear to respond to IVIg. *Rheumatology (Oxford), 47,* 208–211

Carveth, D.L., & Carveth, J.H. (2003). Fugitives from Guilt: Postmorden demoralization and the new hysterias. *American Imago, 60,* 445-479.

Castelli, L., Tesio, V., Colonna, F., Molinaro, S., Leombruni, P., Bruzzone, M., ... & Torta, R. (2012). Alexithymia and psychological distress in fibromyalgia: prevalence and relation with quality of life. *Clinical and Experimental Rheumatology, 30 (6 Suppl 74),* 70-7.

Cathebras, P., Lauwers, A., & Rousset, H. (1998). Fibromyalgia. A critical review. *Annales de Médecine Interne, 149,* 406-414.

Cathey, M.A., Wolfe, F., Kleinheksel, S.M., Millner, S., & Petteti, K.H. (1988). Functional ability and work status in patients with fibromyalgia. *Arthitis Care Research, 1*, 1 – 15

Cerón, A.M., Centelles, F., Abellana, M., & García, S. (2010). Fibromialgia y trastornos de personalidad. *Semergen, 9,* 501-506.

Cifre, I., Sitges, C., Fraiman, D., Muñoz, M.Á., Balenzuela, P., González-Roldán, A., ... & Montoya, P. (2012). Disrupted functional connectivity of the pain network in fibromyalgia. *Psychosomatic Medicine, 74,* 55-62.

Cherry, B.J., Zettel-Watson, L., Shimizu, R., Roberson, I., Rutledge, D.N., & J., Jones, C.J. (2012). Cognitive performance in women aged 50 years and older with and without fibromyalgia. *Journals of Gerontology, Series B: Psychological Sciences and Social Sciences,* doi:10.1093/geronb/gbs122

Clauw, D.J. (2009). Fibromyalgia: an overview. *The American Journal of Medicine, 122,* S3-S13.

Clauw, D.J. (2014). Fibromyalgia: a clinical review. *Jama, 311,* 1547-1555.

Clauw, D.J., & Crofford, L.J. (2003). Chronic widespread pain and fibromyalgia: what we know, and what we need to know. *Best Practice & Research Clinical Rheumatology, 17,* 685-701.

Coderre, T.J., Katz, J., Vaccarino, A.L., & Melzack, R. (1993). Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain, 52,* 259-285.

Cohen, H., Buskila, D., Neumann, L., & Ebstein, R.P. (2002). Confirmation of an association between fibromyalgia and serotonin transporter promoter region

(5-HTTLPR) polymorphism, and relationship to anxiety-related personality traits. *Arthritis & Rheumatism, 46,* 845-847.

Collado, A. (2006). Fibromialgia: entidad multidisciplinar. *Dolor. Investigación Clínica y Terapéutica, 21*, 95-99.

Collado, A. (2008). Fibromialgia, una enfermedad más visible. *Revista de la Sociedad Española del Dolor, 8,* 517-520.

Conte, P.M., Walco, G.A., & Kimura, Y. (2003). Temperament and stress response in children with juvenile primary fibromyalgia syndrome, *Arthritis and Rheumatism, 48,* 2923-2930.

Contreras, F., Echevarria, C., Gaviria, A.M., Martínez, K., Pineda, R., Quiceno, J.M., ... & Yépez, M. (2006). Rasgos de personalidad, estrategias de afrontamiento y dolor en pacientes con diagnóstico de fibromialgia. *Psicología y Salud, 16,* 129-138.

Cook, D.B., Lange, G., Ciccone, D.S., Liu, W.C., Steffener, J., & Natelson, B.H. (2004). Functional imaging of pain in patients with primary fibromyalgia. *Journal of Rheumatology, 31,* 364-378.

Costa, P.T.Jr. (1987). Influence of the normal personality dimension of neuroticism on chest pain symptoms and coronary artery disease. *American Journal of Cardiology, 60*, 20J-26J.

Costa, P.T.Jr. & McCrae R.R. (1987) Neuroticism, somatic complaints, and disease: is the bark worse than the bite? *Journal of Personality, 55*, 299-316.

Costa, D.C., Tannock, C., & Brostoff, J. (1995). Brainstem perfusion is impaired in chronic fatigue syndrome. *QJM, 88,* 767-773.

Costa, P.T., Zonderman, A.B., Engel, B.T., Baile, W.F., Brimlow, D.L. & Brinker, J. (1985). The relation of chest pain symptoms to angiographic findings of coronary artery stenosis and neuroticism. *Psychosomatic Medicine, 47,* 285-293.

Costigan, M., Scholz, J., & Woolf, C.J. (2009). Neuropathic pain: a maladaptive response of the nervous system to damage. *Annual Review of Neuroscience, 32,* 1–32.

Craggs, J.G., Staud, R., Robinson, M.E., Perlstein, W.M., & Price, D.D. (2012). Effective connectivity among brain regions associated with slow temporal summation of C-fiber-evoked pain in fibromyalgia patients and healthy controls. *The Journal of Pain, 13,* 390-400.

Critchley, H.D., Wiens, S., Rotshtein, P., Öhman, A., & Dolan, R.J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience, 7,* 189-195.

Crofford, L.J., & Demitrack, M.A. (1996). Evidence that abnormalities of central neurohormonal systems are key to understanding fibromyalgia and chronic fatigue. *Rheumatic Disease Clinics of North America, 2,* 267–284.

Crofford, L.J., Young, E.A., Engleberg, N.C., Korszun, A., Brucksch, C.B., McClure, L.A., ... & Demitrack, M.A. (2004). Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. *Brain, Behavior, and Immunity, 18,* 314-325.

Cuevas, A.M., López, F., García, A., & Díaz, M.C. (2008). Personalidad y estrategias de afrontamiento en pacientes con fibromialgia. *Behavioral Psychology/Psicología Conductual, 16,* 289-306

Cupini, L.M., Matteis, M., Troisi, E., Sabbadini, M., Bernardi, G., Caltagirone, C., & Silvestrini, M. (1996). Bilateral simultaneous transcranial Doppler monitoring of flow velocity changes during visuospatial and verbal working memory tasks. *Brain, 119,* 1249-1254.

Damasio, A.R. (1999). The Feeling of What Happens: Body and Emotion in the Making of Consciousness. New York, Harcourt Brace.

Damasio, A.R. (2004). William James and the modern neurobiology of emotion. In: Evans D, Cruse P, editors. Emotion, evolution, and rationality. Oxford: Oxford. University Press, pags. 3–14.

Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L.B., Parvizi, J., & Hichwa, R.D. (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. *Natural Neuroscience, 3,* 1049–1056.

De Civita, M., Bernatsky, S. y Dobkin, P.L. (2004). The role of depression in mediating the association between sexual abuse history and pain in women with fibromyalgia. *Psychology, Health and Medicine, 9,* 450-455.

De Souza, J.B., Potvin, S., Goffaux, P., Charest, J., & Marchand, S. (2009) The deficit of pain inhibition in fibromyalgia is more pronounced in patients with comorbid depressive symptoms. *Clinical Journal of Pain, 25,* 123–7.

Deary, I.J., Scott, S., & Wilson, J.A. (1997). Neuroticism, alexithymia and medically unexplained symptoms. *Personality and Individual Differences, 22,* 551-564.

Deetjen, P., & Speckmann, E.J. (1994). *Physiologie*. Urban und Schwarzenberg, Munich.

Deppe, M., Ringelstein, E.B., & Knecht, S. (2004). The investigation of functional brain lateralization by transcranial Doppler sonography. *Neuroimage, 21,* 1124-1146.

Desmeules, J.A., Cedraschi, C., Rapiti, E., Baumgartner, E., Finckh, A., Cohen, P., ... & Vischer, T.L. (2003). Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis & Rheumatism, 48,* 1420–1429.

Deus, J. (2009). Dimensión emocional de la respuesta cerebral al dolor en pacientes con fibromialgia (FM). *Revista del Colegio Oficial de Psicólogos de Cataluña, 220,* 19-26.

Diatchenko, L., Slade, G.D., Nackley, A.G., Bhalang, K., Sigurdsson, A., Belfer, I., ... & Maixner, W. (2005). Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Human Molecular Genetic, 14,* 135–143.

Dick, B.D., Verrier, M.J., Harper, K.T., & Rashiq, S. (2008). Disruption of cognitive function in fibromyalgia syndrome. *Pain, 139,* 610-616.

Dougherty, P.M., Palecek, J., Paleckova, V., Sorkin, L.S., & Willis, W.D. (1992). The role of NMDA and non-NMDA excitatory amino acid receptors in the excitation of primate spinothalamic tract neurons by mechanical, chemical, thermal, and electrical stimuli. *The Journal of Neuroscience, 12,* 3025-3041.

Droste, C., Kardos, A., Brody, S., Greenlee, M.W., Roskamm, H., & Rau, H. (1994). Baroreceptor stimulation: Pain perception and sensory thresholds. *Biological Psychology, 37,* 101–113.

Dunn, B.D., Galton, H.C., Morgan, R., Evans, D., Oliver, C., Meyer, M., ... & Dalgleish, T. (2010). Listening to Your Heart How Interoception Shapes Emotion Experience and Intuitive Decision Making. *Psychological Science, 21,* 1835–1844.

Duschek, S., Dietel, A., Schandry, R., & Reyes del Paso, G.A.R. (2009). Increased sensitivity to heat pain in chronic low blood pressure. *European Journal of Pain, 13,* 28-34.

Duschek, S., Heiss, H., Buechner, B., & Schandry, R. (2009). Reduction in pain sensitivity due to pharmacological elevation of blood pressure in chronically low blood pressure. *Journal of Psychophysiology, 23,* 104–112

Duschek, S., Heiss, H., Schmidt, F.H., Werner, N., & Schuepbach, D. (2010). Interactions between systemic hemodynamics and cerebral blood flow during attentional processing. *Psychophysiology, 47*, 1159-1166.

Duschek, S., Hellmann, N., Merzoug, K., Reyes del Paso, G.A., & Werner, N.S. (2012). Cerebral blood flow dynamics during pain processing investigated by functional transcranial Doppler sonography. *Pain Medicine, 13*, 419-426.

Duschek, S., Mück, I., & Reyes del Paso, G.A. (2007). Relationships between baroreceptor cardiac reflex sensitivity and pain experience in normotensive individuals. *International Journal of Psychophysiology, 65*, 193-200.

Duschek, S., & Schandry, R. (2003). Functional transcranial Doppler sonography as a tool in psychophysiological research. *Psychophysiology, 40*, 436-454.

Duschek, S., & Schandry, R. (2006). Deficient adjustment of cerebral blood flow to cognitive activity due to chronically low blood pressure. *Biological Psychology, 72*, 311–317.

Duschek, S., Schuepbach, D., & Schandrya, R. (2008). Time-locked association between rapid cerebral blood flow modulation and attentional performance. *Clinical Neurophysiology, 119*, 1292–1299.

Duschek, S., Schwarzkopf, W., & Schandry, R. (2008). Increased pain sensitivity in low blood pressure. *Journal of Psychophysiology, 22*, 20-27.

Duschek, S., Werner, N.S., Limbert, N. Winkelmann A., & Montoya, P. (2014). Attentional bias towards negative information in patients with fibromyalgia syndrome. *Pain Medicine, 15*, 603-612.

Duschek, S., Werner, N.S., & Reyes del Paso, G.A. (2013). The behavioral impact of baroreflex function: a review. *Psychophysiology, 50*, 1183-1193.

Duschek, S., Werner, N.S., Winkelmann, A., & Wankner, S. (2013). Implicit memory function in fibromyalgia syndrome. *Behavioral Medicine, 39*, 11-16.

Dworkin, B.R., Elbert, T., Rau, H., Birbaumer, N., Pauli, P., Droste, C., & Brunia, C.H. (1994). Central effects of baroreceptor activation in humans: Attenuation of skeletal reflexes and pain perception. *Proceding of the Natural Academy of Sciences USA, 91*, 6329–6333.

Dysvik, E., Natvig, G.K., Eikeland, O., & Lindstrom, T.C. (2005). Coping with chronic pain. *International Journal of Nursing Studies, 42*, 297-305.

Edwards, R.R., Bingham, C.O., Bathon, J., & Haythornthwaite, J.A. (2006). Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. *Arthritis Care & Research, 55*, 325-332.

Eisenberger, N.I. (2012). The neural bases of social pain: evidence for shared representations with physical pain. *Psychosomatic Medicine, 74*, 126–135.

Eisenberger, N.I, & Lieberman, M.D. (2004). Why rejection hurts: a common neural alarm system for physical and social pain. *Trends in Cognitive Science, 8*, 294–300

Epstein, S.A., Kay, G., Clauw, D., Heaton, R., Klein, D., Krupp, L., ... & Zisook. (1999). Psychiatric disorders in patients with Fibromyalgia: a multicenter investigation. *Psychosomatics, 1*, 57–63.

Evengard, B., Nilsson, C.G., Lindh, G., Lindquist, L., Eneroth, P., Fredrikson, S., ... & Henriksson, K.G. (1998). Chronic fatigue syndrome differs from fibromyalgia. No evidence for elevated substance P levels in cerebrospinal fluid of patients with chronic fatigue syndrome. *Pain, 78*, 153-155.

Eysenck, H.J. (1967). *The biological basis of personality*. Springfield, IL: Charles C. Thomas.

Eysenck, S.B.G., & Eysenck, H.J. (1969). Scores on Three Personality Variables as a Function of Age. Sex and Social Class. *British Journal of Social and Clinic Psychology, 8*, 69-76.

Eysenck, H.J., & Eysenck, M.W. (1985). *Personality and individual differences: a natural science approach.* New York: Plenum.

Eysenck, H.J. & Eysenck, S.B.G. (1968). *Manual for the Eysenck Personality Inventory*. San Diego: Educational and Industrial Testing Service.

Feine, J.S., Bushnell, M.C., Miren, D., & Duncan, G.H. (1991). Sex differences in the perception of noxious heat stimuli. *Pain, 44,* 255-262.

Fernández-Solà J. (2004). Síndrome de fatiga crónica y su relación con la fibromialgia. *Revista Española de Reumatología, 31,* 535-537.

Fietta, P., Fietta, P., & Manganelli, P. (2007). Fibromyalgia and psychiatric disorders. *Acta Biomedica, 78*, 88-95.

Fitzcharles, M.A., & Boulos, P. (2003). Inaccuracy in the diagnosis of fibromyalgia syndrome: analysis of referrals. *Rheumatology (Oxford), 42,* 263–267.

France, C.R. (1999). Decreased pain perception and risk for hypertension: considering a common physiological mechanism. *Psychophysiology, 36*, 683-692.

Fukuda, K., Straus, S.E., Hickie, I., Sharpe, M.C., Dobbins, J.G., & Komaroff, A. (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Internal Medicine, 121,* 953-959.

Furlan, R., Colombo, S., Perego, F., Atzeni, F., Diana, A., Barbic, F., ... & Sarzi-Puttini, P. (2005). Abnormalities of cardiovascular neural control and reduced orthostatic tolerance in patients with primary fibromyalgia. *The Journal of Rheumatology, 32,* 1787-1793.

Füstös, J., Gramann, K., Herbert, B.M., & Pollatos, O. (2013). On the embodiment of emotion regulation: interoceptive awareness facilitates reappraisal. *Social Cognitive and Affective Neuroscience, 8*, 911-917.

García-Fructuoso, F.J., Lao-Villadóniga, J.I., Beyer, K., & Santos, C. (2006). Relación entre genotipos del gen catecol O-metiltransferasa y la gravedad de la fibromialgia. *Reumatología Clínica, 2*, 168-172.

García, J., & Pascual, A. (2006). *Aprender a vivir con fibromialgia*. Barcelona: Edika Med.

Gatchel, R., & Weisberg, J.N. (2000). *Personality characteristics of patients with pain.* New York: Guildford press.

Geisser, M.E., Casey, K.L., Brucksch, C.B., Ribbens, C.M., Appleton, B.B., & Crofford, L.J. (2003). Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia: association with mood, somatic focus, and catastrophizing. *Pain, 102*, 243-250.

Geisser, M.E., & Roth, R.S. (1998). Knowledge of and agreement with pain diagnosis: relation to pain beliefs, pain severity, disability, and psychological distress. *Journal of Occupational Rehabilitation, 8*, 73-88.

Gerrits, M.M., van Oppen, P., van Marwijk, H.W., Penninx, B.W., & van der Horst, H.E. (2014). Pain and the onset of depressive and anxiety disorders. *Pain, 155*, 53-59.

Ghione, S. (1996). Hypertension-Associated Hypalgesia evidence in experimental animals and humans, pathophysiological mechanisms, and potential clinical consequences. *Hypertension, 28,* 494-504.

Giesecke, T., Williams, D.A., Harris, R.E., Cupps, T.R., Tian, X., Tian, T.X., ... & Clauw, D.J. (2003). Subgrouping of fibromyalgia patients on the basis of

pressure- pain thresholds and psychological factors. *Arthritis & Rheumatism, 48,* 2916–2922.

Giesecke, T., Gracely, R.H., Williams, D.A., Geisser, M.E., Petzke, F.W., & Clauw, D.J. (2005). The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. *Arthritis & Rheumatism, 52 (5),* 1577-1584.

Giller, C.A., Bowman, G., Dyer, H., Mootz, L., & Krippner, W. (1993). Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery, 32,* 737-742.

Glazer, D., Buskila, H., Cohen, R.P., Ebstein, L., & Neumann, L. (2010). Differences in the personality profile of Fibromyalgia patients and their relatives with and without Fibromyalgia. *Clinical and Experimental Rheumatology, 28,* S27–S32.

Glass, J.M. (2006). Cognitive dysfunction in fibromyalgia and chronic fatigue syndrome: new trends and future directions. *Current Rheumatology Reports, 8,* 425-429.

Glass, J.M. (2008). Fibromyalgia and cognition. *Journal Clinical Psychiatry, 69,* 20-24.

Glass, J.M., Park, D.C., Minear, M., & Crofford, L.J. (2005). Memory beliefs and function in fibromyalgia patients. *Journal of Psychosomatic Research, 58,* 263-269.

Godinho, F., Magnin, M., Frot, M., Perchet, C., & Garcia-Larrea, L. (2006). Emotional modulation of pain: is it the sensation or what we recall? *Journal of Neuroscience, 26,* 11454–61.

Goldenberg, D.L (1996). Fibromyalgia, chronic fatigue syndrome, and myofacial pain. *Current Opinion in Rheumatology, 8,* 113–123.

Goldenberg, D.L. (2003). *Fibromialgia una guía completa para comprender y aliviar el dolor.* Barcelona: Paidós.

Goldenberg, D.L., Simms, R.W., Geiger, A., & Komaroff, A.L. (1990). High frequency of fibromyalgia in patients with chronic fatigue seen in a primary care practice. *Arthritis & Rheumatism, 33,* 381-387.

Gómez, P., Soriano, J., Monsalve, V., Cerdá, G., Mínguez, A., Moliner, S., Villanueva, V., Asensio, J. M., López, M.D. y De Andrés, J. (2008). Calidad de vida y personalidad en pacientes con fibromialgia. Interpsiquis 2008. 9º Congreso Virtual de Psiquiatría y Neurociencias.

Gowers, W.R. (1904). The development of the concept of fibrositis. *British Medical Journal, 1,* 117-121.

Gowers, W.R. (1904). A lecture on lumbago: its lessons and analogues*:* delivered at the national hospital for the paralysed and epileptic. *British Medical Journal, 1,* 117–121. *First coining of the term fibrositis, which was used for the next 72 years.*

Grace, G.M., Nielson, W.R., Hopkins, M., & Berg, M.A. (1999). Concentration and memory deficits in patients with fibromyalgia syndrome. *Journal of Clinical and Experimental Neuropsychology, 21,* 477-287.

Gracely, R.H., & Ambrose, K.R. (2011). Neuroimaging of fibromyalgia. *Best Practice & Research Clinical Rheumatology, 25,* 271-284.

Gracely, R.H., Geisser, M.E., Giesecke, T., Grant, M.A., Petzke, F., Williams, D.A, & Clauw, D.J. (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain, 127,* 835–843.

Gracely, R.H., Petzke, F., Wolf, J.M., & Clauw, D.J. (2002). Functional Magnetic Resonance Imaging Evidence of Augmented Pain Processing in Fibromyalgia. *Arthritis & Rheumatism, 46,* 1333-1343.

Graeff, F.G. (1997). Serotonergic systems. *Psychiatric Clinic of North America, 20,* 723–739.

Graham, W. (1952). The fibrositis syndrome. Treatment services bulletin. Canada. *Department of Veterans' Affairs, 8,* 400-404.

Graham, W. (1953). "The fibrosits syndrome," *Bulletin on the Rheumatic Diseases, 8,* 33–34.

Granges, G., & Littlejohn, G. (1993). Pressure pain threshold in pain-free subjects, in patients with chronic regional pain syndromes, and in patients with fibromyalgia síndrome. *Arthritis & Rheumatism, 36,* 642–646.

Guermazi, M., Ghroubi, S., Sellami, M., Elleuch, M., Feki, H., Andre, E., ... & Elleuch, M.H. (2008). Fibromyalgia prevalence in Tunisia. *La Tunisie Medicale, 86,* 806-811.

Gupta, A., Silman, A.J., Ray, D., Morriss, R., Dickens, C., MacFarlane, G.J., ... & McBeth, J. (2007). The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. *Rheumatology, 46,* 666-671.

Gursoy, S., Erdal, E., Herken, H., Madenci, E., ALs¸ehirli, B., & Erdal, N. (2003). Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome. *Rheumatology International, 23,* 104–107.

Hagglund, K.J., Deuser, W.E., Buckelew, S.P., Hewett, J., & Kay, D.R. (1994). Weather, beliefs about weather, and disease severity among patients with fibromyalgia. *Arthritis Care Research, 7,* 130-135.

Hallberg, L.R.M., & Carlsson, S.G. (1998). Psychosocial vulnerability and maintaining forces related to fibromyalgia. *Scandinavian Jcaring Science, 12,* 95-103.

Harkins, S.W., Price, D.D., & Braith, J. (1989). Effects of extraversion and neuroticism on experimental pain, clinical pain, and illness behavior. *Pain, 36,* 209-18.

Harris, R.E., Clauw, D.J., Scott, D.J., McLean, S.A., Gracely, R.H., & Zubieta, J.K. Decreased central mu-opioid receptor availability in fibromyalgia. *Journal of Neuroscience, 27,* 10000-10006.

Hassett, A.L., Cone, J.D., Patella, S.J., & Sigal, L.H. (2000). The role of catastrophizing in the pain and depression of women with fibromyalgia syndrome. *Arthritis & Rheumatism, 43,* 2493-2500.

Helleday, U. (1986). Om mysitis chronica (rheumatica). Ett bidrag till dess diagnostik och behandling. *Nordiskt Medicinskt Arkiv, 8,* 1-17

Hench, P.K. (1976). Nonarticular rheumatism. Arthritis & Rheumatism, 19, 1081-88.

Herbert, B.M., Pollatos, O., & Schandry, R. (2007). Interoceptive sensitivity and emotion processing: an EEG study. *International Journal of Psychophysiology, 65,* 214-227.

Herbert, B.M., Ulbrich, P., & Schandry, R. (2007). Interoceptive sensitivity and physical effort: Implications for the self-control of physical load in everyday life. *Psychophysiology, 44,* 194-202.

Hoffman, D.L., & Dukes, E.M. (2008). The health status burden of people with fibromyalgia: a review of studies that assessed health status with the SF-36 or the SF-12. *International Journal of Clinical Practice, 62,* 115-126.

Holmes, G.P., Kaplan, J.E., Gantz, N.M., Komaroff, A.L., Schonberger, L.B., Straus, S.E., ... & Brus, I. (1988). Chronic fatigue syndrome: a working case definition. *Annals of Internal Medicine, 108,* 387-389.

Holzer, P. (1991). Capsaicin: cellular targets, mechanisms of action, and selectivity for thin sensory neurons. *Pharmacological Review, 43,* 143-201.

Hosoi, M., Molton, I., Jensen, M., Ehde, D., Amtmann, S., O'Brien, S., ... & Kubo, C. (2010). Relationships among alexithymia and pain intensity, pain interference, and vitality in persons with neuromuscular disease: Considering the effect of negative affectivity. *Pain, 149*, 273-277.

Huber, A., Suman, A.L., Biasi, G., & Carli, G. (2009). Alexithymia in fibromyalgia syndrome: associations with ongoing pain, experimental pain sensitivity and illness behavior. *Journal of Psychosomatic Research, 66*, 425-433.

Hudson, J., Goldenberg, D.L., Pope, H.G., Keck, P.E., & Schelesinger, L. (1992). Comorbidity of Fibromyalgia with medical and psychiatric disorder. *The American Journal of Medicine, 4*, 363-367.

Hudson, J.I., Hudson, M.S., Pliner, L.F., Goldenberg, D.L., & Pope, H.G., Jr. (1985). Fibromyalgia and major affective disorder: a controlled phenomenology and family history study. *American Journal of Psychiatry, 142*, 441–446.

Hudson, J.I., & Pope, H.G., Jr. (1989). Fibromyalgia and psychopathology: is fibromyalgia a form of "affective spectrum disorder"? *Journal of Rheumatology Supplentt, 19*, 15–22.

Jackson, J.L., & Kroenke, K. (2008). Prevalence, impact, and prognosis of multisomatoform disorder in primary care: a 5-year follow-up study. *Psychosomatic Medicine, 70*, 430–434.

James, W. (1884). What is an emotion? *Mind, 9*, 188-205

Jennings, J.R., & van der Molen, M.W. (2005). Preparation for speeded action as a psychophysiological concept. *Psychological Bulletin, 131*, 434-459.

