Modulación afectiva de la actividad cerebral para aliviar el dolor: estudio de la conectividad funcional mediante EEG

UNIVERSIDAD DE GRANADA

Autor: Guzmán Alba Lasso

Director: Miguel Ángel Muñoz García

Tutor: Jaime Vila Castellar

Departamento de Personalidad, Evaluación y Tratamiento Psicológico

Programa Oficial de Doctorado en Psicología (RD1393/2007)

Tesis Doctoral

Enero, 2021

Editor: Universidad de Granada. Tesis Doctorales
Autor: Guzmán Alba Lasso
ISBN: 978-84-1306-887-9
URI: http://hdl.handle.net/10481/69098

AGRADECIMIENTOS

Esta tesis va de estudiar la conectividad funcional fisiológica. En otras palabras, las conexiones dentro del organismo. El espíritu holístico de este trabajo quedaría incompleto si no reconociera en este pequeño espacio que me ofrece el apartado agradecimientos las conexiones con personas que han permitido el desarrollo de este trabajo, mi crecimiento como investigador y, por qué no decirlo, mi crecimiento como persona en estos años de doctorado.

En primer lugar, quiero empezar agradeciendo a mi director de tesis Miguel Ángel Muñoz. Miguel Ángel fue y será por siempre mi maestro Jedi porque esta conexión entre nosotros se ha convertido en una huella de memoria. Gracias Miguel por el aguante, los consejos, los debates y ser tanto mentor como compañero de fatigas.

Otra conexión importante en este camino ha sido el equipo de trabajo que me he encontrado aquí en Granada. Gracias a Jaime y Mari Carmen, pueden estar orgullosos de haber construido un equipo donde se crece en ciencia, se crece en arte y hay mucha humanidad. No podré olvidar las reuniones de grupo ni las cenas ni las rutas por la naturaleza. Gracias a los seniors por sus puntos de vista en las reuniones y por sus consejos y a l@s compañer@s y amig@s que hecho aquí. Gracias por el tiempo que pasamos juntos tanto en el laboratorio como fuera de él, gracias por las risas, por escucharme cuando lo necesité y por todos los buenos momentos.

Las estancias en Brasil con el equipo José García Vivas Miranda y en Boston con el de Plamen Ivanov también son piezas fundamentales. Gracias por acogerme y cuidar de mi en esos momentos. Otra persona ajena a la UGR que quiero agradecerle es a Julián González: el primero en formarme en conectividad funcional, quién me inicio en Matlab y cuyo trabajo con él me permitió tener el currículum para optar a mi FPI.

He reservado el párrafo final a mi familia. Gracias mamá, gracias bro, por estar siempre ahí apoyándome y ser el mayor pilar de mi vida. Quisiera dedicar de manera especial esta tesis a mi padre que falleció 3 meses antes de que iniciara este proyecto. ¡Papá este trabajo va por ti!

INDICE

LISTADO DE FIGURAS

Figuras Tesis

Figuras Artículo 1

Figuras Artículo 2

Figuras Artículo 3

LISTADO DE TABLAS

Tablas Artículo 1

Tablas Artículo 2

Tablas Artículo 3

RESUMEN

En España la prevalencia del dolor crónico es del 16.6% (Dueñas et al., 2015). Aproximadamente, el 50% de pacientes, refieren limitaciones en su vida diaria, el 30% sentimientos de tristeza y/o ansiedad, y el 47.2% que el dolor afecta a su vida familiar. Teniendo en cuenta esto, no es de extrañar que las patologías relacionadas con el dolor crónico supongan uno de los gastos económicos más elevados para los sistemas de salud en las sociedades desarrolladas. Dado el alto impacto que tiene el dolor en la salud, la Unidad de Tratamiento del Dolor emitió en 2011 un informe a través del Ministerio de Sanidad, Política Social e Igualdad de España en el que sostiene que el dolor es un problema multidimensional, cuyo abordaje debe ser multidisciplinar, con programas de intervención integrales en el que se traten sus distintas dimensiones.

Los estudios fisiológicos han sido clave en la compresión del dolor y en la elaboración de tratamientos eficaces. Los estímulos dolorosos provocan cambios en la sincronización entre regiones cerebrales y un incremento de la actividad simpática. Cuando la experiencia dolorosa se prolonga en el tiempo, se observa una actividad simpática anormal, una conectividad funcional cerebral alterada (entre zonas sensoriales, atencionales y afectivas) y una sensibilización central hacia estímulos nociceptivos. Todos estos cambios, se traducen en dificultades en el procesamiento de estímulos afectivos, así como en el desarrollo de patologías comórbidas tales como depresión y ansiedad. Más aún, los estudios que intentan comprender la influencia del dolor sobre el procesamiento afectivo, ponen de maniefiesto que los pacientes con dolor crónico, presentan un sesgo atencional hacia el dolor que dificulta procesar estímulos con carga afectiva. El *modelo de la atención motivada hacia el dolor* (Van Damme et al., 2010), propone que el dolor mantenido es un potente motivador que capta los recursos atencionales compitiendo con otros estímulos relevantes. Así, se observa que, en tareas puramente cognitivas, los pacientes con dolor crónico muestran una peor ejecución que voluntarios sanos. Sin embargo, ¿Cómo esta sobrecarga atencional puede afectar al procesamiento de estímulos afectivos? ¿Es posible modular el dolor mediante estímulos afectivos?