Jensen, K.B., Kosek, E., Petzke, F., Carville, S., Fransson, P., Marcus, H., ... & Gracely, R. (2009). Ingvar M. Evidence of dysfunctional pain inhibition in fibromyalgia reflected in rACC during provoked pain. *Pain, 144*, 95-100.

Jensen, K.B., Petzke, F., Carville, S., Fransson, P., Marcus, H., Williams, S.C., ... & Kosek, E. (2010). Anxiety and depressive symptoms in fibromyalgia are related to poor perception of health but not to pain sensitivity or cerebral processing of pain. *Arthritis & Rheumatism*, *62*, 3488-3495.

Jensen, M.P., Turner, J.A., Romano, J.M., & Lawler, B.K. (1994). Relationship of pain specific beliefs to chronic pain adjustment. *Pain, 57*, 301-309.

Johnson, M., Paananen, M., Rahinantti, P., & Hannonen, P. (1997). Depressed fibromialgia patients are equipped with an emphatic competence dependent self-esteem. *Clinical Rheumatology, 16*, 578-584.

Jueptner, M., & Weiller, C. (1995). Review: does measurement of regional cerebral blood flow reflect synaptic activity?—Implications for PET and fMRI. *Neuroimage*, *2* (2PA), 148-156.

Karp, J.F., Reynolds, C.F., Butters, M.A., Dew, M.A., Mazumdar, S., Begley, A.E., ... & Weiner, D.K. (2006). The relationship between pain and mental flexibility in older adult pain clinic patients. *Pain Medicine, 7*, 444-452.

Karsdorp, P.A., & Vlaeyen, J.W. (2009) Active avoidance but not activity pacing is associated with disability in fibromyalgia. *Pain, 147*, 29-35.

Katkin, E.S. (1984). Blood, sweat, and tears individual differences in autonomic self-perception. *Psychophysiology, 22*, 125–137.

Keefe, F.J., Brown, G.K., Wallston, K.A., & Caldwell, D.S. (1989). Coping with rheumatoid arthritis pain: catastrophizing as a maladaptive strategy. *Pain*, *37*, 51-56.

Keefe, F.J., Rumble, M.E., Scipio, C.D., Giordano, L.A., & Perri, L.M. (2004). Psychological aspects of persistent pain: current state of the science. *The Journal of Pain, 5*, 195-211.

Kentle, R.L. (1989). Headache symptomology and neuroticism in a college sample. *Psychology Reports, 65,* 976-978.

Kersh, B.C., Bradley, L.A., Alarcon, G.S., Alberts, K.R., Sotolongo, A., Martin, M.Y., … & Triana-Alexander, M. (2001). Psychosocial and health status variables independently predict health care seeking in Fibromyalgia. *Arthritis Care & Research, 45,* 362-371.

Klein, T.A., Endrass, T., Kathmann, N., Neumann, J., Von Cramon, D.Y., & Ullsperger, M. (2007). Neural correlates of error awareness. *NeuroImage, 34,* 1774-1781.

Knecht, S., Deppe, M., Backer, M., Ringelstein, E.B., & Henningsen, H. (1997). Regional cerebral blood flow increases during preparation for and processing of sensory stimuli. *Experimental Brain Research, 116,* 309-314.

Kontos, H.A. (1989). Validity of cerebral arterial blood flow calculations from velocity measurements. *Stroke, 20,* 1-3.

Kosek, E., Ekholm, J., & Hansson, P. (1996). Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls. *Pain, 64,* 415-423.

Kosek, E., & Hansson, P. (1997). Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. *Pain, 70,* 41-51.

Koskenvuo, M., Langinvainio, H., Kaprio, J., & Sarna, S. (1984). Health related psychosocial correlates of neuroticism: a study of adult male twins in Finland. *Acta Geneticae Medicae Gemellologiae (Roma), 33,* 307-320.

Kroenke, K., Shen, J., Oxman, T.E., Williams, Jr J.W., & Dietrich, A.J. (2008). Impact of pain on the outcomes of depression treatment: results from the RESPECT trial. *Pain, 134,* 209–215.

Kuchinad, A., Schweinhardt, P., Seminowicz, D.A., Wood, P.B., Chizh, B.A., & Bushnell, M.C. (2007). Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? *The Journal of Neuroscience, 27,* 4004-4007

Lacey, J.I., & Lacey, B.C. (1970). Some autonomic-central nervous system interrelationships. In: Black, P. (Ed.), Physiological Correlates of Emotion (pp. 205–227). Academic Press, New York.

Lachaine, J., Beauchemin, C., & Landry, P.A. (2010). Clinical and economic characteristics of patients with fibromyalgia syndrome. *The Clinical Journal of Pain, 26,* 284-290.

Lahey, B.B. (2009). Public Health Significance of Neuroticism. *American Psychologist, 64,* 241–256.

Lake, R.I., Eaves, L.J., Maes, H.H., Heath, A.C., & Martin, N.G. (2000). Further evidence against the environmental transmission of individual differences in neuroticism from a collaborative study of 45,850 twins and relatives on two continents. *Behavior Genetics, 30,* 223-33.

Lautenbacher, S., & Rollman, G.B. (1997). Possible deficiencies of pain modulation in fibromyalgia. *The Clinical Journal of Pain, 13,* 189-196.

Lee, K. (2006). History of Fibromyalgia. Health's Disease and Condition content is reviewed by the Medical Review Board. http://chronicfatigue.about.com/od/fibromyalgia/p/historyfm.htm.

Liu, H., Brown, J.L., Jasmin, L., Maggio, J.E., Vigna, S.R., Mantyh, P.W., & Basbaum, A.I (1994) Synaptic relationship between substance P and the substance P receptor: light and electron microscopic characterization of the mismatch between neuropeptides and their receptors. *Proceding of the National Academy of Science of the USA, 91,* 1009–1013

Lledó, A., Pastor, M.A., Pons, N., López, S., Rodríguez, J., & Bruehl, S. (2010). Control beliefs, coping and emotions: Exploring relationships to explain fibromyalgia health outcomes. *International Journal of Clinical and Health Psychology, 10*, 459-476.

Loggia, M.L., Berna, C., Kim, J., Cahalan, C.M., Gollub, R.L., Wasan, A.D., ... & Napadow, V. (2014). Disrupted brain circuitry for pain related reward/punishment in Fibromyalgia. *Arthritis & Rheumatology, 66*, 203-212.

Loggia, M.L., Juneau, M., & Bushnell, M.C. (2011). Autonomic responses to heat pain: Heart rate, skin conductance, and their relation to verbal ratings and stimulus intensity. *Pain, 152*, 592-598.

Loggia, M.L., Mogil, J.S., & Bushnell, M.C. (2008). Experimentally induced mood changes preferentially affect pain unpleasantness. *The Journal of Pain, 9*, 784-791.

Logothetis, N.K., Pauls, J., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412*, 150-157.

Lorenz, J., Minoshima, S., & Casey, KL. (2003). Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain, 126*, 1079–1091.

Luminet, O., Bagby, R.M., Wagne r, H., Taylor, G.J., & Parker, J.D. (1999). Relations between alexithymia and the five-factor model of personality: a facet-level analysis. *Journal of Personality Assessment, 73*, 345-358.

Lumley, M.A., Stettner, L., & Wehmer, F. (1996). How are alexithymia and physical illness linked? A review and critique of pathways. *Journal of Psychosomatic Research, 41*, 505–518

Luo, Z.D., & Cizkova, D. (2000). The role of nitric oxide in nociception. *Current Review of Pain, 4*, 459-466.

Malin, K., & Littlejohn, G. (2012). Personality and Fibromyalgia Syndrome. *The Open Rheumatology Journal*, *6*, 273–285.

Malt, E.A., Olafsson, S., Lund, A., & UrsIn, H. (2002). Factors explaining variance in perceived pain in women with Fibromyalgia. *BMC Musculoskeletal Disorders*, *3*, 2-8.

Martínez-Lavin, M. (2004). Fibromyalgia as a sympathetically maintained pain syndrome. *Current Pain and Headache Reports*, *8*, 385-389.

Martínez-Lavin, M., & Hermosillo, A.G. (2000). Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. *Seminars of Arthritis & Rheumatism*, *29*, 197–199.

Martínez-Sánchez, F. (1996). The Spanish version of the Toronto Alexithymia Scale (TAS-20). *Clínica y Salud*, *7*, 19-32.

Martínez, M.P., Sánchez, A.I, Miró, E., Medina, A., & Lami, A. (2011). The relationship between the fear-avoidance model of pain and personality traits in Fibromyalgia patients. *Journal of Clinical Psychology in Medical Settings*, *4*, 380-391.

Martínez-Lavin, M., Vidal, M., Barbosa, R.E., Pineda, C., Casanova, J.M., & Nava, A. (2002). Norepinephrine-evoked pain in fibromyalgia. A randomized pilot study. *BMC Musculoskeletal Disorders, 3:2.*

Mas, A.J., Carmona, L., Valverde, M., & Ribas, B. (2008). Prevalence and impact of fibromyalgia on function and quality of life in individuals from the general population: results from a nationwide study in Spain. *Clinical & Experimental Rheumatology*, *26*, 519-526.

Mata, P., González, L., López, M., Camino, M., de Felipe, V., & Castel, B. (2009). Fibromialgia y psicopatología asociada. Ejemplar dedicado al XLIII Congreso

de la Sociedad Española de Medicina Psicosomática. *Cuadernos de Medicina Psicosomática, 89/90,* 31.

McCain, G.A. (1996). A cost-effective approach to the diagnosis and treatment of fibromyalgia. *Rheumatic Disease Clinics of North America, 22,* 323-349.

McDermid, A.J., Rollman, G.B., & McCain, G.A. (1996). Generalized hypervigilance in fibromyalgia: evidence of perceptual amplification. *Pain, 66,* 133–144.

Macfarlane, G.J., Norrie, G., Atherton, K., Power, C., & Jones, G.T. (2009). The influence of socioeconomic status on the reporting of regional and widespread musculoskeletal pain: results from the 1958. British birth cohort study. *Annals of Rheumatology Diseases, 68,* 1591–1595.

McLean, S.A., Williams, D.A., & Clauw, D.J. (2005). Fibromyalgia after motor vehicle collision: evidence and implications. *Traffic Injury Prevention, 6,* 97-104.

McMahon, S.B., & Wall, K.M. (2006). *Melzack's textbook of pain*. Philadelphia (PA): Elsevier.

Meerwijk, E.L., Ford, J.M., & Weiss, S.J. (2013). Brain regions associated with psychological pain: implications for a neural network and its relationship to physical pain. *Brain Imaging and Behaviour, 7,* 1–14.

Meller, S.T., & Gebhart, G.F. (1993). Nitric oxide (NO) and nociceptive processing in the spinal cord. *Pain, 52,* 127-136.

Melzack, R., & Wall, P. (1965). Pain mechanism. A new theory. *Science, 150,* 971-979.

Mengshoel, A.M., Saugen, E., Forre, O., & Vøllestad, N.K. (1995). Muscle fatigue in early fibromyalgia. *The Journal of Rheumatology, 22,* 143-150.

Mikkelsson, M., Latikka, P., Kautiainen, H., Isomeri, R., & Isomaki, H. (1992). Muscle and bone pressure pain threshold and pain tolerance in fibromyalgia patients and controls. *Archives of Physical Medicine and Rehabilitation, 73*, 814–818.

Millea, P.J., & Halloway, R.L. (2000). Fibromyalgia. *American Family Physician, 1*, 32-38.

Moldofsky, H., & Lue, F.A. (1980). The relationship of alpha and delta EEG frequencies to pain and mood in 'fibrositis' patients treated with chlorpromazine and L-tryptophan. *Electroencephalography and Clinical Neurophysiology, 50*, 71–80

Montoya, P., Pauli, P., Batra, A., & Wiedemann, G. (2005). Altered processing of pain-related information in patients with fibromyalgia. *European Journal of Pain, 9*, 293-293.

Mosso, A. (1881). Uber den Kreislauf des Blutes im menschlichen Gehirn. Leipzig: Von Veit; 1881.

Motzkin, J.C., Philippi, C.L., Wolf, R.C., Baskaya, M.K., & Koenigs, M. (2014). Ventromedial prefrontal cortex lesions alter neural and physiological correlates of anticipation. *Journal of Neuroscience, 30,* 10430-37

Mountz, J.M., Bradley, L.A., Modell, J.G., Alexander, R.W., Triana-Alexander, M., Aaron, L.A., ... & Mountz, J.D. (1995). Fibromyalgia in women. *Arthritis & Rheumatism, 38*, 926-938.

Munguía, D., Legaz, A., & Alegre, C. (2007). *Guía de práctica clínica sobre el síndrome de fibromialgia para profesionales de la salud.* Madrid: Elsevier.

Munguía-Izquierdo, D., Legaz-Arrese, A., Moliner-Urdiales, D., & Reverter-Masía, J. (2008). Neuropsicología de los pacientes con síndrome de fibromialgia: relación con dolor y ansiedad. *Psicothema, 20,* 427-431.

Murray, G. (1929). Myofibrositis as simulator of other maladies. *Lancet, 1*, 113-6.

Murray, C.J.L., Vos, T., Lozano, R., AlMazroa, M.A., & Memish, Z.A. (2013). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010 (vol 380, pg 2197, 2012). *Lancet*, 381-628.

Napadow, V., LaCount, L., Park, K., As-Sanie, S., Clauw, D.J., & Harris, R.E. (2010). Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis & Rheumatology, 62,* 2545–55.

Neeck, G., & Riedel, W. (1994). Neuromediator and hormonal perturbations in fibromyalgia syndrome: results of chronic stress?. *Baillière's Clinical Rheumatology, 8*, 763-775.

Netter, P., & Hennig, J. (1998). The fibromyalgia syndrome as a manifestation of neuroticism? *Z Rheumatol, 57 (Supl. 2)*, 105-108.

Neumann, L., & Buskila, D. (2003). Epidemiology of fibromyalgia. *Current Pain and Headache Reports, 7*, 362–368.

Ngian, G.S., Guymer, E.K., & Littlejohn, G.O. (2011). The use of opioids in fibromyalgia. *International Journal of Rheumatic Diseases*, *14,* 6-11.

Nijs, J., & De Meirleir, K.E.N.N.Y. (2005). Impairments of the 2-5A synthetase/RNase L pathway in chronic fatigue syndrome. *In Vivo*, *19*, 1013-1021.

Nordahl, H.M., & Stiles, T.C. (2007). Personality styles in patients with fibromyalgia, major depression and healthy controls. *Annals of Generic Psychiatry, 6*, 273-80.

Offenbaecher, M., Bondy, B., De Jonge, S.I.L.V.I.A., Glatzeder, K., Krüger, M., Shoeps, P., & Ackenheil, M. (1999). Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. *Arthritis & Rheumatism, 42*, 2482-2488.

Park, D.C., Glass, J.M., Minear, M., & Crofford, L.J. (2001). Cognitive function in fibromyalgia patients. *Arthritis & Rheumatism, 44*, 2125-2133.

Peng, X., Robinson, R.L., Mease, P., Kroenke, K., Williams, D.A., Chen, Y., ... & Hann, D. (2015). Long-term evaluation of opioid treatment in fibromyalgia. *The Clinical Journal of Pain, 31,* 7-13.

Peri J. (2009). ¿Qué tienen que cambiar los pacientes con fibromialgia para que mejore su calidad de vida? Comunicación presentada en el XLIII Congreso de la Sociedad Española de Medicina Psicosomática. Junio, Barcelona.

Pericot-Nierga, I., Hernández-Ferràndiz, M., Lozano-Gallego, M., Vilalta-Franch, J., Cruz-Reina, M.M., & López-Pousa, S. (2009). Cognitive profile in fibromyalgia. Comparison with a mild cognitive impairment group. *Medicina Clínica (Barcelona), 133,* 91-94.

Petrovic, P., & Ingvar, M. (2002). Imaging cognitive modulation of pain processing. *Pain, 95,* 1-5.

Petzke, F., Clauw, D.J., Ambrose, K., Khine, A., & Gracely, R.H. (2003). Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. *Pain, 105,* 403-13.

Petzke, F., Gracely, R.H., Park, K.M., Ambrose, K., & Clauw, D.J. (2003). What do tender points measure? Influence of distress on 4 measures of tenderness. The *Journal of Rheumatology, 30*, 567-574.

Petzke, F., Khine, A., Williams, D., Groner, K., Clauw, D.J., & Gracely, R.H. (2001). Dolorimetry performed at 3 paired tender points highly predicts overall tenderness. *The Journal of Rheumatology, 28,* 2568–2569.

Peyron, R., Laurent, B., & Garcia-Larrea, L. (2000). Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiologie Clinique/Clinical Neurophysiology, 30, 263-288.

Pilowsky, I., & Katsikitis, M. (1994). A classification of illness behavior in pain clinic patients. *Pain, 57*, 91–94.

Ploghaus, A., Narain, C., Beckmann, C.F., Clare, S., Bantick, S., Wise, R., ... & Tracey, I. (2001). Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *The Journal of Neuroscience, 21*, 9896-9903.

Ploghaus, A., Tracey, I., Gati, J.S., Clare, S., Menon, R.S., & Matthews, P.M. (1999). Dissociating Pain from Its anticipation in the human brain. *Science, 284*, 1979-1981.

Pollatos, O., Auer, D.P., Schandry, R., & Kaufmann, C. (2004). Autonomic awareness: neural activity during the perception of cardiovascular stimuli. In 10th Annual Meeting of the Organization for Human Brain Mapping, Budapest, Hungary, p. TU285.

Pollatos, O., Füstös, J., & Critchley, H.D. (2012). On the generalised embodiment of pain: how interoceptive sensitivity modulates cutaneous pain perception. *Pain, 153*, 1680-1686.

Pollatos, O., Herbert, B.M., Matthias, E., & Schandry, R. (2007). Heart rate response after emotional picture presentation is modulated by interoceptive awareness. *International Journal of Psychophysiology, 63*, 117-124.

Pollatos, O., Herbert, B.M., Wankner, S., Dietel, A., Wachsmuth, C., Henningsen, P., & Sack, M. (2011). Autonomic imbalance is associated with reduced facial recognition in somatoform disorders. *Journal of Psychosomatic Research, 71*, 232-239.

Pollatos, O., Kirsch, W., & Schandry, R. (2005). On the relationship between interoceptive awareness, emotional experience, and brain processes. *Cognitive Brain Research, 25*, 948-962.

Pollatos, O., & Schandry, R. (2004). Accuracy of heartbeat perception is reflected in the amplitude of the heartbeat-evoked brain potential. *Psychophysiology, 41,* 476-482.

Porges, S.W. (1992). Autonomic regulation and attention. In B. A. Campbell, H. Hayne, & R. Richardson (Eds.), Attention and information processing in infants and adults (pp. 201–223). Hillsdale, NJ: Erlbaum Associates.

Price, D., & Staud, R. (2005). Neurobiology of fibromyalgia syndrome. *Journal of Rehumatology Supplement, 32*, 22-28.

Price, D., Staud, R., Robinson, M., Mauderli, A., Cannon, R., & Vierck, C. (2002). Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain, 99,* 49-59.

Pujol, J., López-Solà, M., Ortiz, H., Vilanova, J.C., Harrison, B.J., Yücel, M., ... & Deus, J. (2009). Mapping brain response to pain in fibromyalgia patients using temporal analysis of FMRI. *PLoS One, 4,* e5224.

Pujol, J., Macià, D., Garcia-Fontanals, A., Blanco-Hinojo, L., López-Solà, M., Garcia Blanco, S., ... & Deus, J. (2014). The contribution of sensory system functional connectivity reduction to clinical pain in fibromyalgia. *Pain, 155,* 1492-1503.

Qiu, Y., Noguchi, Y., Honda, M., Nakata, H., Tamura, Y., Tanaka, S., … & Kakigi, R. (2006). Brain processing of the signals ascending through unmyelinated C fibers in humans: an event-related functional magnetic resonance imaging study. *Cerebral Cortex, 16*, 1289–1295

Queiroz, L.P. (2013). Worldwide epidemiology of fibromyalgia. *Current Pain and Headache Reports, 17,* 1-6

Quimby, L.G., Block, S.R., & Gratwick, G.M. (1988). Fibromyalgia: generalized pain intolerance and manifold symptom reporting. *Journal of Rheumatology, 15*, 1264–1270.

Ramírez, C., Esteve, R., & López, A.E. (2001). Neuroticismo, afrontamiento y dolor crónico. *Anales de Psicología, 17,* 129-137.

Rau, H., Brody, S., Larbig, W., Pauli, P., Vohringer, M., Harsch, B., … & Birbaumer, N. (1994). Effects of PRES baroreceptor stimulation on thermal and mechanical pain threshold in borderline hype and normotensives. *Psychophysiology, 31*, 480–385.

Rau, H., & Elbert, T. (2001). Psychophysiology of arterial baroreceptors and the etiology of hypertension. *Biological Psychology, 57,* 179-201.

Rau, H., Elbert, T., Geiger, B., & Lutzenberger, W. (1992). PRES: The controlled noninvasive stimulation of the carotid baroreceptors in humans. *Psychophysiology, 29*, 165-172.

Reid, G.J., Gilbert, C.A., & McGrath, P.J. (1994). Development of a pain coping questionnaire. *Third International Symposium on Pediatric Pain.* Filadelfia.

Reyes del Paso, G.A.R., Garrido, S., Pulgar, Á., & Duschek, S. (2011). Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia syndrome. *Journal of Psychosomatic Research, 70,* 125-134.

Reyes del Paso, G.A.R., Garrido, S., Pulgar, Á., Martín-Vázquez, M., & Duschek, S. (2010). Aberrances in autonomic cardiovascular regulation in fibromyalgia syndrome and their relevance for clinical pain reports. *Psychosomatic Medicine, 72,* 462-470.

Reyes del Paso, G. A. R., González, I., & Hernández, J. A. (2004). Baroreceptor sensitivity and effectiveness varies differentially as a function of cognitive-attentional demands. *Biological Psychology, 67,* 385-395.

Reyes del Paso, G.A., & Perales, M.C. (2011). Haemodialysis curse is associated tochanges in pain threshold and in the relations between arterial pressure andpain. Nefrología, 31, 738–742.

Reyes del Paso, G.A., Pulgar, A., Duschek, S., & Garrido, S. (2012). Cognitive impairment in fibromyalgia syndrome: the impact of cardiovascular regulation, pain, emotional disorders and medication. *European Journal of Pain*, *16*, 421-429.

Roguin, A. (2002). Christian Johann Doppler: the man behind the effect. *The British Journal of Radiology, 75*, 615-619.

Rojas, A., Zapata, A.L., Anaya, J.M. & Pineda, R. (2005). Predictores de calidad de vida en pacientes con fibromialgia. *Revista Colombiana de Reumatología, 12*, 295-300

Rollman, G.B., & Harris, G. (1987). Detectability, discriminability, and perceived magnitud of painful electric shock. *Perceptual Psychophysiology*, *42*, 257-268.

Roy, C., & Sherrington, C. (1890). On the regulation of the blood supply of the brain. *Journal of Physiology, 11*, 85–108.

Ruda, M.A. (1993). Gender and Pain. *Pain, 63*, 1-2.

Rusch, N., Spoletini, I., Wilke, M., Bria, P., Di Paola, M., & Di Iulio, F. (2007). Prefrontal-thalamic-cerebellar gray matter networks and executive functioning in schizophrenia. *Schizophrenia Research, 93*, 79-89.

Russell, I.J. (1994). Biochemical abnormalities in fibromyalgia syndrome. *Journal of Musculoskelatal Pain*, *2*, 101-115.

Russell, I.J., Orr, M.D., Littman, B., Vipraio, G.A., Alboukrek, D., Michalek, J.E., ... & Mackillip, F. (1994). Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthritis & Rheumatism*, *37*, 1593-1601.

Sandín, B., Chorot, P., Santed, M.A., & Jiménez, P. (1996). Dimensiones de la alexitimia y estados emocionales de ansiedad, depresión e ira. *Psiquis: Revista de Psiquiatria, Psicologia y Psicosomatica, 17,* 37-45.

Sauer, S.E., Burris, J.L., & Carlson, C.R. (2010). New directions in the management of chronic pain: self-regulation theory as a model for integrative clinical psychology practice. *Clinical Psychology Review, 30,* 805-814.

Schandry, R. (1981). Heartbeat perception and emotional experience. *Psychophysiology, 18,* 483-488.

Scudds, R.A., Rollman, G.B., Harth, M., & McCain, G.A. (1987). Pain perception and the personality measures as discriminators in the classification of fibrosis. *Journal of Rheumatology, 14,* 563–569.

Sephton, S.E., Studts, J.L., Hoover, K., Weissbecker, I., Lynch, G., Ho, I., … & Salmon, P. (2003). Biological and psychological factor associated with memory function in fibromyalgia syndrome. *Health Psychology, 22,* 592-597.

Sifneos, P.E. (1973). The prevalence of ‘‘alexithymic’’ characteristic mechanisms in psychosomatic patients. *Psychotherapy and Psychosomatics, 21,* 133-136.

Smythe, H.A., & Moldofsky, H. (1977). “Two contributions to understanding of the “fibrositis” syndrome,” *Bulletin on the Rheumatic Diseases, 28,* 928–931.

Sorensen, J., Graven-Nielsen, T., Henriksson, K.G., Bengtsson, M., & Arendt-Nielsen, L. (1998). Hyperexcitability in fibromyalgia. *Journal of Rheumatology, 25,* 152–5.

Staud, R. (2002). Evidence of involvement of central neural mechanisms in generating FM pain. *Current Rheumatology Reports, 4,* 299–305.

Staud, R., Bovee, C.E., Robinson, M.E., & Price, D.D. (2008). Cutaneous C-fiber pain abnormalities of fibromyalgia patients are specifically related to temporal summation. *Pain, 139,* 315-323.

Staud, R., Craggs, J., Perlstein, W., Robinson, M., & Price, D. (2008). Brain activity associated with slow temporal summation of C-fiber evoked pain in fibromyalgia patients and healthy controls. *European Journal of Pain, 12,* 1078-1089.

Staud, R., Price, D., Robinson, M., Mauderli, A., & Vierck, C. (2004). Maintenance of windup of second pain requires less frequent stimulation in fibromyalgia patients compared to normal controls. *Pain, 110,* 689-696.

Staud, R., Robinson, M.E., & Price, D.D. (2007). Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. *The Journal of Pain, 8,* 893-901.

Staud, R., Robinson, M.E., Vierck, C.J., & Price, D.D. (2003). Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. *Pain, 101,* 167-174.

Staud, R., & Smitherman, M.L. (2002). Peripheral and central sensitization in fibromyalgia: pathogenetic role. *Current Pain and Headache Reports, 6,* 259-266.

Staud, R., Vierck, C., Cannon, R., Mauderli, A., & Price, D. (2001). Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain, 99,* 165-175.

Staud, R., Vierck, C., Robinson, M., & Price, D. (2005). Effects of N-Methyl-D-Aspartate receptor antagonist dextromethaphan on temporal summation of pain are similar in fibromyalgia patients and normal control subjects. *The Journal of Pain: Official Journal of American Pain Society, 6.5,* 323-332.

Steinweg, D.L., Dallas, A.P., & Rea, W.S. (2011). Fibromyalgia: unspeakable suffering, a prevalence study of alexithymia. *Psychosomatics, 52*, 255-262.

Stockman, R. (1904). The causes, pathology, and treatment of chronic rheumatism. *Edinburgh Medical Journal, 15, 107–116.*

Stroobant, N., & Vingerhoets, G. (2000). Transcranial Doppler ultrasonography monitoring of cerebral hemodynamics during performance of cognitive tasks: a review. *Neuropsychology Review*, *10*, 213-231.

Strusberg, I., Mendelberg, R.C., Serra, H.A., & Strusberg, A.M. (2002). Influence of weather conditions on rheumatic pain. *Journal of Rheumatology*, *29*, 335-338

Suhr, J.A. (2003). Neuropsychological impairment in fibromyalgia: relation to depression, fatigue, and pain. *Journal of Psychosomatic Research, 55*, 321-329.

Sullivan, M.J., Thorn, B., Haythornthwaite, J.A., Keefe, F., Martin, M., Bradley, L.A., & Lefebvre, J.C. (2001). Theoretical perspectives on the relation between catastrophizing and pain. *The Clinical Journal of Pain*, *17*, 52-64.

Sumpton, J.E., & Moulin, D.E. (2013). Fibromyalgia. *Handbook of Clinical Neurology*, *119*, 513-527.

Szirmai, I., Amrein, I., Pálvögyi, L., Debreczeni, R., & Kamondi, A. (2005). Correlation between blood flow velocity in the middle cerebral artery and EEG during cognitive effort. *Cognitive Brain Research, 24,* 33-40.

Taylor, G.J. (2000). Recent development in alexithymia theory and research. The *Canadian Journal of Psychiatry, 45*, 134–142.

Thieme, K., Rose, U., Pinkpank, T., Spies, C., Turk, D.C., & Flor, H. (2006). Psychophysiological responses in patients with fibromyalgia syndrome. *Journal of Psychosomatic Research, 61,* 671-679.

Thieme, K., Spies, C., Sinha, P., Turk, D.C., & Flor, H. (2005). Predictors of pain behaviors in fibromyalgia syndrome. *Arthritis Care & Research, 53*, 343-350.

Thieme, K., Turk, D.C., Gracely, R.H., Maixner, W., & Flor, H. (2015). The relationship among psychological and psychophysiological characteristics of fibromyalgia patients. *The Journal of Pain, 16,* 186-196.

Tirelli, U., Chierichetti, F., Tavio, M., Simonelli, C., Bianchin, G., Zanco, P., & Ferlin, G. (1998). Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. *The American Journal of Medicine, 105,* 54S-58S.

Torebjork, H.E., & Hallin, R.G. (1974). Identification of afferent C units in intact human skin nerves. *Brain Research, 67,* 387-403.

Traut, E. F. (1968). Fibrositis. *Journal of the American Geriatrics Society, 16,* 531-538.

Turriziani, P., Oliveri, M., Salerno, S., Costanzo, F., Koch, G., & Caltagirone, C. (2008). Recognition memory and prefrontal cortex: dissociating recollection and familiarity processes using rTMS. *Behavioural Neurology, 19,* 23-27.

Van der Zwan, A., & Hillen, B. (1991). Review of the variability of the territories of the major cerebral arteries. *Stroke, 22*, 1078-1084.

Van der Zwan, A., Hillen, B., Tulleken, C.A., & Dujovny, M. (1993). A quantitative investigation of the variability of the major cerebral arterial territories. *Stroke, 24,* 1951-1959.

Van der Zwan, A., Hillen, B., Tulleken, C.A., Dujovny, M., & Dragovic, L. (1992). Variability of the territories of the major cerebral arteries. *Journal of Neurosurgery, 77,* 927-940.

Van Middendorp, H., Lumley, M.A., Jacobs, J.W., van Doornen, L.J., Bijlsma, J.W., & Geenen, R. (2008). Emotions and emotional approach and avoidance strategies in fibromyalgia. *Journal of Psychosomatic Research, 64,* 159-167.

Van Wilgen, C.P., van Ittersum, M.W., Kaptein, A.A., & van Wijhe, M. (2008). Illness perceptions in patients with fibromyalgia and their relationship to quality of life and catastrophizing. *Arthritis & Rheumatism, 58,* 3618-3626.

Vargas-Alarcón, G., Fragoso, J. M., Cruz-Robles, D., Vargas, A., Lao-Villadóniga, J.I., García-Fructuoso, F., … & Martínez-Lavín, M. (2007). Catechol-*o*-methyltransferase gene haplotypes in Mexican and Spanish patients with fibromyalgia. *Arthritis Research & Therapy, 9,* 1–7.

Veldhuijzen, D.S., Sondaal, S.F.V., & Oosterman, J.M. (2012). Intact cognitive inhibition in patients with fibromyalgia but evidence of declined processing speed. *The Journal of Pain, 13,* 507-515.

Verdejo-García, A., López-Torrecillas, F., Calandre, E.P., Delgado-Rodríguez, A., & Bechara, A. (2009). Executive function and decision-making in women with fibromyalgia. *Archives of Clinical Neuropsychology, 24,* 113-122.

Vierck, C.J., Cannon, R.L., Fry, G., Maixner, W., & Whitsel, B.L. (1997). Characteristics of temporal summation of second pain sensations elicited by brief contact of glabrous skin by a preheated thermode. *Journal of Neurophysiology, 78,* 992-1002.

Vohs, K.D., Baumeister, R.F., Schmeichel, B.J., Twenge, J.M., Nelson, N.M., & Tice, D.M. (2008). Making choices impairs subsequent self-control: a limited-resource account of decision making, self-regulation, and active initiative. *Journal of Personality and Social Psychology, 94,* 883–898

Wager, T.D., Rilling, J.K., Smith, E.E., Sokolik, A., Casey, K.L., Davidson, R.J., … & Cohen, J.D. (2004). Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science, 303,* 1162Y7.

Watson, D., & Pennebaker, J.W. (1989). Health complaints, stress and distress: exploring the central role of negative affectivity. *Psychological Review, 96*, 234-254.

Weiss, S., Sack, M., Henningsen, P., & Pollatos, O. (2014). On the interaction of self-regulation, interoception and pain perception. *Psychopathology, 47,* 377-382.

Werner, N.S., Duschek, S., & Schandry, R. (2009). Relationships between affective states and decision-making. *International Journal of Psychophysiology, 74*, 259-265.

Wiens, S. (2005). Interoception in emotional experience. *Current Opinion in Neurology, 18,* 442-447.

Wiens, S., & Palmer, S.N. (2001). Quadratic trend analysis and heartbeat detection. *Biological Psychology, 58*, 159-175.

Winkelstein, B.A. (2004). Mechanisms of central sensitization, neuroimmunology and injury biomechanics in persistent pain: implications for musculoskeletal disorders. *Journal of Electromyography and Kinesiology, 14*, 87–93

Wise, T.N., & Mann, L.S. (1994). The relationship between somatosensory amplification, alexithymia and neuroticism. *Journal of Psychosomatic Research, 38*, 515-521.

Wolfe, F. (1997). The relation between tender points and fibromyalgia symptom variables: evidence that fibromyalgia is not a discrete disorder in the clinic. *Annals of Rheumatic Diseases, 56*, 268–71.

Wolfe, F. (2010). "New American College of Rheumatology criteria for fibromyalgia: a twenty-year journey." *Arthritis Care and Research, 5*, 583–584.

Wolfe, F., Anderson, J., Harkness, D., Bennett, R.M., Caro, X.J., Goldenberg, D.L., ... & Yunus, M.B. (1997). A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. *Arthritis & Rheumatism, 40,* 1560-1570.

Wolfe, F., Clauw, D.J., Fitzcharles, M., Goldenberg, D.L., Häuser, W., Katz, R.S., ... & Winfield, J.B. (2011). Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR preliminary diagnostic criteria for Fibromyalgia. *Rheumatology, 38,* 1113-1122.

Wolfe, F., Clauw, D.J., Fitzcharles, M.A., Goldenberg, D.L., Katz, R.S., Mease, P., …& Yunus, M.B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity". *Arthritis Care and Research, 5,* 600–610.

Wolfe, F., & Potter, J. (1996). Fibromyalgia and work disability: Is fibromyalgia a disabling condition? *Rheumatic Diseases Clinics of North America, 22,* 369–391

Wolfe, F., Ross, K., Anderson, J., Russell, I.J., & Hebert L. (1995). The prevalence and characteristics of fibromyalgia in the general population. *Arthritis and Rheumatism, 38,* 19-28.

Wolfe, F., Smythe, H.A., Yunus, M.B., Bennett, R.M., Bombardier, C., Goldenberg, D.L., …& Sheon, R.P. (1990). The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis & Rheumatism, 33,* 160-172.

Wynne-Jones, G., Macfarlane, G.J., Silman, A.J., & Jones, G.T. (2006). Does physical trauma lead to an increase in the risk of new onset widespread pain? *Annals of the Rheumatic Diseases, 65,* 391-393.

Yunus, M.B. (2007). Fibromyalgia and overlapping disorders: The unifying concept of central sensitivity syndromes. *Seminars in Arthritis and Rheumatism, 36,* 339-356.

Yunus, M.B. & Masi, A.T. (1985). Juvenile Primary Fibromialgia syndrome: a clinical study of thirty-three patients and matched normal controls, *Arthritis & Rheumatism, 28,* 138-145.

Yunus, M., Masi, A.T., Calabro, J.J., Miller, K.A., & Feigenbaum, S.L. (1981). Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. *Seminars in Arthritis and Rheumatism, 11*, 151-171.

Zautra, A.J., Fasman, R., Reich J.W., Harakas, P., Johnson, L.M., Olmsted, M.E., & Davis, M.C. (2005) Fibromyalgia: evidence for deficits in positive affect regulation. *Psychosomatic Medicine, 67*, 147–155.

6. ANEXO. PARTICIPACIÓN EN OTRAS LÍNEAS DE INVESTIGACIÓN

A continuación se realiza una breve referencia a otras líneas de investigación en las que he trabajado activamente y que inicialmente estaban programadas para ser incluidas en la presente Tesis Doctoral. No obstante, al estar más alejadas del tema central de la tesis, y para mantener un volumen más adecuado de ésta, finalmente se decidió que no formaran parte de la misma.

6.1 INFLUENCIAS INHIBITORIAS DEL SISTEMA BARORRECEPTOR SOBRE EL DOLOR

Los cambios en los estados del sistema cardiovascular modulan el procesamiento del dolor a nivel del SNC y por tanto, la experiencia subjetiva del dolor, lo que constituye una importante fuente de influencias anti-nociceptivas (Bruehl y Chung, 2004). En este sentido, los barorreceptores (mecanoreceptores de estiramiento-presión ubicados en el arco aórtico, el seno carotídeo y pulmones; sensibles al estiramiento vascular ocasionado por los cambios en la presión arterial) forman parte de un importante sistema implicado en la regulación autonómica y las interrelaciones periférico-centrales complejas. Como se ha referenciado en el *apartado 1.1.4*, el sistema baroreceptor se divide en dos ramas: cardiovascular y central (Duschek, Werner y Reyes del Paso, 2013; Reyes del Paso, González y Hernández, 2004). La primera de ellas consiste en un feedback negativo por el que es regulada a corto plazo la presión sanguínea (generando cambios compensatorios en la tasa cardiaca y el tono vasomotor). La rama central conlleva la modulación de la actividad del SNC a través de la actividad cardiovascular. De esta manera, la estimulación de los barorreceptores, por los incrementos en presión sanguínea, produce un control inhibitorio generalizado en el cerebro (Rau y Elbert, 2001), incluyendo una reducción en la nocicepción (Bruehl y Chung, 2004; Droste y cols., 1994; Dworkin y cols., 1994; Rau y cols., 1994). Este control inhibitorio del SNC inducido por la estmulación de los baroreceptores determina la relación entre presión sanguínea y dolor (Bruehl y Chung, 2004; France, 1999). Al respecto de esta relación, existen estudios que confirman como pacientes con hipertensión arterial experimentan menos dolor en comparación con individuos

normotensos, mientras que las personas con hipotensión arterial tienen mayor sensibilidad al dolor que las personas normotensas (Bruehl y Chung, 2004; Duschek, Dietel, Schandry y Reyes del Paso, 2009; Duschek, Schwarzkopf y Schandry, 2008; France, 1999; Ghione, 1996; Reyes del Paso y Perales, 2011). Existen además estudios que muestran una reducción del dolor mediante la elevación farmacológicamente inducida de los niveles de presión sanguínea (Duschek, Heiss, Buechner y Schandry, 2009).

Siguiendo este planteamiento, se pueden estimular mecánicamente los barorreceptores carótidos mediante succión en el cuello, una estimulación que "simula" un incremento natural en presión sanguínea (Rau, Elbert, Geiger y Lutzenberger, 1992). Uno de los efectos más estudiados mediante esta técnica ha sido la inducción de hipoalgesia y elevación en los umbrales de dolor (Duschek, Mück y Reyes del Paso, 2007; Rau y Elbert, 2001).

No obstante, la relación entre las rama cardiovascular y central del sistema barorreceptor no ha sido aún esclarecida. Con el objetivo de esclarecer tal relación, y como base para futuros estudios centrados en la fibromialgia, se plantea un estudio adicional a esta Tesis Doctoral *(Anexo, estudio 1)*. Además de ello, de forma novedosa, también se incluye un estudio *(Anexo, estudio 2)* que propone la posibilidad de estimulación de los baroreceptores de forma natural mediante ciertas maniobras respiratorias. Esta idea se basa esencialmente en datos que confirman la estimulación de los baroreceptores mediante los cambios en presión sanguínea provocados por la respiración. Aunque los estudios que se presentan en el apartado de anexos no están específicamente centrados en la fibromialgia, sino en la evaluación del efecto antinoceptivo en general de estos métodos, los resultados de los mismos podrían servir como base para estudios centrados en esta enfermedad de forma específica.

ANEXO, ESTUDIO 1. THE EFFECT OF BARORECEPTOR STIMULATION ON PAIN PERCEPTION DEPENDS ON THE ELICITATION OF THE REFLEX CARDIOVASCULAR RESPONSE: EVIDENE OF THE INTERPLAY BETWEEN THE TWO BRANCHES OF THE BARORECEPTOR SYSTEM.

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The effect of baroreceptor stimulation on pain perception depends on the elicitation of the reflex cardiovascular response: Evidence of the interplay between the two branches of the baroreceptor system

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ABSTRACT

We examined the impact of baroreceptor stimulation on pain and cardiovascular responses in 39 healthy participants. Carotid baroreceptors were stimulated with external suction (−50 mmHg, stimulation) or pressure (+8 mmHg, control). Pain was induced by pressure to the nail of the left-index finger and quantified by a visual analog scale. Pain decreased heart rate (HR) and increased blood pressure (BP). Baroreceptor stimulation further decreased HR and reduced the BP increase. Pain experience failed to differ between baroreceptor stimulation conditions. However, significant results were obtained when trials were categorized according to the magnitude of the HR deceleration elicited by baroreceptor stimulation. In trials with strong baroreceptor-elicited HR deceleration pain intensity was lower than in trials both with inactive baroreceptor stimulation (pressure trials) or trials with small baroreceptor-elicited HR responses. Anti-nociceptive effects of baroreceptor stimulation depend on the activation of the reflex cardiovascular response. Central nervous inhibition due to baroreceptor stimulation only occurs if the peripheral cardiovascular response is engaged.

1. Introduction

The baroreceptors are stretch-pressure receptors located in the aortic arch and the carotid sinus which are involved in autonomic regulation and complex peripheral-central interrelations. The baroreceptors can be seen as a system that can be subdivided into cardiovascular and central branches (Duschek, Werner, & Reyes del Paso, 2013; Reyes del Paso, González, & Hernández, 2004). The former consist of a negative feedback loop by which blood pressure (BP) is regulated through reflex modulation of cardiac and vasomotor activity (i.e. the baroreflex). Afferent information from the baroreceptors is relayed to the nucleus of the tractus solitarius (NTS). The NTS integrates the input from the baroreceptors and modulates the output to excitatory projections to vagal motor neurons and inhibitory influences on nuclei controlling spinal sympathetic neurons (nucleus ambiguus, dorsal motor nucleus, and caudal and rostral ventrolateral medulla oblongata) through which the cardiovascular reflex response is executed (Dampney, Polson, Potts, Hirooka, & Horiuchi, 2003).

The central branch of the baroreceptor system consists of a negative feedback pathway to the brain by which cardiovascular function modulates central nervous system (CNS) activity. Through this loop stimulation, the baroreceptors produce a generalized inhibitory effect on brain structures (Rau & Elbert, 2001). The NTS interconnects with the reticular formation, from which ascending input is transmitted to the lateral-medial, prefrontal, anterior insular, and anterior cingulate cortices (Dembowsky & Seller, 1995). The thalamus, hypothalamus, central nucleus of the amygdala, ventral hippocampus, and periaqueductal gray receive prominent baroreceptor input from the NTS (Basile et al., 2013; Castle, Comoli, & Loewy, 2005; Ishikawa & Nakamura, 2006; Rogers & Fryman, 1998). Mediated by these connections, information arising from the cardiovascular system impacts cortical activity while reciprocally higher-order cognitive-emotional states may modulate functional characteristics of the baroreflex (Duschek, Werner, et al., 2013; Reyes del Paso, González, Hernández, Duschek, & Gutiérrez, 2009; Reyes del Paso, Mata, & Martín-Vázquez, 2012).

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Devices have been designed for mechanical stimulation of the carotid baroreceptors through neck-cuff techniques (e.g. Eckberg, Cavanaugh, Mark, & Abboud, 1975; Raine & Cable, 1999; Rau, Elbert, Geiger, & Lutzenberger, 1992, see Cooper & Hainsworth, 2009, for a review). These allow the investigation of the effects of baroreceptor stimulation on cardiovascular and CNS functions. Baroreceptor activation by neck suction (a manipulation causing an increase in transmural pressure that stretches the baroreceptors simulating an increase in BP) has shown to produce a generalized inhibitory effect on the brain that, e.g., decreases somatic muscle tone, stimulates sleep, inhibits spinal somatic sensory pathways and the startle reflex, reduces sham rage and anxiety, and decreases event-related potentials (Dworkin et al., 1994; Nyklíček, Wijnen, & Rau, 2005; Rau & Elbert, 2001; Rau et al., 1994; Rau, Pauli, Brody, Elbert, & Birbaumer, 1993).

One of the most studied effects of baroreceptor carotid stimulation consists of an anti-nociceptive effect (Droste et al., 1994; Dworkin et al., 1994; Rau et al., 1994). Baroreceptors afferents are involved in the modulation of nociception and the sensitivity to pain (Bruehl & Chung, 2004). Electrical, pharmacological and mechanical baroreceptor stimulation produce anti-nociceptive effects (Bossut & Maixner, 1996; Droste et al., 1994). Similar anti-nociceptive results have been obtained with the stimulation of cardiopulmonary baroreceptors (D'Antono, Ditto, Sita, & Miller, 2000). Pain processing is also modulated by natural variations in baroreceptor activity across the cardiac cycle. During the systolic phase, where baroreceptor load is maximal, nociceptive responses are weaker than during the diastole phase (Edwards et al., 2003; Gray, Minati, Paletti, & Critchley, 2010). This baroreceptor-mediated CNS inhibition is one of the mechanisms mediating the well-known association between BP and pain sensitivity (France, 1999). The experience of pain is inversely correlated with BP levels (Bruehl & Chung, 2004; France, 1999; Ghione, 1996; Reyes del Paso & Perales, 2011), such that patients with arterial hypertension perceive less pain and have lower pain sensitivity than normotensive subjects, a phenomenon known as hypertension-induced hypoalgesia (Ghione, 1996). The perception of pain is also reduced in healthy individuals with moderately high BP values (Bruehl & Chung, 2004; France, 1999). On the other hand, individuals with arterial hypotension have higher sensitivity and an increased perception of pain compared to normotensive subjects (Duschek, Schwarzkopf, & Schandry, 2008; Duschek, Dietel, Schandry, & Reyes del Paso, 2009). Furthermore, experimentally induced BP increases lead to reduced response to pain (Duschek, Heiss, Buechner, & Schandry, 2009).

A question still not fully understood concerns the relation between the cardiovascular and central branches of the baroreceptor system. The available studies that have analyzed the effect of baroreceptor stimulation through neck-cuff techniques have focused either on the cardiovascular effects or on CNS function, but none of these studies have explicitly addressed the interrelation between the cardiovascular and the central effects. One hypothesis suggests a functional equivalence between the two branches of the baroreceptor system, by which enhanced responsivity of the cardiovascular branch (i.e. greater cardiovascular changes elicited by increases in BP or carotid baroreceptor stimulation) would implicate a stronger inhibition of cortical arousal (Duschek, Mück, & Reyes del Paso, 2007; Reyes del Paso, Garrido, Pulgar, Martín-Vázquez, & Duschek, 2010). This hypothesis has been addressed using baroreceptor reflex sensitivity (BRS) as a measure of the strength of the cardiac branch. BRS is defined as the sensitivity with which the baroreceptors modulate interbeat interval (IBI) as a function of the transient changes in systolic BP (SBP) (i.e. the change induced in IBI per unit change in SBP; Parati, di Rienzo, Mancia, 2000; Reyes del Paso, González, & Hernández, 2010). Supporting this hypothesis, BRS was found to be inversely related to cognitive performance (Duschek, Muckenthaler, Werner, & Reyes del Paso, 2009; Reyes del Paso et al., 2009, 2012; Yasumasu, Reyes del Paso, Takahara, & Nakashima, 2006), sensitivity to experimentally evoked pain (Duschek et al., 2007; Reyes del Paso, Garrido, Pulgar, & Duschek, 2011), clinical pain (Reyes del Paso, Garrido, et al., 2010), cortical arousal indexed by contingent negative variation (CNV) (Duschek, Wörsching, & Reyes del Paso, 2013), and worry proneness (Delgado, Vila, & Reyes del Paso, 2014). However, in some of these studies the relation between BRS and pain (Duschek et al., 2007) and cognitive performance (Reyes del Paso et al., 2009, 2012) were modulated by tonic BP, suggesting that the inhibitory effect only occurs in individuals with relatively high BP levels. Similarly, most of the studies investigating the anti-nociceptive effect of carotid baroreceptor stimulation by neck suction have found that this effect is modulated by tonic BP, as the reduction of pain is observed only in individuals with BP levels above the mean (Angrilli, Mini, Mucha, & Rau, 1997; Brody et al., 1997; D'Antono et al., 2000; Elbert, Rockstroh, Lutzenberger, Kessler, & Pietrowsky, 1988; Rau et al., 1994). Taken together, these studies support a relevant role for tonic BP in modulating the inhibitory effect of the baroreceptors on CNS functioning (Duschek, Werner, et al., 2013; Duschek, Wörsching, et al., 2013).

The aim of this study is to analyze the relationship between the cardiovascular and central nervous branches of the baroreceptor system. A neck-cuff technique is used to induce baroreceptor stimulation. The concurrent effects on cardiovascular responsiveness and CNS inhibition are observed. Cardiovascular responsiveness is assessed with heart rate (HR) and BP changes. CNS inhibition is assessed by the influence on pain perception. The functional equivalence hypothesis would anticipate a reduction in pain perception concurrent with successfully induced cardiovascular response. We further asked whether baseline levels of BP or BRS moderated either the cardiovascular or central functional responses to baroreceptor stimulation. Specifically, the objectives of the study were: (1) to assess the effect of pain evocation on HR and BP, and analyze the modulation exerted by the baroreceptor manipulation on the elicited-cardiovascular response. We expected that pain evocation would produce an increase in BP and HR. Stimulation of the carotid baroreceptors was expected to interact with this response, reducing the cardiovascular response elicited by pain. We also expected that individuals with greater BRS would display a lower BP and HR increase to pain stimulation during the neck suction condition. (2) To assess the effect of baroreceptor stimulation on pain ratings. Stimulation of the baroreceptors was expected to produce an anti-nociceptive effect reducing pain experience. Furthermore, we hypothesized that pain experience would be lower in trials in which baroreceptor stimulation evokes larger HR deceleration in comparison with trials in which baroreceptor stimulation evokes smaller HR slowing. (3) To assess the associations between BP level, BRS and pain perception. We predicted a negative association between BP and pain experience as well as a negative association between BRS and pain. We expected this association to be modulated by tonic BP in the sense that it might only arise in participants with BP above the mean.