Actualmente, se han desarrollado tratamientos no farmacológicos cuyo objetivo es enseñar a pacientes a modular su actividad fisiológica para reducir su dolor. El uso del neurofeedback muestra potenciales beneficios no sólo para reducir el dolor, sino también para mejorar el estado de ánimo, los problemas de ansiedad y las dificultades en el sueño. Dentro de las distintas características de la señal de electroencefalografía (EEG) que se puede entrenar, la modulación de la densidad espectral del ritmo sensoriomotor (SMR) es de los más empleados en el tratamiento de síndromes de dolor crónico. Recientemente, se ha encontrado que el entrenamiento SMR produce cambios en la conectividad funcional cerebral que se relacionan con una reducción del dolor en las pacientes. Sin embargo, se desconoce si el entrenamiento en neurofeedback puede revertir las alteraciones a nivel autonómico que también presentan estos pacientes.

El objetivo general de la presente tesis es estudiar la conectividad funcional cerebral y la actividad periférica relacionada con la modulación del dolor. La conectividad funcional, es un tipo de medida que refleja la dependencia estadística que existe entre dos fuentes de actividad fisiológica sin necesidad de que exista una conexión física. La conectividad entre dos regiones cerebrales, se interpreta como un reflejo de la integración de la información que cada área aporta para el procesamiento de una tarea cognitiva o un estado emocional. Además, estas medidas ofrecen la posibilidad de estudiar la sincronización entre regiones cerebrales, las respuestas periféricas y las variables psicológicas. La investigación de la relación central-periferia ha dado lugar a nuevos temas de investigación, como el Modelo de Integración Neurovisceral y la *network physiology* (Thayer & Lane, 2009; Ivanov & Bartsch, 2013), que ponen el foco en el estudio de la interacción entre el sistema nervioso central y el sistema nervioso autónomo. Pese al creciente interés en el estudio holístico de la fisiología, son escasos los estudios que exploran la conectividad entre el sistema nervioso central y la actividad periférica, entendida como una red interconectada y dependiente, y su influencia en la modulación del dolor.

La presente tesis se articula en tres estudios presentados en formato artículo. El primero, está destinado a poner a prueba la metodología de análisis en conectividad funcional mediante EEG, relacionándola con la actividad periférica y variables psicológicas. En concreto, se estudió la relación entre la variabilidad de la tasa cardíaca (HRV), la variabilidad de la conectividad funcional y la flexibilidad cognitiva. La literatura previa parece señalar que existe una relación positiva entre la HRV en reposo y la flexibilidad cognitiva (Gillie & Thayer, 2014). Sin embargo, se desconoce la relación de estas variables con la actividad cerebral en reposo (Liu et al., 2018). La tarea experimental consistió en realizar el "*Test de Cambios*" (Seisdedos, 2004) para luego realizar un registro de la tasa cardíaca y de la actividad cerebral en reposo. Los resultados señalaron que la HRV y la variabilidad de la conectividad en el EEG estuvieron relacionadas entre sí y con la flexibilidad cognitiva. Los análisis de regresión lineal múltiple, revelaron que el principal predictor de la flexibilidad cognitiva era la variabilidad de la conectividad del EEG y no la HRV, tal y como proponen otros autores (Thayer & Lane, 2009). Más aún, el análisis de correlaciones parciales reveló que la relación entre HRV y flexibilidad cognitiva estaba mediada por la variabilidad de la conectividad funcional del EEG. En conclusión, el estudio de los procesos psicológicos basados únicamente en la actividad fisiológica central o periférica puede dar lugar a una visión parcial y sesgada del fenómeno que se pretende estudiar.

En el estudio segundo, se investigó el efecto del dolor tónico sobre el procesamiento de estímulos afectivos, a través del análisis de las respuestas periféricas y la conectividad funcional cerebral. La tarea experimental consistió en el visionado de imágenes afectivas (agradables, neutrales y desagradables) con y sin dolor mientras se registraba los cambios en conductancia, tasa cardíaca y actividad eléctrica cerebral. En la condición no dolor, los resultados mostraron el patrón de respuesta característico a imágenes afectivas: aumento en conductancia y desaceleración cardíaca en imágenes agradables y desagradables, comparadas con imágenes neutrales. Sin embargo, cuando estas imágenes se presentaron en paralelo con el dolor, el patrón fisiológico cambió, no encontrándose diferencia entre los tres tipos de imágenes. Por otro lado, la conectividad funcional cerebral cambió entre la condición dolor y no dolor, encontrándose un aumento

de la conectividad entre regiones cerebrales relacionadas con el procesamiento atencional. Estos resultados parecen indicar que el dolor reduce la atención hacia otros estímulos, apuntando a la existencia de un sesgo atencional hacia el dolor que podría explicar las dificultades en el procesamiento de estímulos afectivos presentes en pacientes con dolor crónico.

El objetivo del tercer estudio, fue comprobar cómo afecta un entrenamiento en neurofeedback a la conectividad funcional cerebral y a la *network physiology* en pacientes con dolor crónico. Un grupo de pacientes con fibromialgia realizó un entrenamiento en autorregulación del ritmo sensoriomotor (SMR) mientras otro recibía un entrenamiento falso. El análisis del rendimiento en la tarea de neurofeedback, señaló que aproximadamente la mitad del grupo de entrenamiento real habían aprendido a modular su actividad cerebral, mientras que el resto no. El grupo que obtuvo buen rendimiento, informó de niveles más bajos de dolor después del entrenamiento comparado con el grupo que no entrenó y con el que no aprendió la tarea. Asimismo, se observó una reducción en la conectividad funcional entre los electrodos centrales con el resto de electrodos y la actividad cardíaca después del entrenamiento. Pese a las limitaciones del estudio, los hallazgos parecen indicar que el neurofeedback es un método eficaz para reducir el dolor en pacientes con fibromialgia y que el entrenamiento en la autorregulación del SMR de un nodo de la *network physiology* afecta al resto de nodos de la red.