2. Method

2.1. Participants

Thirty-nine psychology students (20 men and 19 women) aged between 18 and 23 years took part in the study. None of them suffered from any cardiovascular or pain disease or was receiving pharmacological treatment affecting the cardiovascular system or pain perception. Table 1 shows means (±SD) of the baseline cardiovascular and pain variables measured. None of the participants fulfill hypertension criteria (SBP > 140 mmHg and DBP > 90 mmHg, WHO, 1978). Each participant received a course credit for their participation.

Table 1
Means and standard deviations (SD) of basal pain parameters (kg) and baseline systolic (SBP) and diastolic (DBP) blood pressure (mmHg), heart rate (HR, bpm), baroreceptor reflex sensitivity (BRS, ms/mmHg), and number of baroreflex sequences detected.

	Mean	SD
Threshold	2.81	1.29
Tolerance	7.48	2.29
Pain intensity 1	3.93	1.38
Pain intensity 2	5.15	1.57
Pain intensity 3	6.26	1.96
SBP	114.76	12.93
DBP	71.96	10.01
HR	69.72	11.38
BRS	25.44	12.33
No. seq.	16.77	15.18

2.2. Apparatus

Carotid baroreceptors were mechanically stimulated with a laboratory-built pneumatic device under computer control. A pump allow for the production of negative and positive pressures (±50 mmHg) which by solenoid valves and tubes were transmitted to two baby respiratory masks (5 cm height, 4 cm width in its internal dimension) located at the neck, superficial to both carotid sinuses (Jennings, Eddy, Hout, Shapiro, & Gianaros, 2005). The baby masks were fixed to the neck by a cuff. First, the carotid sinuses bifurcations were identified by manual palpation of the carotid horns (boney protrusions within the carotid triangle of the neck). Baroreceptors were stimulated by suction (−50 mmHg). As a control condition a positive pressure (+8 mmHg) was used. The objective of this control condition is to create the sensation of a change in pressure without the distension of the artery. In this regard, both negative pressure (stimulation) and positive pressure (control) produces similar intensities of somatic sensations and are not discriminable. In both conditions duration of baroreceptor manipulation was 10 s.

Pain was evoked by a wireless pressure algometer Traker Freedom (JTECH Medical, Lawndale, USA) with a surface stimulation area of 1 cm^2. A computer controlled the stimulation pressure and rate of increase in pressure (kg/s) administered by the algometer. The algometer was inserted in a screw-piston specifically designed to fix and press the fingernails allowing for a reliable maintenance of stimulation pressure.

A Task Force Monitor (CNSystems, Graz, Austria) was used for the beat-to-beat cardiovascular recordings. To record two bipolar ECGs, four electrodes were applied to the chest, two close to the shoulders, and two at the lower rib cage (Einthoven I and II). Continuous BP measurements were taken from the first phalange of the second and third fingers of the right hand. The hand was positioned at the level of the heart. Oscillometric BP was taken from the left brachial artery. The device recalibrates continuous finger BP according to brachial artery BP every 60 s without interrupting recording. Sampling rate was 1000 Hz for ECG and 200 Hz for continuous finger BP.

2.3. Procedure

As a first step, pain threshold (pressure at which the participant started to feel pain) and tolerance (maximum stimulation pressure that can be tolerated) were measured in the nail of the index finger of the left hand. For two left-handed participants stimulation was performed in the right hand and the BP recordings locations were shifted to the left hand. Pressure in the algometer was increased at a rate of 1 kg/s. Once threshold and tolerance values were obtained, three intermediate pain intensities were defined for each participant according to the following formula: DF = (tolerance − threshold)/4; Intensity 1 = threshold + 1DF, Intensity 2 = threshold + 2DF, Intensity 3 = threshold + 3DF. Then electrodes (ECG), transducers for BP (brachial and fingers) and the neck cuff were attached. Participants were examined in a semi-lying position that improved the efficiency of the neck cuff when administering negative pressure. Then a rest baseline of 5 min was recorded. Afterwards we administered three trials of baroreceptor stimulation (suction) and three trials with the control condition (pressure) interspersed and in a counterbalanced order. After that the pain stimulation phase began. Each participant received 36 pain stimuli consisting of 6 trials per each of the 3 levels of pain pressure intensity and for the two conditions of baroreceptor manipulation (suction vs. pressure) in a counterbalanced order. Pain duration was 5 s. Previous pilot observations with the device showed variability in the time it required to effect the negative pressure on the neck (probably as a function of interindividual anatomical neck differences). To avoid this time variability we started pain stimulation when a pressure of −10 mmHg was crossed. In the control condition pain stimulation were started when pressure crossed a +4 threshold. After each pain trial participants evaluate their subjective experience of pain intensity with one 10-cm line visual analog scale (VAS) ("How strong was the pain?"). The anchor points of the scale were marked as "not at all" and "extremely". After pain evaluation a period of approximately 20 s ensued before the following trial.

2.4. Data reduction and analysis

For the baseline period HR (beats per minute) and brachial-derived SBP and diastolic blood pressure (DBP) (in mmHg) were obtained. BRS was quantified in the time domain based on continuous BP and IBI recordings employing the sequence method (Parati et al., 2000; Reyes del Paso, 1994; Reyes del Paso, González, et al., 2010). This method locates sequences of three to six consecutive cardiac cycles in which SBP increases (by at least 1 mmHg per beat) in combination with an increase in IBI (of at least 1 ms per beat) or sequences in which the decrease of the SBP is accompanied by a decrease in IBI (following the same criteria of minimum change). Each systolic value is paired with the duration of the heart cycle immediately following it a lag of one beat. When one of these reflex sequences was detected, the regression line was computed across all heart cycles of the given sequence. BRS was expressed as the change in IBI (in ms) per mmHg SBP change, measured by the slope of the regression line.

For the baroreceptor-pain stimulation phase, second-by-second HR and finger-continuous SBP, DBP and mean arterial pressure (MAP) were calculated and expressed as difference scores with respect to the mean value of the 5 s previous to the beginning of stimulation. Pain scores were aggregated by pain intensity level and baroreceptor condition.

2.5. Statistical analysis

Analysis of the effect of baroreceptor manipulation (without pain elicitation) on cardiovascular variables were performed with a (2 × 6) repeated measures ANOVAs, the first factor baroreceptor condition (suction vs. control) and the second factor response pattern (seconds). Analysis of the effect of pain evocation on cardiovascular variables were performed with a (3 × 2 × 8) repeated measures ANOVAs, with the factors pain intensity (1, 2 and 3), baroreceptor condition (suction vs. control) and response pattern (seconds). During the baroreceptor stimulation condition alone a 6 s time windows was used as in previous reference studies on neck suction (e.g. Rau et al., 1992, 1993). However, in order to observe the full cardiovascular response to pain this time window was been increased to 8 s. Analysis of pain intensity scores (VAS) was performed with a (3 × 2) repeated measures ANOVAs, with the factors pain intensity (1, 2 and 3) and baroreceptor condition (suction vs. control).

We then analyzed the influence of the magnitude of the HR response to baroreceptor stimulation on pain ratings. We chose HR as the criterion to evaluate the effectiveness of baroreceptor stimulation as previous studies have shown that the reflex-induced short-term increase in IBI is the most clearly identifiable effect associated with effective baroreceptor stimulation (Eckberg et al., 1975; Raine & Cable, 1999; Rau et al., 1992). Taking SBP as a criterion would be more problematic, as changes in BP can subsequently affect baroreceptor activity itself, and alterations in BP can modulate baroreceptors other than the carotid sinus baroreceptors such as aortic or the cardiopulmonary baroreceptors (D'Antono et al., 2000). Furthermore, HR shows stronger variation in response to baroreceptor stimulation (up to −35 bpm in our sample) than SBP (up to −9 mmHg in our sample), and reactivity values computed across participants differed more reliably from 0 for HR (all values lower than −2 bpm) than for SBP (all values between 0 and −0.45 mmHg).

In a first step, we divided trials into those in which the HR difference score at s 3 after the beginning of neck suction was lower (stronger HR effect) or higher (lower HR effect) than the overall median HR change across participants. The 3 s interval was chosen because the HR response to baroreceptor stimulation was larger at this time point in the no-pain condition and pain evocation is near their midpoint at this time. This grouping of trials was performed according the overall group median HR response score separately for each pain pressure intensity. However, this procedure led to missing data in some participants for some trial types in some pain intensity levels and these could not be included in the repeated measures analysis. Among the 27 available participants for this analysis the mean numbers of trials were 9.1 ± 3.1 and 8.9 ± 3.1 for the stronger and weaker baroreceptor effect, respectively. Comparisons of participants available for this analysis with those with missing data showed no differences in gender, age or BMI (all $ps > 4$). In a second step, the sorting of trials into the two sets was performed on a within-participant basis by selecting trials in which the differential HR score at s 3 was below or above the mean value of trials in which the suction condition was employed. This strategy has the advantage of using the complete participant data set and thereby avoiding possible bias due to excluding participants.

Data were analyzed using the multivariate test statistic (Wilks' lambda). Results are presented reporting the F value associated with the Wilks' lambda statistic. Associations between pain and cardiovascular variables were assessed by Pearson correlations. For correlations with the elicited cardiovascular response the time-period associated with the greater differences between the two baroreceptor conditions was selected (second 3). We assessed the influence of tonic baseline BP levels in regression analyses by creating a BRS × baseline SBP level interaction term. A significant effect of the interaction term would support the dependence of the relationship between BRS and pain on BP levels. We also examined in some analyses the additional influence of SBP levels. Two blood pressure groups were formed based on median split according to baseline SBP. Significance level was set at .05.

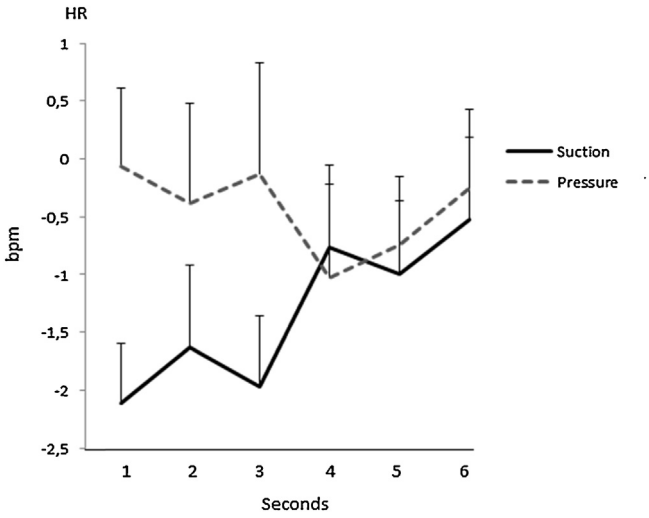

Fig. 1. Heart rate (HR) response to baroreceptor manipulation (Error bars represent SE).

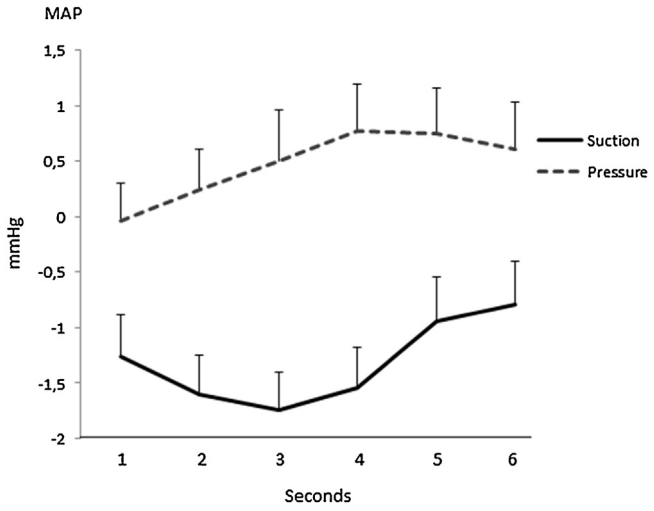

Fig. 2. Mean arterial pressure (MAP) response to baroreceptor manipulation.

3. Results

3.1. Effect of baroreceptor manipulation on cardiovascular variables

The HR response to baroreceptor manipulation yielded the expected changes (interaction effect Condition × Pattern: $F(5, 34) = 2.50$, $p = .050$, $\eta^2 = .269$). Baroreceptor stimulation (suction) produced a short-term decrease in HR ($F(5, 34) = 2.71$, $p = .037$, $\eta^2 = .284$) while the control condition (pressure) did not produce HR changes ($F(5, 34) = 1.29$, $p = .290$, $\eta^2 = .160$) (Fig. 1). Baseline BRS was negatively associated ($r = -.399$, $p = .015$) with the HR response to baroreceptor stimulation at s 3 (i.e. larger HR decreases). The baroreceptor manipulation also yielded the expected decreases in BP (Condition effect: $F(1, 38) = 10.78$, $p = .002$, $\eta^2 = .221$ for SBP; $F(1, 38) = 9.17$, $p = .004$, $\eta^2 = 194$ for DBP; and $F(1, 38) = 13.09$, $p = .001$, $\eta^2 = .256$ for MAP) as well as the interaction Condition × Pattern ($F(5, 34) = 3.50$, $p = .012$, $\eta^2 = .340$ for DBP and $F(5, 34) = 3.74$, $p = .008$, $\eta^2 = 355$ for MAP, while for SBP the interaction did not reach significance: $F(5, 34) = 2.08$, $p = .097$, $\eta^2 = .234$). For the three BP parameters baroreceptor stimulation produced a significant decrease in BP ($p = .030$ for SBP, $p = .037$ for DBP and $p = .001$ for MAP) peaking at seconds 3–4 while the control condition did not produce significant changes. This BP decrease led to reduced BP levels in the stimulation condition in comparison to the control condition (i.e. the main effect of Condition) (Fig. 2).

3.2. Joint effects of pain and baroreceptor stimulation on cardiovascular variables

The joint influence of pain evocation and baroreceptor stimulation produced a decrease in HR (main effect of Pattern: $F(7, 32) = 2.65$, $p = .028$, $\eta^2 = .367$) and this effect was modulated by the baroreceptor manipulation (interaction effect Condition × Pattern: $F(7, 32) = 6.48$, $p < .0001$, $\eta^2 = .545$). The HR decrease was larger in the baroreceptor stimulation condition than in the control condition, leading to significant HR differences between the two baroreceptor conditions (main effect of Condition: $F(1, 38) = 6.23$, $p = .017$, $\eta^2 = .141$) (Fig. 3). Baseline measured BRS was associated with the elicited HR response at s 3 (i.e. larger HR decreases, $r = -.315$, $p = .056$, $r = -.602$, $p < .0001$, and $r = -.342$, $p = .038$ for pain intensities 1, 2, and 3, respectively).

Pain evocation in the baroreceptor control condition induced a mild increase in blood pressure while active-baroreceptor stimulation reduced the concurrent response to pain. Across conditions an increase in BP was associated with pain stimulation (main effect of Pattern: $F(7, 32) = 3.20$, $p = .011$, $\eta^2 = .440$ for SBP; $F(7, 32) = 2.95$, $p = .017$, $\eta^2 = .392$ for DBP; and $F(7, 32) = 2.18$, $p = .063$, $\eta^2 = .323$ for MAP, Fig. 4). The rise in MAP increased with the increase in pain pressure intensity (interaction Intensity × Pattern: $F(14, 25) = 4.17$, $p = .001$, $\eta^2 = .700$). This effect was also marginally observed in DBP (interaction Intensity × Pattern: $F(14, 25) = 1.45$, $p = .071$, $\eta^2 = .522$). The BP changes were modulated by the baroreceptor manipulation (interaction effect Condition × Pattern: $F(7, 32) = 2.95$, $p = .017$, $\eta^2 = .392$ for SBP; $F(7, 32) = 2.35$, $p = .049$, $\eta^2 = .308$ for SBP; and $F(7, 32) = 5.93$, $p < .0001$, $\eta^2 = .565$ for MAP). The BP increase is lower in the baroreceptor stimulation condition than in the control condition, leading to significant BP differences between the two conditions (main effect of the Condition: $F(1, 38) = 22.92$, $p \leq .0001$, $\eta^2 = .376$ for SBP; $F(1, 38) = 26.66$, $p < .0001$, $\eta^2 = .412$ for DBP; and $F(1, 38) = 31.23$, $p < .0001$, $\eta^2 = .451$ for MAP). Baseline BRS was negatively associated with the pain-elicited BP increase during neck suction for pain intensity 1 ($r = -.337$, $p = .041$ for SBP; $r = -.330$, $p = .046$ for DBP; and $r = -.374$, $p = .023$ for MAP, at s 3) and 2 ($r = -.334$, $p = .044$ for SBP; $r = -.335$, $p = .043$ for DBP; and $r = -.337$, $p = .041$ for MAP, at s 3). During pain intensity 3, correlations did not reach significance ($r = -.217$ for SBP; $r = -.317$ for DBP; and $r = -.292$ for MAP, at s 3, all $ps > .05$).

3.3. Effect of baroreceptor manipulation on pain perception

Pain perception did relate directly to pain pressure intensity, but baroreceptor condition, per se, did not alter pain ratings. Ratings were 5.36 ± 2.27, 5.94 ± 2.23, and 6.87 ± 2.14 for the three pressure intensities; (main effect of pain pressure intensity: $F(2, 37) = 71.91$, $p < .0001$, $\eta^2 = .795$, with no main or interaction effect of the baroreceptor condition, all $ps > .2$). We also analyzed whether the predicted anti-nociceptive effect of baroreceptor stimulation could be modulated by tonic BP level by forming BP groups with a median split on the SBP levels. This analysis did not show any trends for the interaction Condition × SBP group ($p = .569$).

Analysis of the effect of baroreceptor stimulation on pain ratings as a function of the magnitude of its effect on HR (based on the across participants median at s 3) showed that pain intensity was lower in trials with greater effect of baroreceptor stimulation on HR ($F(1, 26) = 9.52$, $p = .005$, $\eta^2 = .268$) (Fig. 5). We also compared pain ratings between trials with greater baroreceptor-elicited HR decreases and trials in which the control baroreceptor manipulation was used. Pain intensity was lower in the trials

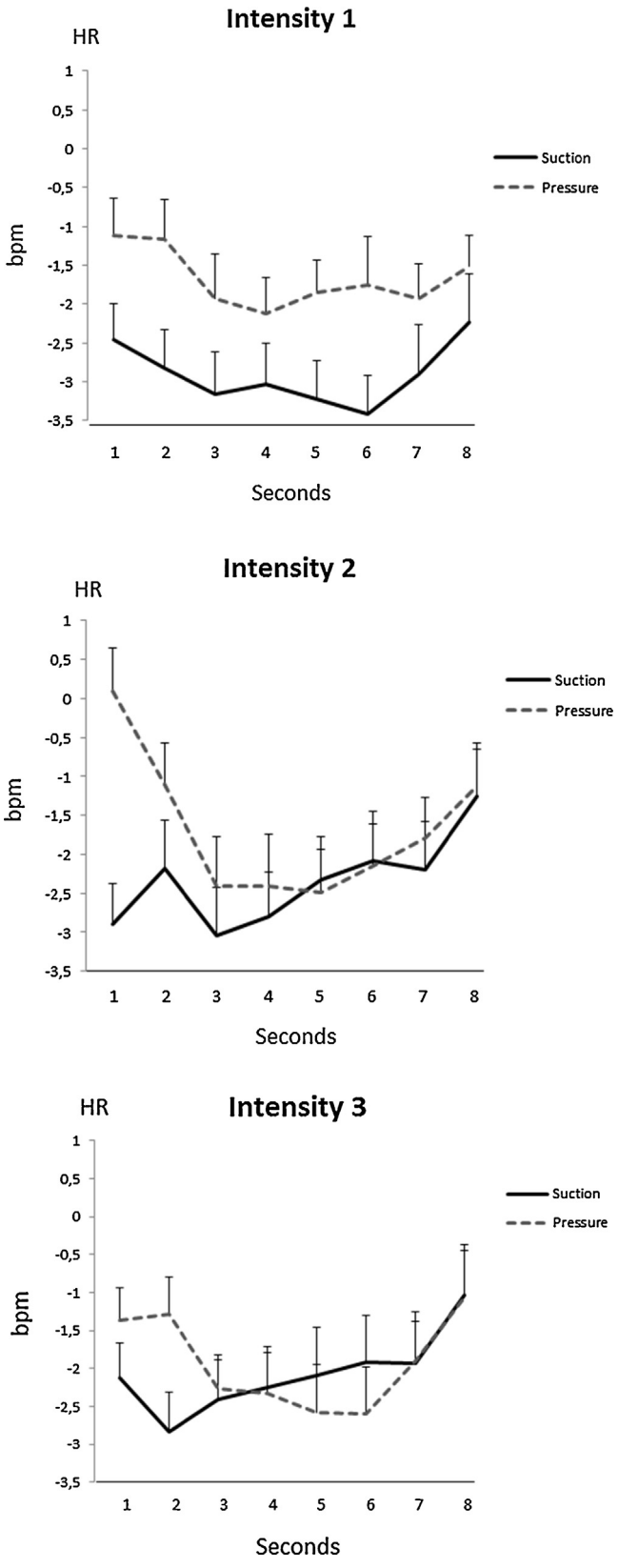

Fig. 3. Heart rate (HR) response to pain evocation as a function of baroreceptor condition and pain intensity.

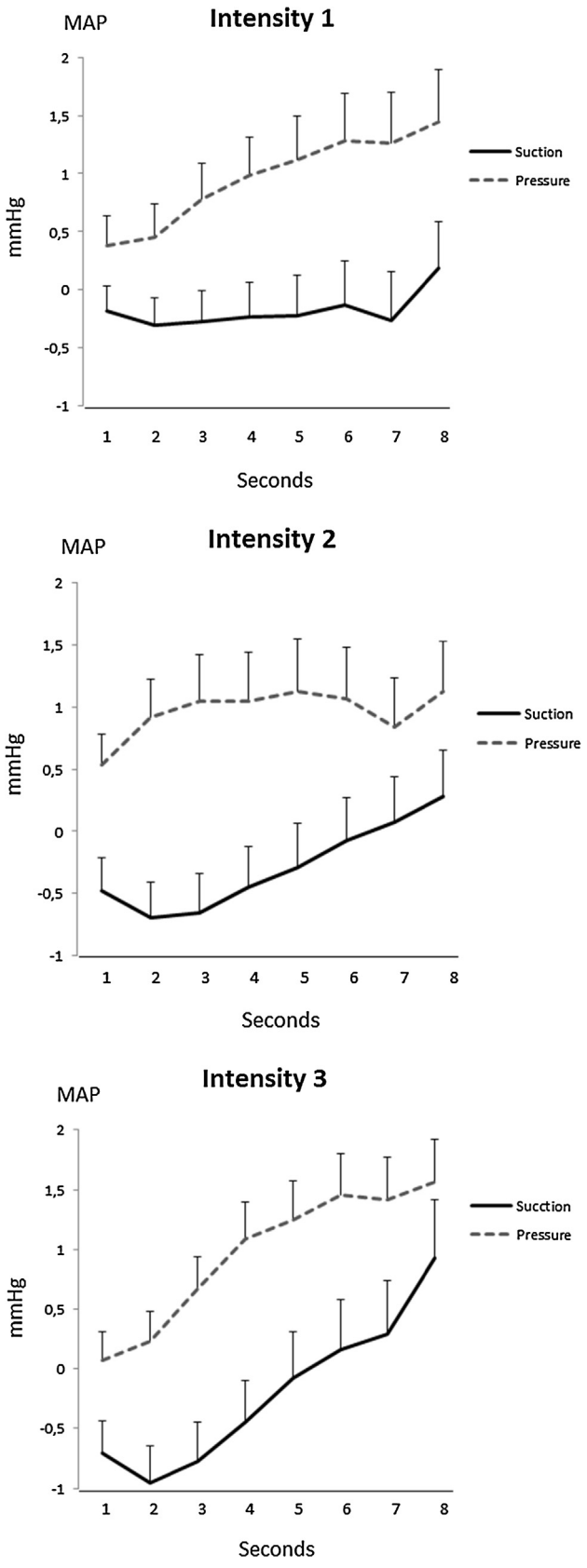

Fig. 4. Mean arterial pressure (MAP) response to pain evocation as a function of baroreceptor condition and pain intensity.

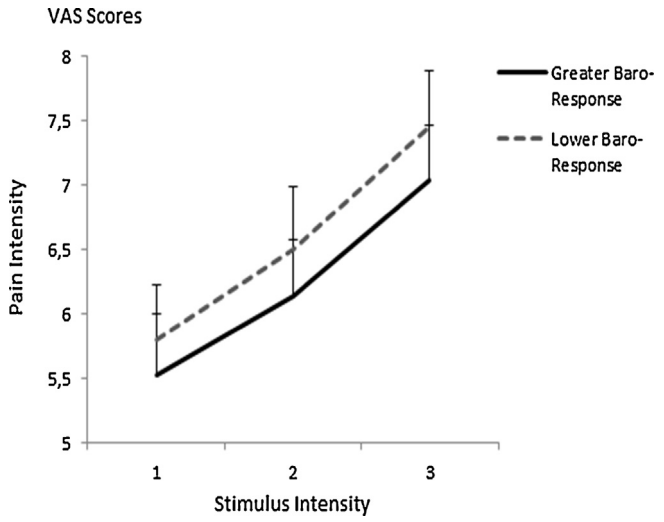

Fig. 5. Averaged pain intensity (VAS scores) in trials with HR (at s 3) below the HR median (greater baroreflex modulation) and trials with HR above the HR median (lower baroreflex modulation).

with HR decreases relative to control trials ($F(1, 28) = 5.17$, $p = .031$, $\eta^2 = .145$). In order to test the reliability of this comparison, we conducted the same analysis using the HR change score at s 2. This analysis revealed a similar result ($F(1, 23) = 6.86$, $p = .015$, $\eta^2 = .230$).

The analysis based on within-participants sorting of trials replicated the aforementioned results. Pain intensity was lower in trials with greater effect of baroreceptor stimulation on HR at s 3 ($F(1, 38) = 10.20$, $p = .003$, $\eta^2 = .212$). Pain ratings were also lower in trials with stronger baroreceptor-elicited HR decreases than during trials in which the control baroreceptor manipulation was used ($F(1, 38) = 5.24$, $p = .028$, $\eta^2 = .121$). Again, pain intensity was lower in trials with greater effect of baroreceptor stimulation on HR at s 2 than in trials with lower baroreceptor-elicited HR changes ($F(1, 38) = 5.06$, $p = .030$, $\eta^2 = .118$).

3.4. Correlations between cardiovascular variables and pain ratings

For the level of pain pressure stimulation 1, BP values during neck suction were positively associated to pain ratings ($r = .555$, $p < .0001$ for SBP; $r = .312$, $p = .053$ for DBP; and $r = .397$, $p = .012$ for MAP, at s 3), indicating that as the baroreceptor stimulation is more effective in reducing BP, less pain is perceived. For HR the association was also positive but did not reach significance ($r = .267$, $p = .101$). However, for the level of pain pressure stimulation 2 and 3 no correlations reached significance.

Correlations between baseline cardiovascular parameters and pain ratings are displayed in Table 2. HR was positively associated to pain ratings but neither BP nor BRS correlated with self-reported pain intensity scores. When these last associations were analyzed by multiple regression analysis, the interaction term BRS × SBP was significant during pain pressure intensity 3 ($\beta = -.328$, $t(37) = -2.05$, $p = .048$) and was marginally significant for pain pressure intensity 1 ($\beta = -.324$, $t(37) = -2.02$, $p = .051$) and 2 ($\beta = -.306$, $t(37) = -1.90$, $p = .066$). The significance of the interaction term shows a dependence of the BRS-self-reported pain relationship on BP levels. For illustrative proposes correlations were $r = -.404$, $r = -.337$ and $r = -.243$ for participants with BP above the SBP median and $r = .115$, $r = .026$, and $r = .199$ for participants with BP below the SBP median (for pain pressure intensities 1, 2, and 3, respectively).

Table 2
Correlations between baseline systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR), and baroreceptor reflex sensitivity (BRS) and pain intensity ratings.

	Intensity 1	Intensity 2	Intensity 3
SBP	.101	.095	.005
DBP	.126	.121	.046
HR	.318†	.324†	.300
BRS	−.093	−.211	−.225

Note: Aggregated pain scores for the two baroreceptor conditions.
† $p < .05$.

4. Discussion

Reliable, mild carotid baroreceptor stimulation was successfully produced by the carotid stimulation device. During the condition of neck suction (stimulation) a significant decrease in HR (35 ms of mean cardiac deceleration) and BP (1.74 mmHg of mean MAP reduction) were obtained. The changes associated with the pressure (control) condition (e.g. 0.77 mmHg of mean MAP increase) did not reach significance. Our objective with the pressure condition was not to produce a valid baroreceptor inhibition (not possible with the current design of the device), but to control for the effect of neck somatic sensations on dependent variables. The validity of the carotid stimulation was further supported by our observation that inter-individual differences in baseline BRS were significantly associated with the elicited HR deceleration following neck suction.

Pain evocation was associated with a rise in BP (that was dependent of pain intensity for DBP and MAP but not for SBP). This result corroborates previous evidence on the BP effects of pain (e.g. Duschek et al., 2007; Reyes del Paso et al., 2011). The joint influence of pain and baroreceptor stimulation produced a decrease in HR; somewhat unexpectedly pain stimulation in the absence of effective baroreceptor stimulation (control condition) failed to yield a HR acceleration. Passive viewing of negatively valenced stimuli is known to be associated with HR decreases (e.g. Palomba, Sarlo, Angrilli, Mini, & Stegagno, 2000). The passive nature of our task in which the participant can view the pain stimulation process may be inducing the HR decrease. Furthermore, our pain elicitation procedure was likely not intense enough to produce a defense reflex; rather the focused attention to the finger may have produced an orienting reflex. The HR deceleration might also have been evoked by the BP increase to pain through the effect of the baroreflex.

In line with our expectations, the baroreceptor manipulation interacted with the cardiovascular response to pain. During pain-baroreceptor stimulation (neck suction) the HR decrease is larger and the BP increase less than during the somatosensory control condition. Furthermore, as predicted, baseline BRS predicted both the HR and BP response to neck suction. These results show the validity of inter-individual differences in BRS as an index of the strength of the baroreflex in regulating cardiovascular activity and the cardiovascular response to carotid baroreceptor stimulation.

Contrary to our expectation and despite the significant cardiovascular changes produced by our baroreceptor manipulation, the neck suction condition, per se, did not produce effects on pain perception – pain perception only responded to suction that yielded a clear HR deceleration. This less than robust condition effect is somewhat consistent with the literature, however. Previous studies do not consistently show a baroreceptor-mediated anti-nociceptive effect but rather suggest that it depends on a number of factors (Rau & Elbert, 2001). For example, Rau et al. (1994) obtained increased thresholds due to carotid baroreceptor stimulation for mechanical but not for thermal pain. Others studies have shown that the size of the anti-nociceptive effect depends on the mode in which baroreceptors were stimulated (Edwards et al., 2003), the technique used for pain assessment (Angrilli et al., 1997; Edwards

et al., 2003), as well as the emotional state during pain elicitation (Mini, Rau, Montoya, Palomba, & Birbaumer, 1995). Previous studies have shown that the effect of carotid baroreceptor stimulation on pain is modulated by tonic BP and that the anti-nociceptive effect is observed only in individuals with BP above the mean. Considering this possibility we also performed the analysis including groups defined by above and below the baseline SBP median as a between-subject factor. Our results failed to find evidence for modulation of the anti-nociceptive effect of baroreceptor stimulation by tonic BP. These results do not replicate the previously reported modulation of tonic BP on the anti-nociceptive effect of carotid baroreceptor stimulation obtained by Elbert et al. (1988) in an age-sample similar than that used here, Brody et al. (1997) both in chronic low back pain patients and in healthy adults, and Angrilli et al. (1997) also in young healthy adults. Two main reasons may be suggested to explain our negative results. Firstly, the relatively low BP in our sample, which is much lower than that found in the previously mentioned studies. The anti-nociceptive effect of baroreceptor stimulation was observed in those studies for individuals with SBP above 130 mmHg (more than 15 mmHg higher than the mean of our sample, in fact almost all our participants fall in their low BP subgroups). The limited BP variability range in our sample, in comparison to these studies, can certainly have limited the possibility of obtaining the expected modulation by tonic BP. Secondly, the sample size of our study (although comparable to the sizes used in those studies) does not have sufficient statistical power to reliably question prior results.

In contrast to the absent condition effect, pain ratings were reduced in the presence of pronounced baroreflex-elicited HR modulation. Pain intensity scores were lower in trials in which baroreceptor stimulation is more effective in reducing HR (measured both at s 2 and s 3 after the onset of pain stimulation) than in trials in which the baroreceptor-elicited HR effect is lower. Additionally, pain intensity scores were also lower in trials with greater baroreceptor-elicited HR reduction than in trials in which the control baroreceptor condition were used. Furthermore, these results were obtained when the sorting of trials was performed both on across-participants and within-participants basis, which underlines the reliability of the comparisons according to the cardiac response. Our correlational results are congruent with the difference obtained in pain reports as a function of the magnitude of the baroreceptor-elicited response. Differential BP scores during neck suction were positively associated to pain ratings; the more effective baroreceptor stimulation in reducing BP, the less pain is perceived. However, this association is only observed for the lower level of pain stimulation and not for the remaining two higher levels. This result is coherent with some studies that suggest that the relation between subjective pain reports and physiological variables arises when the pain stimulation intensities used are relatively near the threshold level, but not when pain intensities are closer tolerance level (Duschek, Hellmann, Merzoug, Reyes del Paso, & Werner, 2012). Extreme stimulation may lead to maximum responses in most of the participants. This ceiling effect reduces variance and in turn may account for the absence of significant correlations at the two top pain levels. Similar results have been obtained in other types of stressful stimulation (e.g. cardiovascular reactivity to psychological stress, Kamarck & Lovallo, 2003), showing that with moderate stimulation levels interindividual differences are more reliably detected relative to both less and greater stimulation. Furthermore, looking at Figs. 3 and 4, especially the plots for HR, it seem that the greater difference between the two baroreceptor conditions arises for the stimulus intensity 1, and that differences as a function of baroreceptor manipulation decreases as pain pressure intensity increases. This suggests the value of choosing near threshold intensities for the studying of baroreceptor elicited anti-nociceptive effects.

We hypothesize a basic equivalence between the two branches of the baroreceptor system such that greater activity in the cardiovascular branch would be associated with stronger CNS inhibition (Duschek et al., 2007; Reyes del Paso, Garrido, et al., 2010; Reyes del Paso et al., 2009). This hypothesis was corroborated as the above results show lower pain perception in trials in which baroreceptor stimulation produces a greater HR effect and a significant association between the magnitude of the elicited BP response to neck suction and pain ratings. These results also suggest that the central inhibitory effect of baroreceptors stimulation is dependent on the elicitation of the baroreceptor-elicited cardiovascular effect as the effect is not observed when the reflex HR response is not elicited or is small.

Baseline BP did not correlate with pain reports. This may be also explained by the relatively low and limited BP variability range in our sample. Baseline HR is associated to pain intensity scores, with participants with higher HR displaying greater pain reports. At physiological level, given that HR under low to moderate level of stress is subjected mainly to vagal control (Reyes del Paso, Langewitz, Mulder, van Roon, & Duschek, 2013), this relation could reflect the association between vagal activity and pain (Duschek et al., 2007). Such an association is supported by the efficacy of techniques such as relaxation, biofeedback or hypnosis which increase vagal tone and also decrease pain (Rainville, 2013). At a psychological level, one can suspect that participants with greater HR are more aroused and anxious, and anxiety and stress have been related to pain (Fernandez, 2002). Overall, no significant correlations were found between baseline BRS and pain intensity ratings. However, as suggested by previous evidence (Duschek et al., 2007; Duschek, Werner, et al., 2013), this relation appeared to be modulated by tonic BP. In fact, when prediction of pain reports are analyzed by multiple regression analysis, we found that the relation between BRS and pain depend of tonic BP levels. BRS was negatively associated to pain intensity reports in participants with higher BP, while no association was found in participants with lower BP. This result corroborates the study of Duschek et al. (2007) and supports the relevance of tonic BP in modulating the inhibitory effects of baroreceptors on CNS functions (Duschek, Werner, et al., 2013; Reyes del Paso et al., 2009).

Our results suggest the need to take into account and measure the cardiovascular response to baroreceptor stimulation when studying their inhibitory central influences; our study suggests that the CNS effect depends on the elicitation of the cardiovascular effects (i.e. the inhibitory effects would appear to arise only if the baroreflex is elicited). In this regards, previous inconsistencies found in literature about the anti-nociceptive effect of baroreceptor stimulation (i.e. Angrilli et al., 1997; Brody et al., 1997; D'Antono et al., 2000; Elbert et al., 1988) might be explained by the lack of consideration of the cardiovascular response elicited by this stimulation.

A limitation of our study is its relatively small sample size, especially when the effect of tonic BP is considered, and the low BP variance in our sample. Future studies should replicate these results with larger samples with greater statistical power in analyzing the effect of tonic BP. This is even more relevant as the current modest sample size is similar to that of previous studies that have analyzed the modulation by tonic BP on the anti-nociceptive effect of carotid baroreceptor stimulation (i.e. Angrilli et al., 1997; Brody et al., 1997; Elbert et al., 1988). A second limitation of the study pertains to the time-locked coordination of the experimental events. As we observed variability in the time our device needed to induce negative pressure on the neck, we started pain stimulation in accordance with a pressure criterion for mmHg pressure applied by the baroreceptor stimulation device. Both pain stimulation and cardiovascular responses were time locked to −10 mmHg pressure in the stimulation condition and to +4 mmHg in the control condition.

Some time differences may exist between suction-pressure onset and reaching the −10 or +4 mmHg criteria. Due to this, the cardiovascular response could have already been initiated when the actual time-locked pain stimulus appeared. However, this possible delay between pain onset and the suction-pressure onset is likely randomly distributed and would actually lead to smaller cardiovascular responses and associations between the cardiovascular response and pain. Future studies should take into account this issue.

In conclusion, the anti-nociceptive effect of carotid baroreceptor stimulation seems to depend upon the elicitation of the reflex cardiovascular response. These results support an interplay between the central and cardiovascular branches of the baroreceptors, by which a greater activity in the cardiovascular branch would be associated to stronger CNS inhibition. Baroreceptor stimulation only alters pain perception when sufficient to elicit the corresponding reflex cardiovascular response.

Acknowledgements

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References

Angrilli, A., Mini, A., Mucha, R. F., & Rau, H. (1997). The influence on flow blood pressure and baroreceptor activity on pain responses. *Physiology and Behaviour*, *62*, 391–397.

Basile, B., Bassi, B., Calcagnini, G., Strano, S., Caltagirone, C., Macaluso, E., Cortelli, P., & Bozzali, M. (2013). Direct stimulation of the autonomic nervous system modulates activity of the brain at rest and when engaged in a cognitive task. *Human Brain Mapping*, *34*.

Bossut, D. F., & Maixner, W. (1996). Effects of cardiac vagal afferent electro stimulation on the responses of trigeminal and trigeminothalamic neurons to noxious orofacial stimulation. *Pain*, *65*, 101–109.

Brody, S., Angrilli, A., Weiss, U., Birbaumer, N., Mini, A., Veit, R., & Rau, H. (1997). Somatosensory evoked potentials during baroreceptor stimulation in chronic low back pain patients and normal controls. *International Journal of Psychophysiology*, *25*, 201–210.

Bruehl, S., & Chung, O. (2004). Interactions between the cardiovascular and pain regulatory systems: An updated review of mechanisms and possible alterations in chronic pain. *Neuroscience and Biobehavioral Reviews*, *28*, 395–414.

Castle, M., Comoli, E., & Loewy, A. D. (2005). Autonomic brain stem nuclei are linked to the hippocampus. *Neuroscience and Biobehavioral Reviews*, *134*, 657–669.

Cooper, V. L., & Hainsworth, R. (2009). Carotid baroreflex testing using the neck collar device. *Clinical Autonomic Research*, *19*, 102–112.

Dampney, R. A. L., Polson, J. W., Potts, P. D., Hirooka, Y., & Horiuchi, J. (2003). Functional organization of brain pathways subserving the baroreceptor reflex: Studies in conscious animals using immediate early gene expression. *Cellular and Molecular Neurobiology*, *23*, 597–616.

D'Antono, B., Ditto, B., Sita, A., & Miller, S. B. (2000). Cardiopulmonary baroreflex stimulation and blood-pressure related hypoalgesia. *Biological Psychology*, *53*, 217–231.

Delgado, L. C., Vila, J., & Reyes del Paso, G. A. (2014). Proneness to worry is negatively associated with blood pressure and baroreflex sensitivity: Further evidence of the blood pressure emotional dampening hypothesis. *Biological Psychology*, *96*, 20–27.

Dembowsky, K., & Seller, H. (1995). Arterial baroreceptor reflexes. In D. Vaitl, & R. Schandry (Eds.), *From the heart to the brain: The psychophysiology of circulation–brain interaction* (pp. 35–60). Frankfurt a.M.: Europaischer Verlag der Wissenschaften.

Droste, C., Kardos, A., Brody, S., Greenlee, M. W., Roskamm, H., & Rau, H. (1994). Baroreceptor stimulation: Pain perception and sensory thresholds. *Biological Psychology*, *37*, 101–113.

Duschek, S., Dietel, A., Schandry, R., & Reyes del Paso, G. A. (2009). Increased sensitivity to heat pain in chronic low blood pressure. *European Journal of Pain*, *13*, 28–34.

Duschek, S., Hellmann, N., Merzoug, K., Reyes del Paso, G. A., & Werner, N. S. (2012). Cerebral blood flow dynamics during pain processing investigated by functional transcranial Doppler sonography. *Pain Medicine*, *13*, 419–426.

Duschek, S., Heiss, H., Buechner, B., & Schandry, R. (2009). Reduction in pain sensitivity due to pharmacological elevation of blood pressure in chronically low blood pressure. *Journal of Psychophysiology*, *23*, 104–112.

Duschek, S., Mück, I., & Reyes del Paso, G. A. (2007). Relationships between baroreceptor cardiac reflex sensitivity and pain experience in normotensive individuals. *International Journal of Psychophysiology*, *65*, 193–200.

Duschek, S., Muckenthaler, M., Werner, H. S., & Reyes del Paso, G. A. (2009). Relationships between features of cardiovascular control and cognitive performance. *Biological Psychology*, *81*, 110–117.

Duschek, S., Schwarzkopf, W., & Schandry, R. (2008). Increased pain sensitivity in low blood pressure. *Journal of Psychophysiology*, *22*, 20–27.

Duschek, S., Werner, N. S., & Reyes del Paso, G. A. (2013). The behavioural impact of baroreflex function: A review. *Psychophysiology*, *50*, 1183–1193.

Duschek, S., Wörsching, J., & Reyes del Paso, G. A. (2013). Interactions between autonomic cardiovascular regulation and cortical activity: A CNV study. *Psychophysiology*, *50*, 388–397.

Dworkin, B. R., Elbert, T., Rau, H., Birbaumer, N., Pauli, P., Droste, C., & Brunia, C. H. (1994). Central effects of baroreceptor activation in humans: Attenuation of skeletal reflexes and pain perception. *Proceedings of the National Academy of Sciences United States of America*, *91*, 6329–6333.

Eckberg, D. L., Cavanaugh, M. S., Mark, A. L., & Abboud, F. M. (1975). A simple neck suction device for activation of carotid baroreceptors. *Journal of Laboratory and Clinical Medicine*, *85*, 167–173.

Edwards, L., McIntyre, D., Carroll, D., Ring, C., France, C. R., & Martin, U. (2003). Effects of artificial and natural baroreceptor stimulation on nociceptive responding and pain. *Psychophysiology*, *40*, 762–769.

Elbert, T., Rockstroh, B., Lutzenberger, W., Kessler, M., & Pietrowsky, R. (1988). Baroreceptor stimulation alters pain sensation depending on tonic blood pressure. *Psychophysiology*, *25*, 25–29.

Fernandez, E. (2002). *Anxiety, depression, and anger in pain: Research finding and clinical options*. Dallas. TX: Psychological Resources.

France, C. (1999). Decreased pain perception and risk for hypertension: Considering a common physiological mechanism. *Psychophysiology*, *36*, 683–692.

Gray, M. A., Minati, L., Paletti, G., & Critchley, H. D. (2010). Baroreceptor activation attenuates attentional effects on pain-evoked potentials. *Pain*, *151*, 853–861.

Ghione, S. (1996). Hypertension-associated hypalgesia: Evidence in experimental animals and humans, pathophysiological mechanisms, and potential clinical consequences. *Hypertension*, *28*, 494–504.

Ishikawa, A., & Nakamura, S. (2006). Ventral hippocampal neurons project axons simultaneously to the medial prefrontal cortex and amygdala in the rat. *Journal of Neurophysiology*, *96*, 2134–2138.

Jennings, J. R., Eddy, M. J., Hout, M. C., Shapiro, L. R., & Gianaros, P. J. (2005). A simple device to mildly stimulate the carotid baroreceptors. *Psychophysiology*, *42*(Suppl. 1), S69.

Kamarck, T. W., & Lovallo, W. R. (2003). Cardiovascular reactivity to psychological challenge: Conceptual and measurement considerations. *Psychosomatic Medicine*, *65*, 9–21.

Mini, A., Rau, H., Montoya, P., Palomba, D., & Birbaumer, N. (1995). Baroreceptor cortical effects, emotions and pain. *International Journal of Psychophysiology*, *19*, 67–77.

Nyklíček, I., Wijnen, V., & Rau, H. (2005). Effects of baroreceptor stimulation and opioids on the auditory startle reflex. *Psychophysiology*, *42*, 213–222.

Palomba, D., Sarlo, M., Angrilli, A., Mini, A., & Stegagno, L. (2000). Cardiac responses associated with affective processing of unpleasant film stimuli. *International Journal of Psychophysiology*, *36*, 45–57.

Parati, G., di Rienzo, M., & Mancia, G. (2000). How to measure baroreflex sensitivity: From the cardiovascular laboratory to daily life. *Journal of Hypertension*, *18*, 7–19.

Raine, N. M., & Cable, T. (1999). A simplified paired neck chamber for the demonstration of baroreflex blood pressure regulation. *Advances in Physiology Education*, *22*, S60–S66.

Rainville, P. (2013). Hypnotic analgesia. In S. McMahon, M. Koltzenburg, I. Tracey, & D. C. Turk (Eds.), *Wall & Melzack's textbook of pain*. Elsevier.

Rau, H., Brody, S., Larbig, W., Pauli, P., Vohringer, M., Harsch, B., Kroling, P., & Birbaumer, N. (1994). Effects of PRES baroreceptor stimulation on thermal and mechanical pain threshold in borderline hype and normotensives. *Psychophysiology*, *31*, 480–485.

Rau, H., & Elbert, T. (2001). Psychophysiology of arterial baroreceptors and the etiology of hypertension. *Biological Psychology*, *57*, 179–201.

Rau, H., Elbert, T., Geiger, B., & Lutzenberger, W. (1992). PRES: The controlled non-invasive stimulation of the carotid baroreceptors in humans. *Psychophysiology*, *29*, 165–172.

Rau, H., Pauli, P., Brody, S., Elbert, T., & Birbaumer, N. (1993). Baroreceptor stimulation alters cortical activity. *Psychophysiology*, *30*, 322–325.

Reyes del Paso, G. A. (1994). A program to assess baroreceptor cardiac reflex function. *Behavior Research Methods Instruments and Computers*, *26*, 62–64.

Reyes del Paso, G. A., Garrido, S., Pulgar, A., & Duschek, S. (2011). Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia syndrome. *Journal Psychosomatic Research*, *70*, 125–134.

Reyes del Paso, G. A., Garrido, S., Pulgar, A., Martín-Vázquez, M., & Duschek, S. (2010). Aberrances in autonomic cardiovascular regulation in fibromyalgia syndrome and their relevance for clinical pain reports. *Psychosomatic Medicine*, *72*, 462–470.

Reyes del Paso, G. A., González, I., & Hernández, J. A. (2004). Baroreceptor sensitivity and effectiveness varies differentially as a function of cognitive-attentional demands. *Biological Psychology*, *67*, 385–395.

Reyes del Paso, G. A., González, M. I., & Hernández, J. A. (2010). Comparison of baroreceptor cardiac reflex sensitivity estimates from inter-systolic and ECG R–R intervals. *Psychophysiology*, *47*, 1102–1108.

Reyes del Paso, G. A., González, M. I., Hernández, J. A., Duschek, S., & Gutiérrez, N. (2009). Tonic blood pressure modulated the relationship between baroreceptor cardiac reflex sensitivity and cognitive performance. *Psychophysiology*, *46*, 932–938.

Reyes del Paso, G. A., Langewitz, W., Mulder, L. J. M., van Roon, A., & Duschek, S. (2013). The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a re-analysis of previous studies. *Psychophysiology*, *50*, 477–487.

Reyes del Paso, G. A., Mata, J. L., & Martín-Vázquez, M. (2012). Relationships between baroreceptor cardiac reflex sensitivity and cognitive performance: Modulations by gender and blood pressure. *Psychophysiology*, *49*, 138–144.

Reyes del Paso, G. A., & Perales, M. C. (2011). Haemodialysis curse is associated to changes in pain threshold and in the relations between arterial pressure and pain. *Nefrología*, *31*, 738–742.

Rogers, R. C., & Fryman, D. L. (1998). Direct connections between the central nucleus of the amygdala and the nucleus of the solitary tract: An electrophysiological study in the rat. *Clinical and Experimental Pharmacology and Physiology*, *25*, 483–486.

WHO. (1978). *Arterial hypertension. Technical report series no. 628*. Geneva: World Health Organization.

Yasumasu, T., Reyes del Paso, G. A., Takahara, K., & Nakashima, Y. (2006). Reduced baroreflex cardiac sensitivity predicts increased cognitive performance. *Psychophysiology*, *43*, 41–45.

ANEXO, ESTUDIO 2. BREATH-HOLDING DURING EXHALATION AS A SIMPLE MANIPULATION TO REDUCE PAIN PERCEPTION.

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REHABILITATION SECTION

Brief Research Report

Breath-Holding During Exhalation as a Simple Manipulation to Reduce Pain Perception

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Abstract

Objective. Baroreceptor stimulation yields antinociceptive effects. In this study, baroreceptors were stimulated by a respiratory maneuver, with the effect of this manipulation on pain perception subsequently measured.

Methods. Thirty-eight healthy participants were instructed to inhale slowly (control condition) and to hold the air in lungs after a deep inhalation (experimental condition). It was expected that breath-holding would increases blood pressure (BP) and thus stimulate the baroreceptors, which in turn would reduce pain perception. Pain was induced by pressure algometry on the nail of the left-index finger, at three different pressure intensities, and quantified by visual analogue scales. Heart rate (HR) and BP were continuously recorded.