INTRODUCCIÓN

1.-Estudio del dolor y modulación

1.1.-Dolor Crónico: definición, causas y fisiología.

La *International Association for the Study of Pain* (IASP), define el dolor como "una experiencia sensorial y emocional desagradable asociada a un daño tisular actual o potencial, o descrito en términos de dicho daño" (Merskey & Bogduk, 1994). De esta definición, se infiere que una de las principales funciones del dolor es prevenir o tratar un daño físico. Además, pone de manifiesto que el dolor es un fenómeno complejo que debe ser abordado desde una perspectiva multicausal, teniendo en cuenta factores afectivos y cognitivos, más allá de los puramente sensoriales. A pesar del carácter protector del dolor, cuando no puede identificarse una causa clara o se mantiene más allá del daño, el dolor pierde su función adaptativa, pasando a considerarse crónico (Peláez et al., 2019). Entre las patologías del dolor crónico se incluye cualquier enfermedad o condición dolorosa que persista durante más de tres meses, como la artritis reumatoide, la osteoartritis, la lumbalgia, la cefalea crónica o la fibromialgia (Dépelteau et al., 2019; Treede et al., 2015).

Conocer las causas de la cronificación del dolor resulta complejo. En general, se han observado profundos cambios a nivel periférico y central que pueden explicar el paso del dolor agudo a dolor crónico (Apkarian et al., 2011; Rosselló et al., 2015). La estimulación dolorosa se caracteriza por producir un aumento de la actividad simpática, acelerando la tasa cardíaca (HR), disminuyendo la variabilidad de la tasa cardíaca (HRV) y aumentando la conductancia eléctrica de la piel (SCR) (Mischkowski et al., 2019; Tousignant-Laflamme et al., 2005; Treister et al., 2012). Es más, los pacientes con dolor crónico presentan una activación simpática anormal comparados con los controles sanos, tanto en reposo como durante estimulación dolorosa (Tracy et al., 2016; Meeus et al., 2013; Reyes del Paso et al., 2010). A nivel central, se ha observado de manera consistente que el dolor activa una amplia red de regiones cerebrales (Apkarian, 2005). Los estudios de neuroimagen señalan la existencia de cambios en áreas tales como la corteza somatosensorial primaria (SI) y secundaria (SII), la ínsula, la corteza cingulada

anterior (ACC), la corteza prefrontal, el tálamo, la amígdala y la sustancia gris periacueductal (Apkarian et al., 2005; Tracey & Mantyh, 2007). La SI y SII reciben la información nociceptiva proveniente de la periferia a través de núcleos talámicos laterales, conformando el componente sensorial del dolor. Por otra parte, el componente afectivo y cognitivo del dolor se refleja en las proyecciones provenientes de núcleos talámicos mediales hacía la ACC y otras estructuras frontales (Apkarian et al., 2011). Además, existen otras conexiones importantes en el procesamiento del dolor como la proyección de la ínsula con la ACC (Treede et al.,1999). Los datos obtenidos mediante EEG, confirman la existencia de redes relacionadas con el procesamiento del dolor que actúan de manera conjunta. Así, la estimulación dolorosa tónica, provoca un aumento de la conectividad funcional entre electrodos frontales y centrales con el resto de electrodos en las bandas de frecuencias delta, theta, alfa y beta (González-Roldán et al., 2016; Huishi Zhang et al., 2016; Levitt et al., 2017; Nickel et al., 2020). Así mismo, pacientes con fibromialgia presentan una menor conectividad entre electrodos frontales (Choe et al., 2018; Hargrove et al., 2010; Vanneste et al., 2017) y una mayor conectividad entre los electrodos centrales que voluntarias sanas (González-Roldán et al., 2016). El aumento de conectividad en áreas centrales, ha sido relacionado con la sobre activación del área sensoriomotora, mientras que la disminución de la conectividad frontal se relaciona con los problemas cognitivos presentes en fibromialgia (para una revisión ver: Vierck et al., 2013).

En conjunto, estos estudios sugieren que la experiencia dolorosa mantenida produce cambios fisiológicos tanto a nivel central como periférico, que afectarían al procesamiento sensorial, cognitivo y afectivo de estímulos nociceptivos (McCarberg & Peppin, 2019; Yang & Chang, 2019), Más aún, estos cambios funcionales se relacionan con otras patologías que acompañan los trastornos del dolor crónico tales como depresión y ansiedad (Stahlschmidt et al., J. 2020; Xu et al., 2020), problemas atencionales (Moore et al., 2012; Moore et al., 2017) y dificultades en la percepción de estímulos emocionales (Giel et al., 2018; Rosselló et al., 2015; Li et al., 2020; Wieser et al., 2014).

1.2.-Modulación del dolor

Diferentes estudios evidencian la capacidad de las emociones para modular el dolor (Rudhy et al., 2006; Rudhy et al., 2008; Williams & Rhudy, 2009). Rudhy y cols. (2008), pusieron a prueba la capacidad de un conjunto de imágenes, graduadas en valencia y arousal, para modular el dolor en voluntarios sanos. Durante el estudio, se presentó imágenes agradables, desagradables y neutrales, procedentes del *International Affective Picture System* (IAPS) mientras se aplicaba dolor. Los autores concluyen que, si bien la visualización de imágenes influye sobre la percepción de dolor, esto sólo sucede cuando el arousal de dichas imágenes es superior al arousal evocado por el dolor (Rudhy et al., 2008). Tal y como señala la literatura (Bradley, 2009; Hajcak & Foti, 2020), estímulos afectivos altamente activantes capturan la atención por su relevancia biológica. Sin embargo, cuando estímulos afectivos se presentan junto al dolor, ambos estímulos compiten por los recursos atencionales, modulando la entrada sensorial del estímulo doloroso. Esto lleva a una segunda pregunta: ¿es posible que el dolor afecte al procesamiento de los estímulos afectivos de la misma manera que los estímulos afectivos influyen en la percepción del dolor?