Results. Pain perception was lower when pain pressure was administered during the breath-holding phase versus the slow inhalation phase, regardless of the pressure intensity. During breath-holding, a rapid increase in BP and decrease in HR were observed, demonstrating activation of the baroreceptor reflex.

Conclusion. Pain perception is reduced when painful stimulation is applied during breath-holding immediately following a deep inhalation. These results suggest that a simple and easy-to-perform respiratory maneuver could be used to reduce acute pain perception.

Key Words. Respiration; Pain; Baroreceptor Reflex; Blood Pressure; Heart Rate

Introduction

The baroreceptors are pressure-stretch receptors located within the aortic arch, carotid sinus, and lungs involved in autonomic regulation and blood pressure (BP) control [1,2]. Furthermore, stimulation of the baroreceptors produces a generalized inhibitory effect on the central nervous system (CNS) [3], which included a reduction in nociception [4–7]. Electrical, pharmacological, or mechanical baroreceptor stimulation produces antinociceptive effects [4,8–10]. This baroreceptor-induced CNS inhibition is one of the principal mechanisms explaining the relationship between BP and pain [7,11]. The experience of pain is inversely associated with BP levels; patients with arterial hypertension experience less pain compared with normotensive individuals, and individuals with arterial hypotension have higher pain sensitivity versus normotensive subjects [7,11–15]. Furthermore, experimentally induced increases in BP reduce pain perception [16].

The baroreceptors are differentially stimulated during the breathing cycle. BP spontaneously oscillates in phase with respiration. Within each respiratory cycle, BP increases and decreases by between 4 and 6 mm Hg. These BP changes result from intrapleural negative pressure during inhalation, positive intrapleural pressure during exhalation, and variations in pressure, on the abdominal viscera, as exerted by the diaphragm [17].

Accordingly, BP increases during the end stages of inhalation and during the onset of exhalation and decreases during the resting phase of the respiratory cycle, particularly at the onset of inhalation [18]. Deep inhalations can increase these BP oscillations by up to 20 mm Hg [19]. Furthermore, the responsiveness of baroreceptors (similar to other receptors such as the chemoreceptors) are modulated by respiratory CNS afferents [20–23]. Baroreceptor stimulation produces minimal heart rate (HR) responses when produced during the onset and midparts of inhalation, but produces maximal HR responses when stimulation is performed during the final stage of inhalation, and particularly during the onset of exhalation [20]. This effect is in turn modulated by respiratory rate; the modulation exerted by respiratory phase decreases as the respiratory rate increases, and disappears with rates of >20 breaths per minute [20].

Some respiratory maneuvers could be used to further increase the natural oscillation in the stimulation of the baroreceptors during the respiratory cycle. Breath-holding is known to produce relevant cardiovascular effects [24]. Specially, when performed at the beginning of exhalation after a deep inhalation, this specific breath-holding is a powerful stimulus for general autonomic stimulation and specifically produces a baroreceptor-mediated large HR deceleration [25]. This is the result of the additional rise in BP obtained from the increase in lung pressure while maintaining the inspired air within lungs.

In this study, we evaluate the antinociceptive effect of this method for baroreceptor stimulation by analyzing the effect of the respiratory phase in which the pain stimuli is delivered on pain perception. Following a within-subject design, pain evoked by pressure algometry was presented during breath-holding after a deep inhalation (baroreceptor stimulation condition) versus during a slow inhalation (control condition). Using the first respiratory maneuver, we take advantage of the increase in BP, enhanced baroreceptor responsiveness, and vagal cardiac neural traffic present at the beginnings of exhalation, further enhanced by breath-holding. As breath-holding immediately after the deep inhalation would stimulate the baroreceptors, we predicted that pain would be lower during the expiratory holding than during the slow inhalation. Furthermore, to evaluate the changes induced by breathing in the cardiovascular system, HR and BP were continuously recorded.

Method

Participants

Thirty-eight psychology students from the University of Jaén (19 males and 19 females), aged between 18 and 23 years, participated. Exclusionary criteria comprised the presence of pain, cardiovascular, or respiratory diseases, and the use of drugs or pharmacological treatments affecting pain or the cardiovascular system. Participants received course credit for their participation.

Apparatus

Beat-to-beat HR and BP were recorded with a Task Force Monitor (CNSystems, Graz, Austria). Four electrodes were applied to the chest, two at the shoulders and two at the lower rib cage (Einthoven I and II), to record two bipolar electrocardiogram (ECGs). Continuous BP measurements were taken from the first phalange of the second and third fingers of the right hand. The hand was positioned at the level of the heart. Oscillometric BP was taken from the left brachial artery. The device recalibrates continuous finger BP, according to brachial artery BP, every 60 seconds without interrupting recording. Sampling rate was 1000 Hz for ECG and 200 Hz for continuous finger BP.

Pain was evoked by a wireless pressure algometer (Traker Freedom; JTECH Medical, Lawndale) with a surface stimulation area of 1 cm^2. The algometer was inserted in a piston-screw, designed to fix and press the finger nails, allowing for reliable maintenance of stimulation pressure. A computer controlled the stimulation pressure and rate of increase in pressure (kg/s) administered. In healthy young adults, the intraclass correlation (reliability) for pain pressure thresholds measured in the fingers is approximately 0.75 [26].

Procedure

Before the actual experiment, participants were instructed to practice the threshold (pressure at which the participant started feeling pain) and tolerance (maximum stimulation pressure tolerated) concepts and pain evaluation using the visual analogue scales (VAS). A first provisional measurement of threshold-tolerance was obtained, followed by presentation of a sequence of seven ascendant pain pressure stimuli (from 0.9 to 3.6 kg) such that the participant learnt to discern small incremental increases in pain pressure intensity. Definitive threshold-tolerance values were then obtained in the nail of the index finger of the left hand. For two left-handed participants, stimulation was performed in the right hand, and the BP recordings were performed in the left hand. Pressure in the algometer was increased at a rate of 1 kg/s. The mean (±SD) value for the threshold was 2.81 ± 1.29 kg, and 7.48 ± 2.29 for tolerance. Three intermediate pain intensities were subsequently defined for each participant according to the following formula: DF = (tolerance − threshold)/4; Intensity 1 = threshold + 1DF; Intensity 2 = threshold + 2DF; and Intensity 3 = threshold + 3DF. Following this, participants were instructed to perform slow inhalations, lasting at least 7 seconds (control condition), and to inhale deeply and maintain the air in lungs before exhaling during 7 seconds without exerting any active muscular pressure (stimulation condition). This was practiced until participants felt confident in their ability to perform both tasks, following which the stimulation phase began.

Table 1 Descriptive data for applied pain pressures (kg), baseline systolic blood pressure (SBP, mm Hg) and heart rate (HR, bpm)

	Mean	SD	Minimum	Maximum
Pain intensity 1	3.98	1.39	1.90	7.10
Pain intensity 2	5.24	1.56	2.70	8.80
Pain intensity 3	6.37	1.94	3.30	10.60
SBP	114.19	11.86	92.58	135.62
HR	70.46	11.07	50.61	108.07

Participants received three pain stimuli, of 5 seconds duration for each pressure-pain intensity and breathing condition (18 pain stimuli in total). Half of the participants started in the breath-holding, and half in the slow-breathing, condition. In all participants, pain intensity was delivered in an identical sequence, that is, intensity 1, 2, and finally 3. This order was used to avoid any possible interference effect of temporal summation of pain, which is typically observed for moderate-to-intense pain stimulation [27]. During slow inhalation, stimulation pressure commenced when the participant began inhalation. During exhalation, stimulation pressure started when the participant began to maintain the air in their lungs. Once the 5 seconds pain stimulation was discontinued, participants continued breathing normally. Following each pain stimulus, participants were presented with two 10-cm line VAS. These scales indexed the sensory and affective aspects of pain (How strong/unpleasant was the pain?). The anchor points of the scales were marked "not at all" and "extremely." In acute pain contexts, intraclass correlation coefficients between repeated VAS measurements exhibited excellent reliability, with coefficients ranging between 0.95 and 0.98. With intervals of 1 min between measurements, 50% of the paired scores were within 2 mm of each other [28]. Pain evaluation was followed by a period of approximately 20 seconds before the next trial. Participants were informed that the aim of the experiment was to evaluate the effects of breathing on pain perception; they did not receive information concerning the study hypothesis. The experimental protocol was approved by the Bioethics Committee of the University of Jaén.

Data Reduction and Statistical Analysis

Second-by-second HR and finger-continuous systolic BP (SBP) were calculated and expressed as differential scores with respect to the mean value of the 5 seconds previous to the onset of pain stimulation. Pain scores and HR and SBP responses were aggregated by respiratory condition and pain intensity level. Analysis of the effect of respiratory manipulation on pain perception (VAS scores) was performed with a (2 × 3) repeated measures ANOVA, with respiratory phase (slow inhalation vs. breath-holding) and pain intensity (intensities 1, 2, and 3) as within-subjects factors. Analysis of the effect of the respiratory manipulation on HR and SBP responses were performed using a (2 × 3 × 8) repeated measures ANOVA, in which the 8 second-by-second response pattern values were included as a third within-subjects factor. The Huynh–Feldt epsilon correction was applied for the adjustment of the degrees of freedom. Results are reported with the original degrees of freedom and corrected P values. A value of $P < 0.05$ (two-sided) was taken to indicate statistical significance. Table 1 displays descriptive data for applied pain pressures and baseline SBP and HR.

Results

Effect of Breathing Condition on Pain Perception

Pain intensity ($F(2, 36) = 89.58$, $P < 0.001$, $\eta^2 = 0.708$) and unpleasantness ($F(2, 36) = 80.80$, $P < 0.001$, $\eta^2 = 0.686$) increased with increases in the pain pressure applied, and were greater during slow inhalation than during breath-holding ($F(1, 37) = 6.08$, $P = 0.018$, $\eta^2 = 0.141$ for pain intensity; and $F(1, 37) = 8.54$, $P = 0.006$, $\eta^2 = 0.188$ for pain unpleasantness (Figures 1 and 2). No pain intensity × breathing condition interaction was observed for intensity ($P = 0.124$) or unpleasantness ($P = 0.544$).

Effect of Breathing Condition on Cardiovascular Variables

The observed HR response (main effect of Pattern: $F(7, 31) = 83.13$, $P < 0.001$, $\eta^2 = 0.692$) was modulated by the breathing condition (interaction pattern × breathing condition: $F(7, 31) = 18.55$, $P < 0.001$, $\eta 2 = 0.334$). No

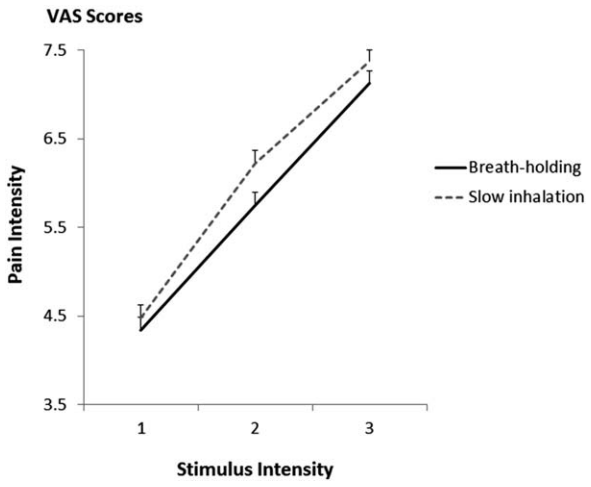

Figure 1 Averaged pain intensity (VAS scores) as a function of pain pressure intensity and respiratory condition in which the pain stimulus was delivered (error bars represent within-subject SE [29]).

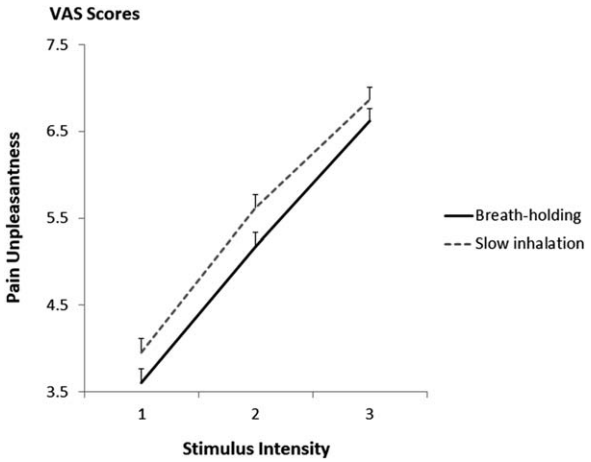

Figure 2 Averaged pain unpleasantness (VAS scores) as a function of pain pressure intensity and respiratory condition in which the pain stimulus was delivered (error bars represent within-subject SE [29]).

main or interaction effect was observed for pain pressure intensity. During breath-holding, a strong-fast HR deceleration was observed up to 4 seconds, while for the slow inhalation, the deceleration response appeared later, at approximately 4 seconds (Figure 3). Differences between the two breathing conditions were significant from 2 to 7 seconds (all $ts > -2.07$, all $Ps < 0.047$), with lower values for the breath-holding condition.

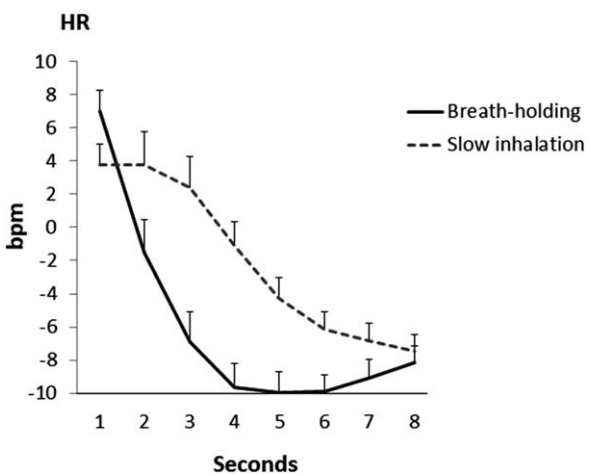

Figure 3 Heart rate response to the breathing manipulation aggregated for the three pain pressure intensities (error bars represent within-subject SE [29]).

The SBP pattern exhibited a biphasic response with an initial increase followed by a decrease (main effect of pattern $F(7, 31) = 18.45$, $P < 0.001$, $\eta^2 = 0.333$); this effect was dependent on the breathing condition (pattern $\times$ breathing condition interaction; $F(7, 31) = 20.57$, $P < 0.001$, $\eta^2 = 0.357$). Furthermore, the pattern $\times$ breathing condition $\times$ pain pressure interaction was also significant ($F(14, 24) = 3.72$, $P = 0.011$, $\eta^2 = 0.079$). A SBP increase was observed during the breath-holding condition, during the first few seconds (up to 4 seconds), followed by a SBP decrease during the remainder of the response. Similar changes were observed in the slow inhalation condition, albeit delayed and reduced in magnitude (Figure 4). For pain intensity 1, SBP was greater during breath-holding compared with slow inhalation, from 1 to 3 seconds, but was lower from 7 to 8 seconds (all $ts > -3.06$, all $Ps < 0.005$). For pain intensities 2 and 3, SBP was greater in the breath-holding condition compared with the slow inhalation condition, from 2 to 4 seconds, but was lower at 8th second (all $ts > -2.90$, all $Ps < 0.007$).

Discussion

Confirming our hypothesis, during breath-holding pain perception was lower relative to the slow inhalation condition; this effect was independent of pain pressure stimulation. As expected, breath-holding produced an increase in BP (mediated by the positive intrachest pressure) and a fast and deep HR deceleration (mediated by the activation of the baroreceptor reflex and its efferent vagal response). During the low inhalation, SBP also increased, and HR decreased, but changes were delayed by 2–3 seconds and were reduced in magnitude. Activation of the baroreceptors due to the increase in BP, via its connections through the CNS (nucleus of the tractus solitarius, reticular formation, thalamus, hypothalamus, amygdala, hippocampus, periaqueductal gray, insula, prefrontal, and cingulate cortex, etc., [3,10,30]) could produce an inhibitory effect on the CNS, with the possible related reduction in pain perception [3–9]. Low pressure baroreceptors located in the lungs, which discharged in a lineal function to tidal-volume amplitude [9,21,23], could also contribute to the obtained antinociceptive effect. However, alternative explanations for our results cannot be ruled out, such as attention-distracting factors associated with differences in cognitive demand during the performance of the two breathing conditions. To minimize the influence of attentional effects, we commenced with pain stimulation only when participants had practiced both breathing conditions and felt confident about their ability to perform them easily. The placebo effect, and participants' general expectations pertaining to the effects of the two breathing conditions, might also have affected the results. However, it is improbable that, in the majority of participants, these unspecific effects would have been systematically biased toward the efficacy of the same breathing condition.

A method frequently used to assess the antinociceptive effect of baroreceptor stimulation consists of mechanical stimulation of carotid baroreceptors using neck–cuff

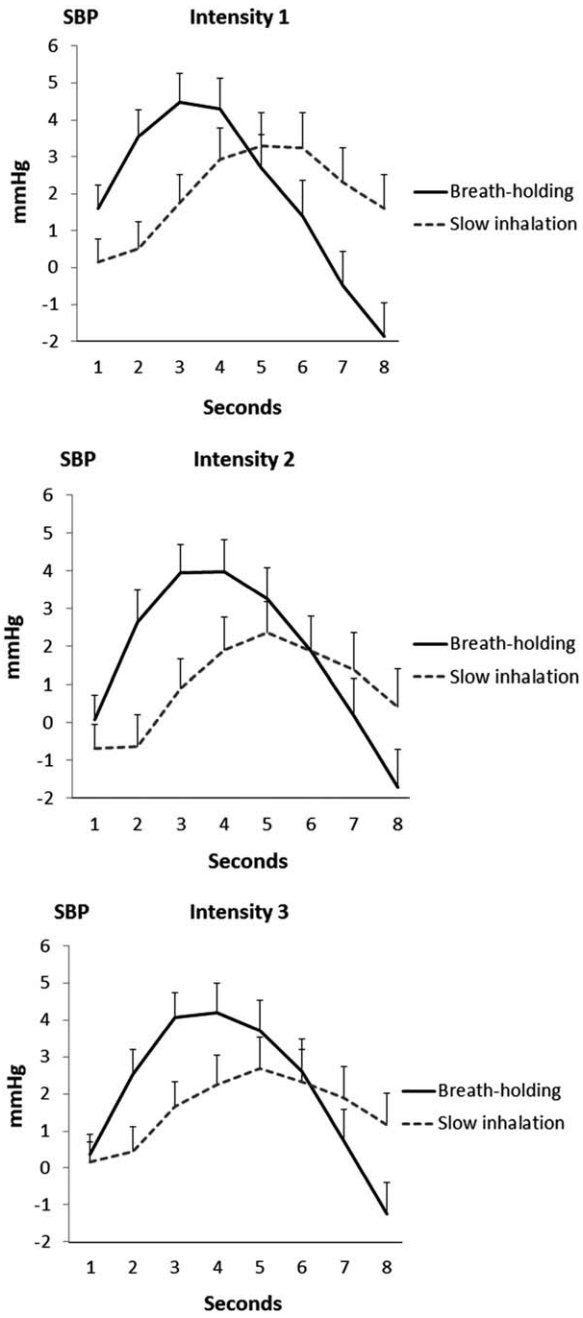

Figure 4 Systolic blood pressure response to the breathing manipulation as a function of pain pressure intensity (error bars represent within-subject SE [29]).

techniques [31]. These techniques induce neck suction (negative pressure) that stretches the baroreceptors and simulates an increase in BP. Although the resulting antinociceptive effect may depend on various factors, mechanical stimulation of the carotid baroreceptors leads to a reliable antinociceptive effect [3,6,10,32–35]. In comparison to classical mechanical stimulation of the carotid baroreceptors through neck-chamber techniques, the respiratory manipulation performed herein appeared to produce stronger baroreceptor stimulation and a more reliable effect on pain perception. Taking the elicited HR deceleration as an index of the magnitude of baroreceptor stimulation, the usual response in studies using neck-chamber techniques is a HR deceleration of approximately 3–4 beats per minute (an increase in heart period of 30–35 ms) [3,5,6,10,31,34]. In our study, we observed a HR deceleration of 10 beats per minute (100 ms of increase in heart period). An analysis of studies using mechanical stimulation of the carotid baroreceptors does not consistently reveal an antinociceptive effect, but rather suggests that this effect depends on a number of factors such as the mode in which the baroreceptors were stimulated, the elicitation (or not) of a concurrent baroreceptor-mediated cardiovascular response, the subjects' level of tonic BP, and so forth [10]. Furthermore, neck chambers are uncomfortable, cannot be adapted to all neck sizes, and require maintenance of a particular body posture to facilitate baroreceptor stimulation and avoid air leaks, and so forth. All these of factors can lower the reliability of its antinociceptive effects. In contrast, the respiratory maneuver used in this study appears more ecological and secure, is straightforward to implement, and does not require the use of a specific device; rather, it only requires the collaboration of the participant and a moderate cognitive and physical condition.

This same baroreceptor-mediated antinociceptive mechanism could be in part implicated in the analgesic effect of slow deep breathing and HR variability biofeedback interventions [36–38]. Furthermore, analgesic effects have been associated with increases in vagal cardiac activity [37,39]. The baroreceptor reflex is the main source of vagal efferent inputs to the CNS and vagal cardiac influences [1,2] and can be exercised and strengthened using slow and deep respiratory patterns [40–43].

Our respiratory manipulation, as it pertains to breath-holding, may share similarities with the Valsalva maneuver, a technique used to evaluate autonomic cardiovascular control integrity [44]. In the Valsalva maneuver, an expiratory pressure of 40 mm Hg must be maintained for 10 seconds through an active strain-pressure muscular force; it is usually required that the subject be connected to a mouthpiece [44]. In contrast, our breath-holding technique is simpler and markedly less intense in pressure, with participants explicitly instructed to not produce an active muscular strain-pressure force with the chest or abdomen.

In terms of limitations, our sample comprised young healthy participants only. Future studies should assess the effect of this breathing manipulation in older participants and patients with chronic pain. This is particularly relevant because baroreflex function tends to decline with age [45] and furthermore patients with chronic pain exhibit impaired baroreceptor functioning [46,47]. Future research should also aim to replicate this result using other pain modalities (e.g., thermal and electrical).

Regarding acute–chronic pain, given the particular characteristics of this respiratory maneuver, possible analgesics effects are limited to acute pain. Furthermore, the study provides limited evidence for a direct link between baroreceptor activation and pain. Future studies should focus on the associations between baroreceptor-related parameters and pain perception. Finally, it should be taken into account that the magnitude of the observed results is low, and the extent to which they are clinically relevant requires validation.

In conclusion, pain perception is reduced when painful stimulation is applied during breath-holding immediately following a deep inhalation. This simple and easy-to-perform respiratory maneuver may be useful as a simple method to reduce pain in cases where an acute, short-duration pain is present or expected (e.g., medical interventions involving needling, bone manipulations, examination of injures, etc.).

References

1 Eckberg DL, Sleight P. Human Baroreflexes in Health and Disease. Oxford: Oxford University Press; 1992.

2 Reyes del Paso GA, Langewitz W, Robles H, et al. A between-subjects comparison of respiratory sinus arrhythmia and baroreceptor cardiac reflex sensitivity as non-invasive measures of tonic parasympathetic cardiac control. Intern J Psychophysiol 1996;22:163–71.

3 Rau H, Elbert T. Psychophysiology of arterial baroreceptors and the etiology of hypertension. Biol Psychol 2001;57:179–201.

4 Droste C, Kardos A, Brody S, et al. Baroreceptor stimulation: Pain perception and sensory thresholds. Biol Psychol 1994;37:101–13.

5 Dworkin BR, Elbert T, Rau H, et al. Central effects of baroreceptor activation in humans: Attenuation of skeletal reflexes and pain perception. Proc Natl Acad Sci USA 1994;91:6329–33.

6 Rau H, Brody S, Larbig W, et al. Effects of PRES baroreceptor stimulation on thermal and mechanical pain threshold in borderline hype and normotensives. Psychophysiology 1994;31:480–5.

7 Bruehl S, Chung O. Interactions between the cardiovascular and pain regulatory systems: An updated review of mechanisms and possible alterations in chronic pain. Neurosci Biobehav Rev 2004;28:395–414.

8 Bossut DF, Maixner W. Effects of cardiac vagal afferent electro stimulation on the responses of trigeminal and trigeminothalamic neurons to noxious orofacial stimulation. Pain 1996;65:101–9.

9 D'Antono B, Ditto B, Sita A, et al. Cardiopulmonary baroreflex stimulation and blood pressure related hypoalgesia. Biol Psychol 2000;53:217–31.

10 Reyes del Paso G, Montoro C, Muñóz C, et al. The effect of baroreceptor stimulation on pain perception depends on the elicitation of the reflex cardiovascular response: Evidence of the interplay between the two branches of the baroreceptor system. Biol Psychol 2014;101:82–90.

11 France C. Decreased pain perception and risk for hypertension: Considering a common physiological mechanism. Psychophysiology 1999;36:683–92.

12 Duschek S, Schwarzkopf W, Schandry R. Increased pain sensitivity in low blood pressure. J Psychophysiol 2008;22:20–7.

13 Duschek S, Dietel A, Schandry R, et al. Increased sensitivity to heat pain in chronic low blood pressure. Eur J Pain 2009;13:28–34.

14 Ghione S. Hypertension-associated hypalgesia: Evidence in experimental animals and humans, pathophysiological mechanisms, and potential clinical consequences. Hypertension 1996;28:494–504.

15 Reyes del Paso GA, Perales MC. Haemodialysis curse is associated to changes in pain threshold and in the relations between arterial pressure and pain. Nefrología 2011;31:738–42.

16 Duschek S, Heiss H, Buechner B, et al. Reduction in pain sensitivity due to pharmacological elevation of blood pressure in chronically low blood pressure. J Psychophysiol 2009;23:104–12.

17 Wallis TW, Robothan JL, Compean R, et al. Mechanical heart-lung interaction with positive end-expiratory pressure. J Appl Physiol 1983;54:1039–47.

18 Parati G, Izzo JL, Gavish B. Respiration and blood pressure. In: Izzo JL, Black HR, eds., Hypertension Primer, Chap. A40. Baltimore: Lippincott, Williams, and Wilkins; 2003:117–20.

19 Guyton AC. Textbook of Medical Physiology, sixth edition. Philadelphia: Saunders; 1981.

20 Eckberg DL, Kifle YT, Roberts VL. Phase relationship between human respiration and baroreflex responsiveness. J Physiol 1980;304:489–502.

21 Davis AL, McCloskey DI, Potter EK. Respiratory modulation of baroreceptor and chemoreceptor reflexes affecting heart rate through the sympathetic nervous system. J Physiol 1977;272:691–703.

22 Davidson NS, Golner S, McCloskey DI. Respiratory modulation of baroreceptor and chemoreceptor reflexes affecting heart rate and cardiac vagal efferent nerve activity. J Physiol 1976;259:523–30.

23 Raczkowska M, Eckberg DL, Ebert TJ. Muscarinic cholinergic receptor modulates vagal cardiac responses in man. J Auton Nerv Syst 1983;7:271–8.

24 Grossman P. Respiration, stress and cardiovascular function. Psychophysiology 1983;20:284–300.

25 Stern RM, Anschel C. Deep inspirations as stimuli for responses of the autonomic nervous system. Psychophysiol 1968;5:132–41.

26 Cathcart S, Pritchard D. Reliability of pain threshold measurement in young adults. J Headache Pain 2006;7:21–6.

27 Staud R, Cannon RC, Mauderli AP, et al. Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. Pain, 2003;102:87–95.

28 Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med 2001;8:1153–7.

29 Franz VH, Loftus GR. Standard errors and confidence intervals in within-subjects designs: generalizing loftus and masson (1994) and avoiding the biases of alternative accounts. Psychon Bull Rev 2012;19:395–404.

30 Delgado LC, Vila J, Reyes del Paso GA. Proneness to worry is negatively associated with blood pressure and baroreflex sensitivity: further evidence of the blood pressure emotional dampening hypothesis. Biol Psychol 2014;96:20–7.

31 Cooper VL, Hainsworth R. Carotid baroreflex testing using the neck collar device. Clin Auton Res 2009;19: 102–12.

32 Edwards L, McIntyre D, Carroll D, et al. Effects of artificial and natural baroreceptor stimulation on nociceptive responding and pain. Psychophysiology 2003;40:762–9.

33 Angrilli A, Mini A, Mucha RF, et al. The influence on low blood pressure and baroreceptor activity on pain responses. Physiol Behav 1997;62:391–7.

34 Elbert T, Rockstroh B, Lutzenberger W, et al. Baroreceptor stimulation alters pain sensation depending on tonic blood pressure. Psychophysiology 1998;25: 25–9.

35 Brody S, Angrilli A, Weiss U, et al. Somatosensory evoked potentials during baroreceptor stimulation in chronic low back pain patients and normal controls. Int J Psychophysiol 1997;25:201–10.

36 Busch V, Magerl W, Kern U, et al. The effect of deep and slow breathing on pain perception, autonomic activity, and mood processing, an experimental study. Pain Med 2012;13:215–28.

37 Chalaye P, Goffaux P, Lafrenaye S, et al. Respiratory effects on experimental heat pain and cardiac activity. Pain Med 2009;10:1334–40.

38 Hassett AL, Radvanski DC, Vaschillo EG, et al. A pilot study of the efficacy of heart rate variability (HRV) biofeedback in patients with fibromyalgia. Appl Psychophysiol Biofeedback 2007;32:1–10.

39 Zunhammer M, Eichhammer P, Busch V. Do cardiorespiratory variables predict the antinociceptive effect of deep and slow breathing? Pain Med 2013; 14:843–54.

40 Lehrer PM, Vaschillo E, Vaschillo B, et al. Heart rate variability biofeedback increases baroreflex gain and peak expiratory flow. Psychosom Med 2003;65:796–80.

41 Bernardi L, Porta C, Spicuzza L, et al. Slow breathing increases arterial baroreflex sensitivity in patients with chronic heart failure. Circulation 2002;105:143–5.

42 Joseph CN, Porta C, Casucci G, et al. Slow breathing improves arterial baroreflex sensitivity and decreases blood pressure in essential hypertension. Hypertens 2005;46:714–8.

43 Reyes del Paso GA, Cea JI, González-Pinto A, et al. Short-term effects of a brief respiratory training on baroreceptor cardiac reflex function in normotensive and mild hypertensive subjects. Appl Psychophysiol Biofeedback 2006;31:37–49.

44 Levin AB. A simple test of cardiac function based upon the heart rate changes induced by the valsalva maneuver. J Am Coll Cardiol 1966;18:90–9.

45 Monahan KD. Effect of aging on baroreflex function in humans. Am J Physiol Regul Integr Comp Physiol 2007;293:R3–R12.

46 Reyes del Paso GA, Garrido S, Pulgar A, et al. Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia syndrome. J Psychosom Res 2011;70:125–34.

47 Reyes del Paso GA, Garrido S, Pulgar A, et al. Aberrances in autonomic cardiovascular regulation in fibromyalgia syndrome and their relevance for clinical pain reports. Psychosom Med 2010;72:462–70.

6.2 CONCIENCIA INTEROCEPTIVA. PERCEPCIÓN Y PROCESAMIENTO DE LAS SEÑALES QUE SURGEN DENTRO DEL CUERPO.

Es bien sabido que la autorregulación es un rasgo humano altamente adaptativo, que permite a las personas inhibir y modificar sus respuestas (Vohs y cols., 2008). Los cambios autonómicos periféricos, y de forma más general, la retroalimentación fisiológica de todo el cuerpo y su percepción (interocepción) se han postulado como factores que desempeñan un papel importante en la experiencia emocional (Katkin, 1984). Algunos estudios apuntan a que la experiencia emocional puede verse afectada ya no por la ocurrencia de cambios periféricos en sí, sino por la propia percepción de los mismos. Estos estudios se basan en la teoría propuesta por William James y Carl Lange (1885), acerca del origen, la naturaleza y la transmisión de las emociones, teoría coloquialmente conocida como la Teoria de las emociones de James-Lange (Cannon, 1987; James, 1884). El modelo en el que se basa esta teoría sostiene que un estímulo emocional inicia automáticamente reacciones viscerales, vasculares o somáticas (cambios en presión arterial, frecuencia cardíaca, tensión muscular, lagrimeo, aceleración respiratoria, etc.), y es la percepción de estas reacciones corporales la que constituye esencialmente el componente emocional de la experiencia. En otras palabras, la teoría establece que como respuesta a las experiencias y estímulos, el Sistema Nervioso Autónomo origina respuestas fisiológicas a partir de las cuales se crean las emociones. El perfeccionamiento posterior de este modelo incluye la noción de marcadores somáticos, que representan cambios involuntarios en el estado interno del cuerpo y señalan la importancia del estímulo para guiar la conducta emocional y cognitiva (por ejemplo, la toma de decisiones) (Damasio, 1999; Damasio, 2004; Damasio y cols., 2000).

Experimentalmente y de forma tradicional, la sensibilidad a los procesos interoceptivos ha sido medida mediante la capacidad de las personas para detectar los latidos de su corazón. De esta forma los participantes son instruidos en la detección de sus latidos concentrándose únicamente en su cuerpo, sin realizar una toma del pulso. Por lo general, los participantes cuentan los latidos de su corazón en silencio y reposo durante un intervalo de tiempo definido (Pollatos y Schandry, 2004; Schandry, 1981) o juzgan la relación temporal y/o simultaneidad entre sus latidos y una serie de tonos

presentados en diferentes intervalos relativos a éstos (Método de los Estímulos Constantes) (Wiens y Palmer, 2001). La percepción del latido del corazón se calcula a partir de la diferencia entre el número de latidos contados y el número de latidos reales evaluados por medio de un electrocardiograma o análogo. A través de esta metodología se ha demostrado que la percepción de los latidos del corazón se asocia con una experiencia emocional más intensa, así como mayores respuestas fisiológicas asociadas al procesamiento emocional (frecuencia cardíaca, potenciales evocados, etc.) (Herbert, Pollatos y Schandry, 2007; Pollatos, Gramann y Schandry, 2007; Pollatos, Herber, Matthias y Schandry, 2007; Pollatos, Kirsch y Schandry, 2005; Schandry, 1981; Wiens, 2005). Además de los cambios observados a nivel fisiológico, existen estudios de neuroimagen funcional que sugieren una estrecha relación entre la detección de los latidos del corazón, el afecto negativo (ansiedad y neuroticismo) y la activación de la ínsula anterior y la corteza cingulada anterior (Pollatos, Auer, Schandry y Kaufmann, 2004). Asunción acorde con datos recientes que muestran que la sensibilidad interoceptiva se asocia con una mejor regulación de la emoción en respuesta al afecto negativo (Füstös, Gramann, Herbert y Pollatos, 2013). No obstante, a parte de su asociación con la experiencia emocional, la conciencia interoceptiva se ha asociado positivamente con la autorregulación de la conducta en situaciones cognitivo-afectivas que van acompañadas de cambios somáticos y/o fisiológicos, como por ejemplo paradigmas que evaluan la carga de trabajo físico o la toma de decisiones (Dunn y cols., 2010; Herbert, Ulbrich y Schandry, 2007; Werner, Duschek y Schandry, 2010).

Así mismo, en la actualidad, se está observando un mayor interés por la evaluación de la conciencia interoceptiva en relación a enfermedades clínicas. Ello es debido a estudios que han sugerido que la menor conciencia interoceptiva podría contribuir a alteraciones en la percepción de los síntomas físicos, además de alteraciones en el procesamiento de las emociones. De esta forma se ha observado una interocepción disminuida en trastornos somatomorfos (Pollatos y cols., 2011; Weiss, Sack, Henningsen y Pollatos, 2014), la cual se ha relacionado a su vez con peor capacidad de autorregulación del dolor (Critchley, Wiens, Rotshtein, Öhman y Dolan, 2004; Weiss y cols., 2014). Pollatos, Fustos y Critchley (2012) muestran en uno de sus estudios que la sensibilidad interoceptiva se relaciona con la experiencia y la tolerabilidad del dolor, sugiriendo que la sensibilidad interoceptiva podría facilitar la detección de los cambios corporales que acompañan a la experiencia dolorosa. Estudios

recientes demuestran que las medidas de percepción dolorosa se asocian con cambios en las reacciones corporales internas como por ejemplo, cambios en frecuencia cardíaca y conductancia de la piel (Breimhorst y cols., 2011; Loggia, Juneau y Bushnell, 2011; Reyes del Paso, Garrido, Pulgar y Duschek, 2011), destacando que los estados corporales y sus representaciones también determinan la experiencia del dolor. Por lo tanto, la sensibilidad interoceptiva y la activación de las representaciones interoceptivas asociadas interactúan con el procesamiento de estímulos dolorosos (Pollatos y cols., 2012).

Datos como los expuestos han estimulado de forma específica la investigación de la conciencia interoceptiva en el contexto de la fibromialgia, dada la superposición entre los trastornos somatomorfos y la fibromialgia en cuanto a la inexistencia de una enfermedad orgánica que explique los síntomas físicos y la aparición de dolor recurrente. Además de ello, es conocida la alta prevalencia de desórdenes emocionales en la fibromialgia, lo que acentúa aún más el estudio de la conciencia interoceptiva en esta enfermedad. Estos estudios, entre los que se incluye uno de los estudios adiccionales a esta Tesis Doctoral *(Anexo, estudio 3)*, podrían ser de especial importancia de cara al desarrollo de pautas específicas de autoregulación física y emocional durante las intervenciones terapeúticas. La mayor sensibilidad interoceptiva ha sido asociada con una mayor capacidad de autoregulación (Weiss y cols., 2014). En este sentido se ha demostrado que la autoregulación física en personas con trastornos de dolor crónico disminuye tanto los síntomas físicos como los psicológicos (Sauer, Burris y Carlson, 2010). Para concluir, hay que tener en cuenta que existen diferencias individuales sustanciales en la capacidad de aprender a detectar los latidos del corazón, donde los hombres parece que aprenden a discriminar los latidos con mayor facilidad que las mujeres (Katkin, 1984).

**Referencias bibliográficas incluidas en el apartado 6.*

ANEXO, ESTUDIO 3. DISMISHED INTEROCEPTIVE AWARENESS IN FIBROMYALGIA SYNDOMRE.

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Diminished Interoceptive Awareness in Fibromyalgia Syndrome

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Abstract

Sensitivity to signals arising within the body (interoceptive awareness) has been implicated in emotion processing; interindividual differences in interoceptive awareness modulate both subjective and physiological indicators of emotional experience and the regulation of emotion-related behaviors. This study investigated interoceptive awareness in patients with fibromyalgia syndrome (FMS), a chronic pain condition accompanied by various affective symptoms. Interoceptive awareness was assessed in 45 FMS patients and 31 healthy individuals using a heartbeat perception task. Cognitive performance, co-morbid psychiatric disorders and medication use were assessed as possible confounding variables. Concerning the primary outcome, patients exhibited markedly reduced heartbeat perception compared to healthy

individuals. Moreover, there was an inverse relationship between interoceptive awareness and FMS symptom severity. Reduced interoceptive awareness may be involved in the affective aspects of FMS pathology. Poor access to bodily signals may restrict patients´ ability to integrate these signals during emotional processing, which, by extension, may preclude optimal emotional self-regulation.

Keywords

Fibromyalgia, chronic pain, interoceptive awareness, heartbeat perception, emotion

Introduction

The perception and processing of signals arising within the body has been ascribed crucial relevance in classical and modern theories of emotion. While the James-Lange theory proposed that affective experience is equivalent to perceived bodily changes during an arousing situation,[1] cognitive theories of emotion view physiological arousal, and the cognitive interpretation thereof, as sine qua non of emotion.[2] In his somatic marker hypothesis, Antonio Damasio emphasized the obligatory body-relatedness of feelings, postulating that somatic information guides both emotional processes and behavior regulation.[3] In recent years, strong evidence has accumulated concerning the behavioral relevance of interindividual differences in the sensitivity to bodily cues, i.e., interoceptive awareness.[4] Interoceptive awareness is commonly operationalized as the ability to perceive one's own heartbeat, which may be relatively easily quantified using mental tracking procedures.[5] In this paradigm, participants are asked to count their heartbeats in defined time intervals, with heartbeat perception indicated by the difference between the number of counted heartbeats and the number of actual heartbeats assessed via electrocardiography (ECG). In a number of cross-sectional studies, groups of healthy subjects with accurate and poor cardiac awareness, defined according to heartbeat perception performance, were compared on parameters of emotion and emotion-related behaviors. Subjects with accurate cardiac interoceptive awareness exhibited greater subjective and physiological responses to affective stimuli, for example in terms of more pronounced heart rate modulations and heightened evoked potentials in electroencephalography (EEG).[5-7] In addition, they demonstrated enhanced memory for emotional words,[8] were more affected by emotional stimulation with respect to cognitive processing, and showed improved coping during aversive

social situations.[9,10] Outside of the field of emotion, high interoceptive individuals performed better on neuropsychological tasks quantifying basic and higher cognitive functions.[11,12] Additional correlates of accurate interoceptive awareness include a more positive body image, assessed via questionnaires, and reduced proneness to experimentally induced distortions in body scheme.[4,13] In further studies, using questionnaire and experimental methods, high interoceptive individuals demonstrated greater expression of empathy,[14] improved behavioral self-control with respect to physical load,[15] and superior regulation of hunger and satiation compared to low interoceptive individuals.[16]

Interoception has also attracted interest within the field of clinical disorders. Low interoceptive awareness is associated with somatosensory amplification, i.e., the tendency to experience normal bodily sensations as disturbing, threatening and noxious, which constitutes an important feature of hypochondriasis.[17,18] In clinical studies, various patient groups have been compared with healthy subjects in terms of heartbeat perception performance. These studies suggested lower levels of cardiac interoceptive awareness in individuals with depression,[19] eating disorders[20] and somatoform disorders.[21,22] In terms of its role in pathogenetic mechanisms, reduced interoceptive awareness is likely to contribute to alterations in physical symptom perception and emotion processing, which constitute relevant characteristics of the aforementioned diseases.[4,22]

The present study is concerned with interoceptive awareness in fibromyalgia syndrome (FMS). FMS is a chronic condition characterized by widespread pain of unknown origin accompanied by symptoms such as morning stiffness, fatigue, sleep disturbance and impaired mental functioning.[23] The prevalence of FMS is estimated at 2–4% in the general population, and

women are more likely to be affected.[24] FMS symptoms markedly reduce quality of life and psychosocial functioning, and can lead to extensive use of health care systems.[25,26] In particular, the observation of diminished interoception in somatoform disorders[21,22] stimulated investigation of this issue in the context of FMS. These syndromes exhibit considerable overlap; both are characterized by physical symptoms that cannot be sufficiently explained by concurrent organic disease, and a high proportion of patients with somatoform disorders suffer from recurrent pain.[23,27,28] It therefore seems plausible to hypothesize that poor interoceptive awareness may also be prevalent in patients with FMS.

According to current knowledge, central nervous sensitization and exaggerated activity of the neural pain matrix (i.e., the cerebral structures involved in nociception) play a key role in FMS pathology.[29] However, it is likely that abnormalities in somatosensory information processing in FMS are not restricted to the pain modality.[30] This notion is supported, for example, by EEG studies demonstrating multiple aberrances in the central nervous processing of non-painful tactile stimuli,[31,32] which is indicative of a more general deficit in bodily perception. Poor sensitivity to somatic signals may be relevant to the affective dysregulation implicated in FMS pathology.[30] In addition to significant co-morbidity between FMS and affective and anxiety disorders,[33] neuroimaging studies point toward more-pronounced hyperactivity in brain areas mediating affective pain processing than in structures related to the sensory pain component.[34,35] In addition, the pain-potentiating effects of negative mood have been hypothesized to be greater in FMS patients compared to healthy individuals and patients with other chronic pain disorders.[36] Other studies on emotional alterations in FMS suggest deficits in emotion recognition,[30] as well as enhanced catastrophizing and alexithymia (i.e., difficulties identifying and describing one´s

own feelings).[37,38] Taking into account the well-known relevance of bodily perception to emotion processing[1-4] and considering the above-described findings concerning the impact of interindividual differences in interoceptive awareness on emotion and emotion-related behaviors,[6-10] it may be hypothesized that poor interoceptive awareness also contributes to the emotional abnormalities that characterize FMS.

The principal aim of the present study was to compare cardiac interoceptive awareness between patients with FMS and healthy individuals. In addition to lower levels of interoceptive awareness in patients, an inverse linear association between interoceptive awareness and FMS symptom severity was hypothesized. Indices of cognitive performance were obtained for use as control variables. There is ample evidence of cognitive decline in FMS, particularly from the fields of attention and executive function (i.e., higher cognitive processing including planning and problem solving).[39-42] As mentioned above, in previous studies individuals with low levels of cardiac interoceptive awareness performed more poorly on task quantifying attention and executive function.[11,12] Therefore, it appeared worthwhile to examine whether the reduction in interoceptive awareness expected in FMS is associated with cognitive deficits related to this condition. Finally, the impact of comorbid affective and anxiety disorders, and the use of psychoactive medication, on interoceptive awareness was analyzed. Taking into account possible effects of emotional disorders and psychoactive drugs on mental function, cognitive performance was also controlled for in this analysis.

Methods

Participants

Forty-five female FMS patients participated in the study. They were recruited via the Fibromyalgia Association of Jaén (Spain). The patients were examined by a rheumatologist and met the American College of Rheumatology criteria for FMS.[43] Exclusion criteria comprised inflammatory causes of pain, neurological disorders, metabolic abnormalities and severe somatic (e.g. cancer) or psychiatric (e.g. psychosis) diseases. The patients' mean score on the Fibromyalgia Impact Questionnaire[44] was 64.05 (SD=18.50). The control group included 31 healthy women recruited from local women´s associations. The control participants met the same exclusion criteria as the patients but were also required to be free of pain disorders. Table 1 lists the demographic data of the sample, as well as information concerning psychiatric diagnoses and medication use. The patient and control groups did not differ significantly in terms of age, Body Mass Index (BMI) or educational level, i.e., years of education (c.f. Table 1.). The study protocol was approved by the Bioethics Committee of the University of Jaén and all subjects provided written informed consent prior to participation.

Clinical Diagnostics

The Structured Clinical Interview for Axis I Disorders of the Diagnostic and Statistical Manual for Mental Disorders (SCID)[45] was applied to assess psychiatric disorders.

The severity of FMS symptoms and functional status were estimated using the Spanish version of the Fibromyalgia Impact Questionnaire (FIQ)[44]. The FIQ is a self-report instrument assessing clinical symptoms (pain, stiffness, morning tiredness, fatigue, depression, anxiety), physical functioning (e.g. locomotion, housework, social function), emotional well-being and ability to work over the past week. It contains 10 items with 10 sub-items for physical functioning. Higher

FIQ scores denote higher symptom severity, greater functional restrictions and lower quality of life.

Assessment of Interoceptive Awareness and Cognitive Testing

The mental tracking task introduced by Schandry[5] was utilized to quantify cardiac interoceptive awareness. The task commenced with a 5-min rest period in which participants were asked to sit quietly and relax as they saw fit. Subsequently, they were instructed to silently count all of the heartbeats that they perceived in their body. The beginning and end of the counting phase were signaled by the investigator. Participants were asked to concentrate only on their heartbeat and were not permitted to take their pulse, or attempt any other physical manipulations that could facilitate heartbeat detection. They were not informed regarding either the length of the counting phase or their performance. The task was performed three times, with counting phases of 25 s, 35 s, and 45 s duration separated by rest periods of 30 s. A heartbeat perception score was calculated according to the following formula:

$$\text{Heartbeat perception score} = 1 - 1/3 \left(\sum |N_{\text{actual heartbeats}} - N_{\text{reported heartbeats}}| / N_{\text{actual heartbeats}}\right)$$

The number of actual heartbeats was indexed by the systolic peaks of cerebral blood blow velocity in the left middle cerebral artery recorded by transcranial Doppler sonography.[46] This method was chosen instead of the more-commonly used ECG recording[5] because the study was part of a larger project in which cerebral blood flow during cognitive and pain processing was investigated.[47,48] The systole does not occur simultaneously in the heart and brain; however, taking a pulse wave velocity of 6 m/s as a basis, the systolic maximum cerebral blood flow occurs with a delay of only approximately 70 ms after the R-wave of the ECG. Due to the 25–45

s duration of the counting phases, it is highly possible that the distortion precipitated by this delay could be discounted.

The heartbeat perception score ranges from 0 to 1, where high scores indicate a small difference between reported and actual heartbeats and thus greater interoceptive awareness. The reliability of the score has been repeatedly confirmed.[9,49]

Cued reaction time (RT) and mental arithmetic tasks were applied to assess attentional and executive function. In the cued RT task, subjects were instructed to respond to a cross on a computer screen (imperative stimulus) as quickly as possible via a key stroke. The imperative stimulus was announced by a visual warning cue 5 s prior to its onset. The task consisted of 15 trials (intertrial intervals 30 s). RT was indexed by the time elapsed between the onset of the imperative stimulus and the keystroke. During the arithmetic task, participants were required to add together single-digit numbers presented next to each other on the screen (15 trials; intertrial intervals 30 s) and to provide their responses as quickly as possible by typing the last digit of the resulting sum using the keyboard. Performance was quantified in terms of RT, i.e., the time between the onset of the numbers and the participant´s response. Both tasks were programmed using the ePrime software package (Psychology Software Tools, Inc., Sharpsburg, PA, USA).

Procedure

The study was conducted across two sessions, which took place on different days. During the first session a clinical psychologist obtained participants´ demographic data and clinical histories, conducted the SCID interview and presented the FIQ. During the second session participants were presented with a series of tasks, during the performance of which cerebral

blood flow recordings were obtained. The heartbeat perception test was completed first, followed by the cued RT and arithmetic tasks.

Participants were asked not to consume analgesic drugs or medication affecting the cardiovascular system in the 24 hours preceding the second session. The use of antidepressants and other medications was not interrupted. In addition, participants were requested not to smoke or drink either alcohol or beverages containing caffeine for 2 hours prior to testing.

Data Analysis

Analysis of variance (ANOVA) was applied for group comparisons. Separate models were computed for the heartbeat perception score, indices of cognitive performance (cued RT, RT in the arithmetic task) and demographic parameters (age, BMI, years of education). To control for possible effects of cognitive performance on interoception, RTs obtained in both tasks were applied as covariates in the model of heartbeat perception score. In the patient group, the Pearson correlation coefficient between heartbeat perception score and FIQ score was computed. During the computation of this correlation, both indices of cognitive performance were partialed out. The effects of psychiatric co-morbidity and medication use on heartbeat perception were analyzed using a stratified analysis in the FMS group, in which patients suffering and not suffering from depression or anxiety disorders, and using or not using antidepressants, analgesics or opiates, were compared. For this purpose, additional ANOVA models were computed. To control for effects of cognitive performance, RTs obtained in both tasks were also included as covariates in these models.