Estudios realizados con pacientes de dolor crónico, ponen de manifiesto alteraciones en las respuestas afectivas (Giel et al., 2018; Rosselló et al., 2015). Roselló y cols. (2015), estudiaron la modulación del reflejo de sobresalto en pacientes con fibromialgia mientras permanecían en entornos virtuales agradables, neutros y desagradables. Los resultados señalaron la ausencia de diferencias en la modulación del reflejo de sobresalto entre los tres tipos de entornos virtuales, indicando dificultades en el procesamiento de estímulos afectivos en pacientes con dolor crónico. Aunque no está claro si los déficits en el procesamiento de estímulos afectivos presentes en el dolor crónico son consecuencia de los trastornos del estado de ánimo concomitantes, algunos autores señalan la existencia de un proceso de *atención motivada hacia el dolor* (Van Damme et al., 2009; Torta et al., 2017). Desde este punto de vista, los cambios estructurales y funcionales implicados en la cronificación del dolor, provocan que cualquier estímulo nociceptivo se vuelva más relevante, compitiendo por los recursos atencionales con el resto de estímulos y afectando a la respuesta atencional (Torta et al., 2017). Varios

estudios han comparado las respuestas cerebrales evocadas por estímulos dolorosos mientras voluntarios sanos realizan tareas atencionales (Seminowicz & Davis, 2007; Valet et al., 2004). En estos estudios se observa que la intensidad del dolor tiene una relación inversa con la ejecución en la tarea. En un estudio, Bingel y cols. (2007) exploraron los efectos distractores de estímulos dolorosos de diferente intensidad en la ejecución en una tarea de memoria N-back. La administración de estímulos dolorosos, redujo la actividad en áreas cerebrales (corteza cingulada anterior y la corteza parietal inferior) relacionadas con la atención y la memoria de trabajo. Wieser y cols. (2012) empleando la técnica de potenciales evocados, concluyeron que el dolor reduce los recursos atencionales dedicados al procesamiento de los estímulos afectivos. Así, cuando pacientes con dolor crónico realizan una tarea cognitiva, la carga atencional hacia el procesamiento del dolor reducirá los recursos disponibles para realizar la tarea, observándose los típicos problemas cognitivos presentes en esta población (Legrain et al., 2009).

1.3.-Neuromodulación en el manejo del dolor.

El neurofeedback es una técnica que se basa en el aprendizaje de la modulación de la actividad cerebral a través de los principios del condicionamiento operante. En un entrenamiento de este tipo, los participantes obtienen un feedback visual o auditivo de su actividad cerebral, incrementando la consciencia del proceso cerebral implicado (Enriquez-Geppert et al., 2017). Dentro de las distintas características de la señal EEG que se puede modular, una de las más utilizadas es la modulación de las bandas de frecuencia (Gruzelier, 2014a). En líneas generales, el procedimiento consiste en elegir la banda de frecuencia que se quiere entrenar (alfa, theta, delta, gamma u otras frecuencias específicas), establecer el tipo de modulación (potenciación, inhibición o ambas) y elegir la localización de los electrodos que se van a entrenar. Por otro lado, también es necesario definir el número de sesiones de entrenamiento, para lograr el éxito en la intervención. En la literatura podemos encontrar protocolos que van desde una única sesión hasta más de treinta, dependiendo del tipo de trastorno, de la población objetivo y de las frecuencias a entrenar (Gruzelier, 2014b),

El entrenamiento del ritmo sensoriomotor (SMR) es muy usado en los entrenamientos de neurofeedback para tratar diferentes patologías (Enriquez-Geppert et al., 2017; Gruzelier, 2014a). Este ritmo se encuentra entre 12 y 15 hercios, observándose una disminución de la amplitud del SMR durante el movimiento corporal real (Pfurtscheller & Aranibar, 1979), o durante la imaginación motora (Pfurtscheller & Neuper, 1997). Específicamente, en la tarea de imaginación del movimiento de una de las manos, se produce una disminución de la amplitud del SMR en el hemisferio contralateral y un aumento de la amplitud en el hemisferio ipsilateral sobre las áreas somatomotoras (Pfurtscheller et al., 1997). Se ha encontrado que este tipo de entrenamiento es capaz de provocar cambios en la conectividad funcional del EEG en reposo, y se han relacionado con mejoras del rendimiento cognitivo y atencional (Kober et al., 2015, Reichert et al., 2016; Gadea et al., 2016). Así, por ejemplo, el entrenamiento en SMR es usado para actuar sobre los síntomas de déficit de atención (Davelaar & Jilek, 2020), para reducir los problemas de memoria en población anciana (Campos da Paz et al., 2018) o mejorar la concentración y la atención en tiradores profesionales (Liu et al., 2018).

El entrenamiento en SMR, ha demostrado potenciales beneficios en el tratamiento de síndromes de dolor crónico (Enriquez-Geppert et al., 2017; Gruzelier, 2014a; Terrasa et al., 2020). La utilidad del entrenamiento se basa en alterar la amplitud de SMR oscilaciones para conseguir transformar los patrones cerebrales asociados al dolor en patrones asociados al bienestar (Jensen et al., 2008; Jensen et al.,2013). Sin embargo, no están claros los mecanismos que explicarían la eficacia del entrenamiento del SMR para aliviar el dolor. Algunos autores señalan que el entrenamiento del SMR produce que los pacientes aumentan su atención hacia estímulos externos, que compiten por los recursos atencionales del dolor (Caro & Winter, 2011; Kayiran et al., 2010), mientras que otros señalan que la eficacia podría estar relacionada con la inhibición de la actividad cerebral somatosensorial y motora asociada con el procesamiento del dolor (Jensen et al., 2008, 2014). En cualquier caso, los pacientes de dolor crónico que reciben entrenamiento en modulación del ritmo SMR, reportan menos dolor y fatiga que grupos control o con tratamiento farmacológico (Caro & Winter; 2011; Kayıran et al., 2010;).

2.-Estudio de la conectividad funcional

Desde el estudio del cerebro, se ha aportado evidencias de la existencia de un conjunto de regiones especializadas en diferentes funciones mentales. Con el desarrollo de las técnicas de registro de actividad cerebral, se ha observado que tareas cognitivas, estados emocionales, y respuestas autonómicas, provocan la activación de un amplio conjunto de regiones cerebrales (Aldhafeeri et al., 2012; Shulman et al., 2010; Valenza et al. 2019). Sin embargo, no basta con conocer qué regiones participan en un determinado proceso mental, también resulta necesario conocer cómo se coordinan entre ellas. En este sentido, la conectividad cerebral nace con el objetivo de estudiar las interacciones entre regiones cerebrales y la contribución de cada una para que se produzca un determinado fenómeno cerebral. Se podría decir que la conectividad permite una aproximación más holística del estudio del cerebro y es una alternativa al reduccionismo funcional (Fallani et al., 2014).

La conectividad funcional cerebral, hace referencia a la dependencia estadística que existe entre los patrones de actividad neuronal de dos nodos cerebrales anatómicamente separados (Sporns et al., 2004). En este tipo de conectividad, se asume que la similitud entre los patrones de actividad neuronal de dos nodos está relacionada con el nivel de sincronización entre ambos, y con la participación en un mismo procesamiento. La conectividad funcional no implica necesariamente la existencia de una conexión física entre las estructuras cerebrales; la literatura parece señalar que las conexiones de una red funcional no correlacionan con la fuerza de las conexiones (número de sinapsis) de la red estructural (Khalsa et al., 2014; Straathof et al., 2019). En otras palabras, la conectividad funcional indica la existencia de sincronización entre dos regiones, pero no informa de la densidad de las conexiones físicas entre ellas (densidad de axones).

El análisis de la conectividad funcional implica una serie de pasos bien definidos y secuenciales (Fallani et al., 2014). De manera resumida podemos separarlos en: registro y preprocesamiento de la actividad cerebral, cálculo de la matriz de conectividad, extracción de la red, extracción de las propiedades de la red y contraste de hipótesis (ver

figure 1). El tipo de análisis de conectividad funcional vendrá determinado por la procedencia de la señal (resonancia magnético funcional (fMRI), EEG, espectroscopia infrarroja o Doppler transcraneal) y definirá dos componentes fundamentales de la red: los nodos y enlaces. Los nodos son los lugares de generación de la señal (*voxels* o sensores), mientras que los enlaces son las uniones de esos nodos. Durante el **preprocesamiento**, las señales se filtran, se segmentan en ventanas y se eliminan aquellas con demasiados artefactos (Keil et al., 2014). El **cálculo de la matriz de conectividad** consiste en la obtención de la conectividad funcional entre cada par de nodos, en base a la técnica de registro cerebral, el paradigma experimental y las hipótesis de partida (Lee & Hsieh, 2014). Los métodos de conectividad funcional se dividen principalmente en lineales y no lineales. Los primeros, asumen que las señales que se relacionan son estacionarias y se distribuyen a lo largo del tiempo de manera normal. Un ejemplo es la coherencia, que consiste en la relación estadística de dos señales en cada frecuencia del EEG. Por el contrario, los métodos de conectividad no lineales, asumen que las señales que se van a relacionar no son estacionarias, y no se distribuyen de manera normal a lo largo del tiempo. Entre las diferentes técnicas de conectividad funcional no lineal, cabe destacar los métodos de análisis de grafos en el tiempo, que consiste en describir redes cerebrales complejas a partir de simples abstracciones en forma de nodos y enlaces. Recientemente, se ha desarrollado el método de análisis de grafos en el tiempo llamado *Motif-Synchronization,* que permite estudiar no la conectividad funcional en un momento dado, si no a lo largo de un periodo temporal (Rosario et al., 2015).

La **extracción de la red,** consiste en la selección de los enlaces que son significativos bien mediante un umbral de conectividad o bien mediante la sustracción de la actividad basal. El **análisis de características** de la red (*small-world de la red cerebral*) hace referencia al cálculo de aspectos distintivos de la red, como el grado de conexiones que recibe cada nodo, el nivel de agrupamiento, probabilidad de conexión entre nodos vecinos, o la variabilidad de las conexiones en una unidad de tiempo. Finalmente, en el **contraste de hipótesis** sometemos a prueba empírica nuestra hipótesis sobre la diferencia entre redes en las condiciones experimentales definidas.