Results

Figure 1 depicts the heartbeat perception score representing cardiac interoceptive awareness in both study groups. The score was significantly lower in FMS patients vs. healthy participants ($F[1, 72]=4.79$, $p=.032$, $\eta^2=.062$). The covariates included in this ANOVA model did not reach significance (cued RT: $F[1, 72]=3.23$, $p=.077$, $\eta^2=.043$; RT in arithmetic task: $F[1, 72]=2.65$, $p=.11$, $\eta^2=.035$). In the patient group, a significant negative correlation between heartbeat perception and FIQ score arose ($r=-.40$, $p<.01$, with both indices of cognitive performance partialed out).

No effects of co-morbid depression or anxiety disorders on heartbeat perception were observed (all ps>.17). Patients taking opiates exhibited lower scores than those not taking this medication (opiate use: M=0.43, SD=0.21; no opiate use: M=0.59, SD=0.26; $F(1, 40)=4.12$, $p=.047$, $\eta^2=.095$). The covariates did not have a significant impact (cued RT: $F[1, 40]=1.71$, $p=.20$, $\eta^2=.041$; RT in arithmetic task: $F[1, 40]=1.39$, $p=.25$, $\eta^2=.034$). Further ANOVA models revealed that antidepressants and anxiolytics had no effect on heartbeat perception (all ps>.44).

RTs in both cognitive tasks were longer in patients than in healthy individuals (cued RT, patients: M=874.40 ms, SD=468.20 ms, healthy individuals: M=558.99 ms, SD=331.25, $F[1, 74]=10.45$, $p<.01$, $\eta^2=.12$; RT in arithmetic task, patients: M=4037.15 ms, SD=1861.20 ms, healthy individuals: M=2856.79 ms, SD=919.17 ms, $F[1, 74]=10.65$, $p<.01$, $\eta^2=.13$).

Discussion

In terms of the main result of the study, patients diagnosed with FMS exhibited markedly lower cardiac interoceptive awareness compared to a group of healthy individuals that did not differ in

age, BMI or education level. Moreover, in the patient group an inverse linear association between interoceptive awareness and symptom severity, indexed by FIQ score, was observed. Building on previous studies demonstrating diminished interoceptive awareness in depression, anorexia nervosa and somatoform disorders,[19-22] our results support the view that poor accuracy in the perception of bodily signals is a common feature of various mental and physical disorders. Performance on cued RT and mental arithmetic tasks was controlled for in the statistical analyses. Therefore, it is unlikely that the reduction in interoceptive awareness observed in the FMS patients was mediated by impaired cognitive function related to this condition (a comprehensive discussion of group differences in cognitive performance is provided elsewhere[47-48]).

It is well-known that emotional experience depends on the perception of bodily cues, where individual differences in interoceptive awareness are associated with the intensity of self-reported emotions and corresponding physiological markers.[5-7,50] Furthermore, brain imaging studies have identified neural structures, such as the insula and anterior cingulate, which link interoceptive awareness with emotion.[50,51] According to Damasio´s somatic marker hypothesis, neural representations of physiological conditions (somatic markers) evoke feeling states, which in turn contribute to behavioral adjustment.[3] It has been claimed that easier access to somatic markers (interoceptive awareness) facilitates emotion processing and supports behavior regulation.[8,10,52] In addition to facilitation of emotion-related behaviors,[8-10] accurate interoceptive awareness is associated, for example, with greater subjective bodily self-control, greater trust in physical function and reduced hypochondriacal concerns.[4]

Poor central nervous feedback pertaining to bodily states may be implicated in emotional dysregulation relevant to mental and bodily disorders.[4,30] A recent study revealed a widespread deficit in emotional self-regulation in patients with somatoform disorders and furthermore indicated an inverse association between interoceptive awareness and self-regulatory capacities, including the abilities to tolerate negative affect, cope with frustration and control impulses.[22] Impaired self-regulation of negative emotions and resultant sustained emotional distress may exacerbate somatic and psychic symptoms.[38] In FMS, impaired affect balance, i.e., increased negative, and blunted positive, affect, has been reported[53] and psychophysiological studies revealed exaggerated responses to unpleasant stimuli in central nervous and peripheral indicators of emotion.[54-56] By extension, proneness to negative emotions may exacerbate the vicious circle between aversive mood states and clinical symptoms including hyperalgesia.[57] Somatosensory amplification may be another factor mediating the association between interoceptive awareness with fibromyalgia. As stated in the Introduction, it has been demonstrated that somatosensory amplification correlates negatively with heartbeat perception performance,[18] whereas increased levels of somatosensory amplification have been reported in FMS patients.[58]

A potential role for poor interoceptive awareness in the pain symptoms of FMS should also be considered. Pain has been linked to interoception in the sense that both modalities provide central-nervous feedback concerning the physiological condition of the body, which is essential for the maintenance of homeostasis.[59-60] Moreover, the central-nervous pathways of interoception and nociception partially overlap.[61] However, empirical research on this relationship remains equivocal. While higher sensitivity to cutaneous pressure pain has been reported in healthy subjects with high vs. low interoceptive awareness,[62] no effect was observed for heat pain

sensitivity.[60] In somatoform disorders, poor interoceptive awareness was found to be associated with low pressure pain tolerance, but not with pain threshold.[22] These contrasting results cannot yet be integrated into a theoretical framework pertaining to the role of interoception in clinical pain. Nonetheless, for FMS it may be speculated that significant involvement of interoception in the alteration of pain processing is less likely compared to affective dysregulation.

One obvious limitation of the present study concerns the fact that interoceptive awareness was investigated without directly assessing its implications for the emotional pathology of FMS. In future research, self-report scales, for example concerning emotional self-regulation or affective styles, as well as experimental paradigms addressing emotion processing, could be applied for this purpose.[22,30,53,57] In addition, relationships between interoception and pain experience should also be explored. Another limitation concerns results from our use of a female-only sample, which restricts the generalizability of the results. The limitations of assessing interoceptive awareness via the heartbeat perception task should also be discussed. Regarding the correlation between the presently applied index with other measures of heartbeat detection, both positive and negative results have been reported.[49,63] Another important question concerns the degree to which cardiac interoceptive awareness can be taken as a proxy of interoception in general. Even though it has been shown that heartbeat perception performance correlates with awareness to gastric functions,[64,65] the generalizability of interindividual differences in interoceptive awareness to different visceral systems remains a subject of debate.[4]

By definition, the quasi-experimental design of the study limits causal interpretation of the results. In addition to the postulated contribution of poor interoceptive awareness to the affective peculiarities associated with FMS, distortion of somatosensory information due to FMS

symptoms - in particular persistent pain - is plausible. Pain represents an attention-demanding condition that may detract from the processing of other bodily signals. This perspective accords with Pennebaker´s competition of cues model, according to which sensory cues compete for attention and an individual can process only a limited amount of information at any given time.[66] This may also explain the greater reduction in interoceptive awareness in the patients who were using opiates. Assuming particularly high pain severity in patients taking opiates, pain may dominate somatosensory information processing, especially 24 hours after discontinuing use of the drug. However, these causal interpretations must remain speculative and prospective analyses are necessary to further clarify this issue.

Cross-cultural differences in the role played by interoception in clinical disorders may also be relevant in the present context. Culture-specific effects with respect to the perception and cognitive processing of signals arising from within the body have been repeatedly described.[68] While members of Western societies exhibited higher interoceptive accuracy in laboratory studies compared to people from non-Western societies, non-Western cultures tend to demonstrate heightened somatic focus and greater emphasis on their bodily states when describing emotional experiences.[68,69] These differences may have important clinical implications, and therefore open up a broad field of exciting future research.

With respect to the potential practical implications of the present findings, the possibility that interoceptive awareness could be purposely manipulated may be of interest. If poor interoception is involved in the somatosensory pathology of FMS, and contributes to the affective dysregulation associated with the condition, improving interoception may be a good target for therapy. However, the available data on deliberately increased interoceptive awareness remain

controversial. It has been shown that interventions such as relaxation and mindfulness training do not substantially alter heartbeat perception.[70,71] Cardiac interoceptive awareness could be improved using a biofeedback procedure, at least for a limited period;[72] however, inconsistent findings have also been reported in this area.[73] At present, very little is known about the possible beneficial effects of training in interoception on emotion processing and clinical symptoms.[4] Future research should aim to study the long-term effects of such interventions and to clarify whether they can facilitate cognitive behavioral approaches to fibromyalgia management.

Conclusions

This study demonstrated markedly reduced cardiac interoceptive awareness in women with FMS. Poor access to bodily signals may limit patients´ ability to integrate these signals during emotional processing, which, by extension, may impede optimal emotional self-regulation. Further research seems worthwhile to explore the precise role of poor interoception in the pathogenetic mechanisms of FMS, and to evaluate the utility of training in interoceptive awareness in the context of FMS treatment.

References

1. James W. What is an emotion? *Mind.* 1884;9:188-205.
2. Schachter S, Singer JE. Cognitive, social and physiological determinants of emotional state. *Psychol Rev*. 1962;69:379-399.
3. Damasio AR. *The feeling of what happens: body, emotion and the making of consciousness.* London: Vintage; 2000.
4. Duschek S, Werner N, Reyes del Paso GA, Schandry R. The contributions of interoceptive awareness to cognitive and affective facets of body experience. *J Individ Differ*. 2015; 36:110-118.
5. Schandry R. Heartbeat perception and emotional experience. *Psychophysiology*. 1981;18:483-488.
6. Pollatos O, Kirsch W, Schandry R. On the relationship between interoceptive awareness, emotional experience, and brain processes. *Cog Brain Res*. 2005;25:948-962.
7. Pollatos O, Herbert BM, Matthias E, Schandry R. Heart rate response after emotional picture presentation is modulated by interoceptive awareness. *Int J Psychophysiol.* 2007;63:117-124.
8. Werner NS, Peres I, Duschek S, Schandry R. Implicit memory for emotional words is modulated by cardiac perception. *Biol Psychol*. 2010;85:370-376.
9. Werner NS, Mannhart T, Reyes del Paso GA, Duschek S. Attention interference for emotional stimuli in interoceptive awareness. *Psychophysiology*. 2014;51:573-578.
10. Werner NS, Kerschreiter R, Kindermann NK, Duschek S. Interoceptive awareness as a moderator of affective responses to social exclusion. *J Psychophysiol*. 2013;27:39-50.

11. Matthias E, Schandry R, Duschek S, Pollatos O. On the relationship between interoceptive awareness and the attentional processing of visual stimuli. *Int J Psychophysiol.* 2009;72:154-159.
12. Werner NS, Jung K, Duschek S, Schandry R. Enhanced cardiac perception is associated with superior decision-making on the Iowa Gambling Task. *Psychophysiology*. 2009;46;1123-1129.
13. Tsakiris M, Tajadura-Jiménez A, Costantini M. Just a heartbeat away from one's body: interoceptive sensitivity predicts malleability of body-representations. Proc Biol Sci. 2011;278:2470-2476.
14. Grynberg D, Pollatos O. Perceiving one's body shapes empathy. *Physiol Behav*. 2014;140C:54-60.
15. Herbert BM, Ulbrich P, Schandry R. Interoceptive sensitivity and physical effort: implications for the self-control of physical load in everyday life. *Psychophysiology*. 2007;44:194-202.
16. Herbert BM, Blechert J, Hautzinger M, Matthias E, Herbert C. Intuitive eating is associated with interoceptive sensitivity. Effects on body mass index. *Appetite*. 2013;70:22-30.
17. Barsky AJ, Wyshak G, Klerman GL. The somatosensory amplification scale and its relationship to hypochondriasis. *J Psychiatr Res*. 1990;24:323-334.
18. Mailloux J, Brener J. Somatosensory amplification and its relationship to heartbeat detection ability. *Psychosom Med*. 2002;64:353-357.

19. Terhaar J, Viola FC, Bär, KJ, Debener S. Heartbeat evoked potentials mirror altered body perception in depressed patients. *Clin Neurophysiol*. 2012;23:1950-1957.

20. Pollatos O, Kurz AL, Albrecht J, Schreder T, Kleemann AM, Schöpf V, Kopietz R, Wiesmann M, Schandry R. Reduced perception of bodily signals in anorexia nervosa. *Eat Behav*. 2008;9:381-388.

21. Mussgay L, Klinkenberg N, Rüddel H. Heart beat perception in patients with depressive, somatoform, and personality disorders. *J Psychophysiol*. 1999;13:27-36.

22. Weiss S, Sack M, Henningsen P, Pollatos O. On the interaction of self-regulation, interoception and pain perception. *Psychopathology*. 2014;47:377-382.

23. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfieled JB, Yunus MB. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res*. 2010;62:600-610.

24. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum*. 1995;38:19-28.

25. Penrod JR, Bernatsky S, Adam V, Baron M, Dayan N, Dobkin PL. Health services costs and their determinants in women with fibromyalgia. *J Rheumatol*. 2004;31:1391-1398.

26. Arnold LM, Crofford LJ, Mease PJ, Burgess SM, Palmer SC, Abetz L, Martin SA. Patients perspectives on the impact of fibromyalgia. *Patient Educ Couns*. 2008;73:114-120.

27. Henningsen P, Loewe B. Depression, pain, and somatoform disorders. *Curr Opin Psychiatry*. 2006;19:19-24.

28. Leiknes KA, Finset A, Moum T, Sandanger I. Overlap, comorbidity, and stability of somatoform disorders and the use of current versus lifetime criteria. *Psychosomatics*. 2008;49;152-162.

29. Gracely RH, Ambrose KR. Neuroimaging of fibromyalgia. *Best Pract Res Clin Rheumatol*. 2011;25:271-284.

30. Weiss S, Winkelmann A, Duschek S. Recognition of facially expressed emotions in patients with fibromyalgia syndrome. *Behav Med*. 2013;39:146-154.

31. Montoya P, Sitges C, Garcia-Herrera M, Izquierdo R, Truyols M, Blay N, Collado D. Abnormal affective modulation of somatosensory brain processing among patients with fibromyalgia. *Psychosom Med*. 2005;67;957-963.

32. Montoya P, Sitges C, García-Herrera M, Rodríguez-Cotes A, Izquierdo R, Truyols M, Collado D. Reduced brain habituation to somatosensory stimulation in patients with fibromyalgia. *Arthritis Rheum*. 2006;54:1995-2003.

33. Epstein SA, Kay GG, Clauw DJ, Heaton R, Klein D, Krupp L, Kuck J, Leslie V, Masur D, Wagner M, Waid R, Zisook S. Psychiatric disorders in patients with fibromyalgia: a multicenter investigation. *Psychosomatics*. 1999;40:57-63.

34. Burgmer M, Pogatzki-Zahn E, Gaubitz M, Wessoleck E, Heuft G, & Pfleiderer B. Altered brain activity during pain processing in fibromyalgia. *Neuroimage*. 2009;44:502-508.

35. Duschek S, Mannhart T, Winkelmann A, Merzoug K, Werner NS, Schuepbach D, Montoya P. Cerebral blood flow dynamics during pain processing in patients with fibromyalgia syndrome. *Psychosom Med*. 2012;74:802-809.

36. Davis MC, Zautra AJ, Reich JW. Vulnerability to stress among women in chronic pain from fibromyalgia and osteoarthritis. *Ann Behav Med*. 2001;23:215-226.

37. Geisser ME, Casey KL, Brucksch CB, Ribbens CM, Appleton BB, Crofford LJ. Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia: association with mood, somatic focus, and catastrophizing. *Pain*. 2003;102:243-250.

38. Huber A, Suman AL, Biasi G, Carli G. Alexithymia in fibromyalgia syndrome: associations with ongoing pain, experimental pain sensitivity and illness behavior. *J Psychosom Res*. 2009;66:425-433.

39. Dick BD, Verrier MJ, Harker KT, Rashiq S. Disruption of cognitive function in fibromyalgia syndrome. *Pain*. 2008;139:610-616.

40. Pericot-Nierga I, Hernández-Ferrándiz M, Lozano-Gallego M, Vilalta-Franch J, Cruz-Reina Mdel M, López-Pousa S. Cognitive profile in fibromyalgia. Comparison with a mild cognitive impairment group. *Med Clin (Barc)*. 2009;133:91-99.

41. Reyes del Paso GA, Pulgar A, Duschek S, Garrido S. Cognitive impairment in fibromyalgia syndrome: The impact of pain, emotional disorders, medication, and cardiovascular regulation. *Eur J Pain*. 2012;16:421-429.

42. Duschek S, Werner NS, Winkelmann A, Wankner S. Implicit memory function in fibromyalgia syndrome. *Behav Med.* 2013;39:11-16.

43. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum*. 1990;33: 160-172.

44. Esteve-Vives J, Rivera Redondo J, Salvat Salvat MI, de Gracia Blanco M, Alegre de Miquel C. Proposal for a consensus version of the Fibromyalgia Impact Questionnaire (FIQ) for the Spanish population. *Reumatol Clin*. 2007;3:21-24.

45. First M, Spitzer R, Gibbon M, Williams J. *Entrevista Clínica Estructurada para los Trastornos del Eje I del DSM–IV (SCIDI).* Barcelona: Masson; 1999.

46. Duschek S, Schandry R. Functional transcranial Doppler sonography as a tool in psychophysiological research. *Psychophysiology.* 2003;40:436-454.

47. Montoro C, Duschek S, Reyes del Paso GA. Aberrant cerebral blood flow responses during cognition: implications for the understanding of cognitive deficits in fibromyalgia. *Neuropsychology*. 2015; 29:173-182.

48. Reyes del Paso GA, Montoro C, Duschek S. Associations between reaction time, cerebral blood flow and heart rate in fibromyalgia: evidence of alterations in attentional control. *J Clin Experiment Neuropsychol*. 2015;37:414-428.

49. Knoll JF, Hodapp V. A comparison between two methods of assessing heartbeat perception. *Psychophysiology.* 1992;29:218-222.

50. Pollatos O, Gramann K, Schandry R. Neural systems connecting interoceptive awareness and feelings. *Hum Brain Mapp.* 2007;28:9-18.

51. Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nat Neurosci*. 2004;7;189-195.

52. Werner NS, Duschek S, Mattern M, Schandry R. Interoceptive sensitivity modulates anxiety during public speaking. *J Psychophysiol*. 2009;23:85-94.

53. Hassett AL, Simonelli LE, Radvanski DC, Buyske S, Savage SV, Sigal LH. The relationship between affect balance style and clinical outcomes in fibromyalgia. *Arthritis Rheum*. 2008;59:833-840.

54. Bartley EJ, Rhudy JL, Williams AE. Experimental assessment of affective processing in fibromyalgia. *J Pain*. 2009;10:1151-1160.

55. González-Roldán AM, Muñoz MA, Cifre I, Sitges C, Montoya P. Altered psychophysiological responses to the view of others' pain and anger faces in fibromyalgia patients. *J Pain*. 2013;14:709-719.

56. Rhudy JL, Delventura JL, Terry EL, Bartley EJ, Olech E, Palit S, Kerr KL. Emotional modulation of pain and spinal nociception in fibromyalgia. *Pain*. 2013;154:1045-1056.

57. Duschek S, Werner N, Limbert N, Winkelmann A, Montoya P. Attentional bias toward negative information in patients with fibromyalgia syndrome. *Pain Med*. 2014;15:603-612.

58. Güleç H, Sayar K. Reliability and validity of the Turkish form of the Somatosensory Amplification Scale. *Psychiatry Clin Neurosci*. 2007;61:25-30.

59. Craig AD. How do you feel? Interoception: The sense of the physiological condition of the body. *Nat Rev Neurosci*. 2002;3:655-666.

60. Craig AD. A new view of pain as a homeostatic emotion. *Trends Neurosci*. 2003;26:303-307.

61. Werner NS, Duschek S, Mattern M., Schandry R. On the relation between pain perception and interoception. *J Psychophysiol*. 2009;23:35-42.

62. Pollatos O', Füstös J, Critchley HD. On the generalised embodiment of pain: how interoceptive sensitivity modulates cutaneous pain perception. *Pain*. 2012;153:1680-1686.

63. Schulz A, Lass-Hennemann J, Sütterlin S, Schächinger H, Vögele. Cold pressor stress induces opposite effects on cardioceptive accuracy dependent on assessment paradigm. *Biol Psychol*. 2013;93:167-174.

64. Whitehead WE, Drescher VM. Perception of gastric contractions and self-control of gastric motility. *Psychophysiology.* 1980;17:552-558.

65. Herbert BM, Muth ER, Pollatos O, Herbert C. Interoception across modalities: on the relationship between cardiac awareness and the sensitivity for gastric functions. *PLoS One.* 2012;7(5).

66. Pennebaker JW. *The psychology of physical symptoms.* New York, NY: Springer; 1982.

67. Ma-Kellams C. Cross-cultural differences in somatic awareness and interoceptive accuracy: a review of the literature and directions for future research. *Front Psychol*. 2014;5(1379).

68. Ma-Kellams C, Blascovich J, McCall C. Culture and the body: East-west differences in visceral perception. *J Pers Soc Psychol.* 2012;102:718-728.

69. Chentsova-Dutton YE, Dzokoto V. Listen to your heart: the cultural shaping of interoceptive awareness and accuracy. *Emotion.* 2014;14:666-678.

70. Fairclough SH, Goodwin L. The effect of psychological stress and relaxation on interoceptive accuracy: Implications for symptom perception. *J Psychosom Res*. 2007;62:289-295.

71. Parkin L, Morgan R, Rosselli A, Howard M, Sheppard A, Evans D, Dunn B. Exploring the relationship between mindfulness and cardiac perception. *Mindfulness.* 2014;5:298-313.

72. Schandry R, Weitkunat R. Enhancement of heartbeat-related brain potentials through cardiac awareness training. *Int J Neurosci.* 1990;53:243-53.

73. O'Brien WH, Reid GJ, Jones KR. Differences in heartbeat awareness among males with higher and lower levels of systolic blood pressure. *Int J Psychophysiol*. 1998;29:53-63.

Table 1. Patients' demographic and clinical characteristics (data are provided as means ± standard deviation (SD) or as the number of participants and percentages) and the results of the group comparison (F-, Chi^2- and p-values).

	FMS patients	**Control group**	**F or Chi^2**	**p**
Age in years (SD)	49.93 (8.81)	47.13 (9.38)	1.74	.19
BMI in kg/m^2 (SD)	26.98 (3.70)	25.41 (4.41)	2.64	.11
Years of education (SD)	11.38 (3.36)	12.73 (3.57)	2.58	.11
Depression (%)	12 (26.66)	3 (9.67)	2.62	.09
Anxiety disorders (%)[1]	21 (40.00)	3 (9.67)	8.38	<.01
Use of anxiolytics (%)[2]	25 (55.55)	11 (35.48)	3.32	.056
Use of antidepressants (%)	21 (46.66)	1 (3.22)	17.37	<.001
Use of analgesics (%)[3]	35 (77.77)	5 (16.13)	29.39	<.001
Use of opiates (%)	16 (35.55)	0 (0.00)	14.33	<.001

[1] Anxiety disorders comprised panic disorder, generalized anxiety disorder, phobias and adjustment disorder.

[2] Participants in the control group were taking anxiolytics, principally for sleeping difficulties.

[3] Participants in the control group were taking analgesics to relieve sporadic pain (e.g. headaches).

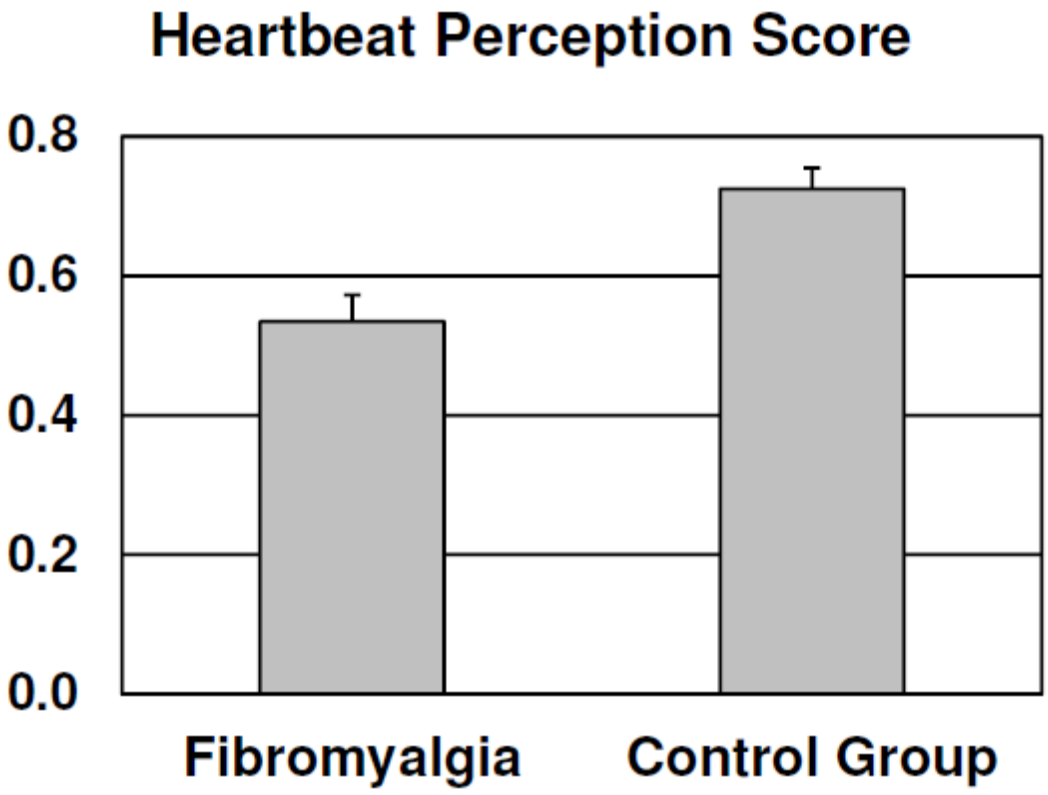

Figure 1. Heartbeat perception scores of both study groups (bars denote standard errors of the mean)