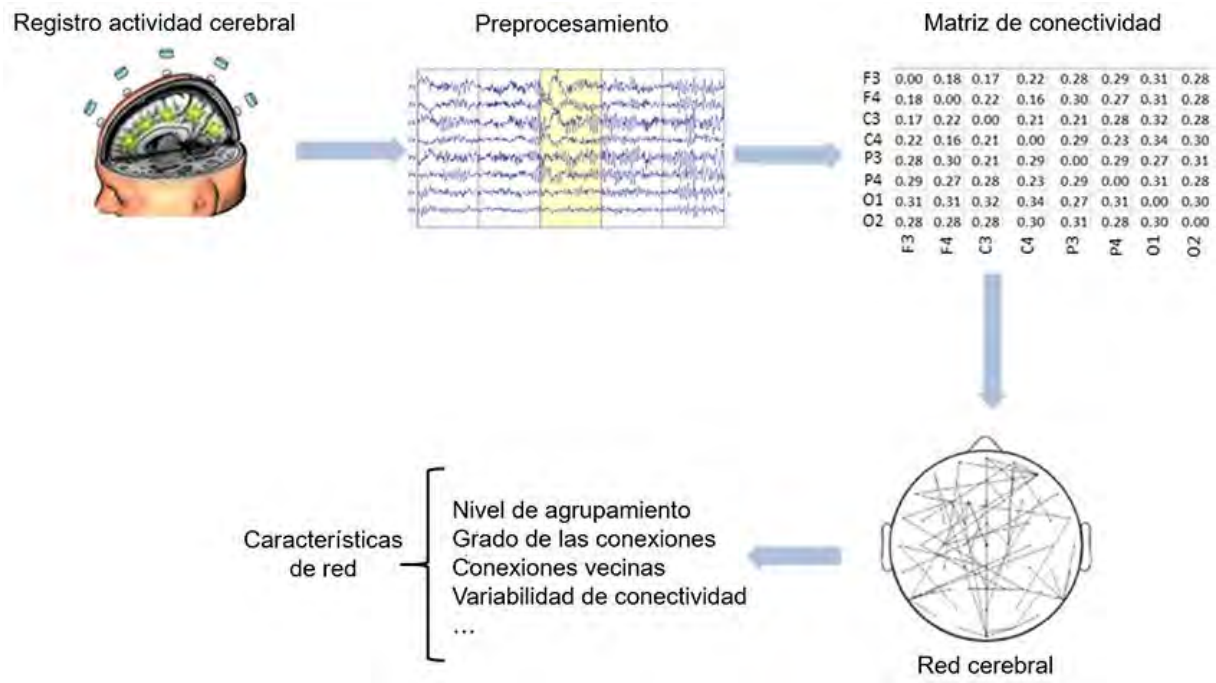

Figure 1. Procedimiento de análisis de la conectividad funcional.

2.1-Índice de la parte imaginaria de la coherencia

La coherencia es un índice de conectividad funcional lineal que consiste en hallar la sincronización entre dos señales dentro de una frecuencia específica. En primer lugar, se realiza un análisis de la señal en el dominio de las frecuencias (mediante la transformación de Fourier o filtrado de la frecuencia de interés). A continuación, se calcula la densidad espectral de la señal x ($S_{xx}(f)$) y de la señal y ($S_{yy}(f)$). También se calcula la correlación cruzada entre las densidades espectrales individuales de ambas señales (densidad espectral cruzada, $S_{xy}(f)$). La coherencia, es la ratio entre la densidad espectral cruzada ($S_{xy}(f)$) de las dos señales y las densidades espectrales individuales de cada una de ellas ($S_{xx}(f)$ y $S_{yy}(f)$).

$$K_{xy}(f) = \frac{S_{xy}(f)}{\sqrt{S_{xx}(f)S_{yy}(f)}}$$

Finalmente, se extrae la parte imaginaria de la coherencia y se transforma a valores absolutos. La extracción de la parte imaginaria de la coherencia, permite eliminar la

actividad de otros nodos cercanos de la red debido a las características de la conductividad del propio cerebro (Nolte et al., 2004).

2.2.-Índice de la *Motif-Synchronization*

La *Motif-Sychronization* es un índice de conectividad funcional no lineal, que consiste en hallar la sincronización entre dos señales a partir de los motifs que se generan en cada una de ellas. Los motifs son pequeños patrones que se forman a partir de dos o más muestras de cambios de voltaje, extraídas de una señal de EEG (Figura 2). En líneas generales, el procedimiento consiste en segmentar la señal de EEG en ventanas temporales, y posteriormente se identifican y clasifican las motifs presentes en dicha ventana. De este modo, si se realizan motifs basadas en tres muestras de la señal de EEG, se pueden obtener 6 tipos de patrones (M1, M2, M3…M6). Una vez obtenidos los motifs para cada canal de EEG, se calcula la sincronización entre los vectores de motif en una ventana temporal dada. Dicho de otro modo, se establece la coincidencia de motifs entre dos canales, obteniendo una matriz binaria de coincidencia/ no coincidencia que serían los enlaces en ese momento temporal (Figura 3). El índice de *Motif-Sychronization* sería los valores de sincronización entre los vectores de motifs de un canal X y un canal Y a lo largo de todo el registro de EEG.

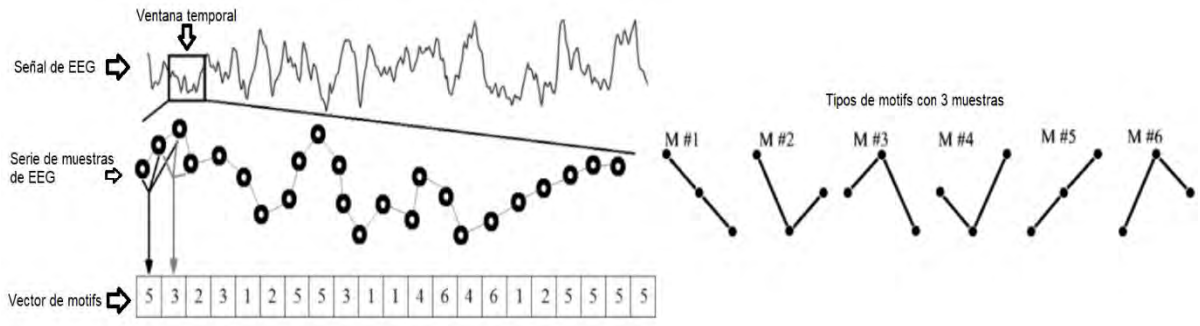

Figure 2. Construcción del vector de motifs de una señal de EEG (basado en Rosario et al., 2015).

La *Motif-Synchronization* muestra una alta resolución temporal, permitiendo estudiar la evolución de la conectividad funcional de una red en el orden de milisegundos. Además, corrige los problemas del volumen de conducción que afectan a la velocidad de trasmisión del impulso nervioso y a su localización. Para ello se realiza correcciones del retraso temporal entre ventanas y se establece un umbral de significación basado en la generación señales subrogadas construidas a partir de las señales de EEG originales.

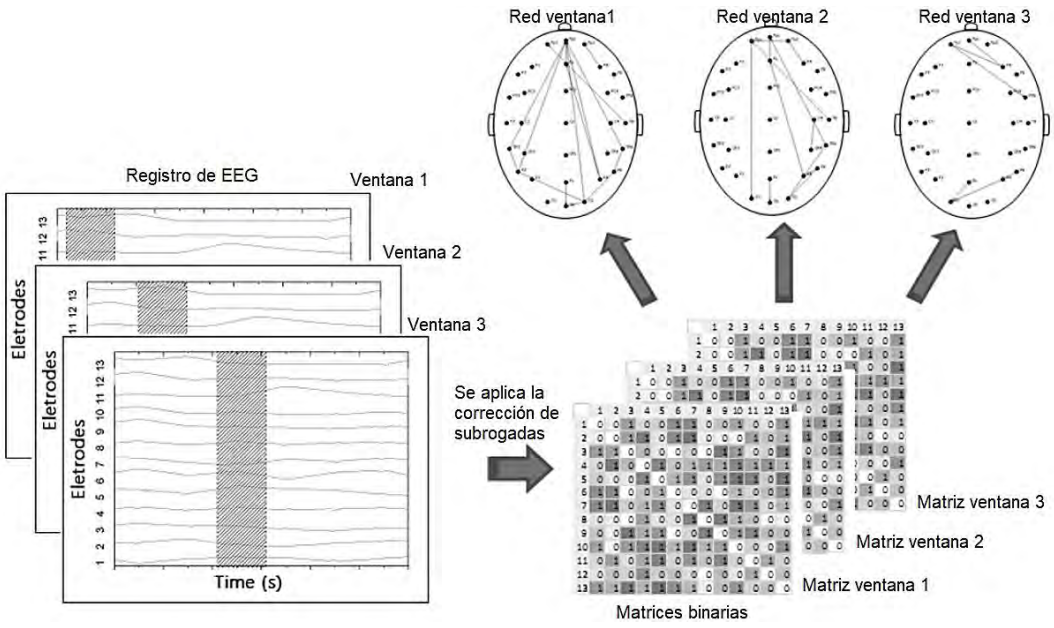

Figura 3. Obtención de la matriz binaria entre canales (basado en Rosario et al., 2015).

2.3.-Interacción entre el sistema nervioso autónomo y el central

En los últimos años, ha surgido el interés por el estudio de la relación entre las respuestas periféricas y cerebrales para comprender de manera integral la fisiología humana y fenómenos complejos, como el envejecimiento (Kumral et al., 2019; Sakaki et al., 2016), el sueño (Bartsch et al., 2015), trastornos psicológicos (Makovac et al., 2016; Thome et al., 2017) y estados mentales (Gould van Praag et al., 2017). Estudios con fMRI y EEG en estado de reposo, señalan que cambios en la actividad autonómica se asocian a cambios en la conectividad funcional de redes cerebrales (Chang et al., 2013; de la Cruz et al., 2019; Ding et al., 2020; Jennings et al., 2016; Kumral et al., 2019; Sakaki et al., 2016; Palva et al., 2013). Recientemente, Chand y cols. (2020) han examiado la dinámica

de la conectividad funcional asociada con la HRV en estado de reposo y después de una tarea de estrés psicosocial. Los resultados señalan un clara relación entre la conectividad funcional y la raiz de la media cuadrática de las diferencias sucesivas entre los períodos cardíacos (intervalos RR) en milisegundos (RMSSD) en estado de reposo. Estos resultados indican la relación funcional dinámica entre el sistema autónomo y las redes cerebrales que varían según las condiciones externas.

Desde el Modelo de Integración Neurovisceral (Thayer & Lane, 2009), se propone la existencia de una red, conocida como red central-autonómica, que conecta la actividad del cerebro con la actividad cardíaca. A partir de este modelo, se ha estudiado principalmente la interacción de la HRV con otros sistemas del organismo en relación con la emoción y las funciones cognitivas. Se ha visto que una alta HRV se asocia a una mejor respuesta inmune, endocrina y cardiovascular al estrés (Weber et al., 2010). Durante la realización de tareas de regulación emocional se observa que alta HRV se asocia a un mayor flujo sanguíneo en áreas cerebrales relacionadas con las emociones (Lane et al., 2009). Asimismo, alta HRV también se asocia a un mayor flujo sanguíneo en el córtex prefrontal medial relacionado con funciones cognitivas (Thayer et al.,2012). Según los datos que aporta el Modelo de Integración Neuroviceral, la HRV sería la principal mediadora en una adaptación flexible para responder a las demandas del ambiente. Otro modelo, la n*etwork physiology* entiende que los distintos sistemas del cuerpo humano actúan como una red integrada (Ivanov et al., 2016). Dentro de la *network physiology,* los distintos sistemas fisiológicos interactúan a través de distintos mecanismos de feedback, para optimizar la función del organismo a la hora de regularse y adaptarse. Esta visión aporta de novedoso al estudio de la relación cerebro-cuerpo el análisis de la conectividad funcional entre los sistemas y la asociación de estas redes con estados de salud y enfermedad (Bashan et al., 2012). El estudio de la conectividad funcional entre sistemas fisiológicos ha llevado a describir en la interacción cerebro-cuerpo canales de comunicación que son específicos de sistemas fisiológicos concretos (Bartsch et al., 2015) y en la red cerebro-corazón se han identificado nuevos mecanismos de feedback y acoplamiento (Valenza et al., 2016).

Como señalábamos al principio, la experiencia dolorosa produce cambios fisiológicos tanto en el sistema nervioso autonómico como central. La estimulación dolorosa acelera la tasa cardíaca, disminuye la variabilidad cardíaca y aumenta la conductancia eléctrica de la piel (Tousignant-Laflamme et al., 2005; Treister at al., 2012). Así mismo, se ha observado que la conectividad funcional de estructuras del sistema nervioso central implicadas en la modulación de las respuestas autonómicas está relacionada con la sensibilidad hacia estímulos dolorosos (Sprenger et al., 2015; Khan & Stroman, 2015) y se encuentra alterada en pacientes con dolor crónico cuando se les compara con participantes sanos (Coulombe et al., 2017; Karafin et al., 2019; Mills et al., 2018). Incluso se han encontrado indicios de que la interacción entre las emociones y el dolor afecta a la conectividad de estructuras del sistema nervioso central que modulan la actividad periférica (Roy et al., 2009). Estos resultados ponen de manifiesto la relación entre redes cerebrales y periferia, y que las alteraciones en la conectividad cerebral podrían estar relacionadas con la activación autonómica simpática que se observa en pacientes con dolor crónico (Benarroch, 2006). Así, se ha encontrado que hay cambios en la actividad y conectividad funcional cerebral asociados a la activación simpática producida por la estimulación dolorosa tónica en voluntarios sanos (Kobuch et al., 2018; Hohenschurz-Schmidt et al., 2020; Sclocco et al., 2018). También se ha encontrado que las alteraciones en la conectividad del área somato-sensorial consecuencia del síndrome de fibromialgia están relacionadas con las disfunciones autonómicas propias de dicho síndrome (Kim et al., 2015). Estos resultados inducen a pensar que resulta necesario estudiar las interacciones entre las respuesta centrales y periféricas para comprender el proceso de cronificación del dolor, así como entender la interacción entre las emociones y la atención en el procesamiento del dolor.

OBJETIVOS

A lo largo de la introducción, se ha expuesto las bases fisiológicas relacionadas con el dolor, así como diferentes aspectos relacionados con su modulación. El objetivo general de la presente tesis es estudiar la conectividad funcional cerebral y de la actividad periférica relacionada con la modulación del dolor. Para alcanzar dicho objetivo, se desarrollaron tres estudios.

- **Objetivo estudio 1.** Explorar las relaciones entre la actividad autonómica, los patrones de conectividad funcional del EEG y variables psicológicas.
    - Objetivo específico 1a. Confirmar si la variabilidad de la tasa cardíaca y la variabilidad de la conectividad funcional del EEG en estado de reposo se relacionan con el rendimiento cognitivo.
    - Objetivo específico 1b. Comprobar si la correlación entre variabilidad de la tasa cardíaca y variabilidad de la conectividad funcional del EEG en estado de reposo se relaciona con el rendimiento cognitivo.
    - Objetivo específico 1c. Establecer cuál es el peso de la variabilidad de la tasa cardíaca y la variabilidad de la conectividad funcional del EEG en el rendimiento cognitivo.
- **Objetivo estudio 2.** Examinar los cambios que produce el dolor tónico en los patrones de respuestas autonómicas y conectividad funcional del EEG en distintos contextos afectivos.
    - Objetivo específico 2a. Comparar los patrones de conductancia y tasa cardíaca ante imágenes afectivas (agradables, desagradables y neutrales) sin dolor y con dolor.
    - Objetivo específico 2b. Comparar los patrones de conectividad funcional del EEG ante imágenes afectivas (agradables, desagradables y neutrales) sin dolor y con dolor.

- **<u>Objetivo estudio 3</u>.** Comprobar si es posible alterar la conectividad central-periférica (*network physiology*) mediante un entrenamiento en neuromodulación del ritmo sensoriomotor (SMR) en pacientes con fibromialgia.
    - Objetivo específico 3a. Comprobar si el entrenamiento en neurofeedback produce cambios en actividad cerebral.
    - Objetivo específico 3b. Comprobar si un entrenamiento en neurofedback modifica la conectividad del área somatosensorial con el resto del cerebro y con la actividad cardíaca en estado de reposo.

ESTUDIO 1

Alba, G., Vila, J., Rey, B., Montoya, P., & Muñoz, M. Á. (2019). The Relationship Between Heart Rate Variability and Electroencephalography Functional Connectivity Variability Is Associated with Cognitive Flexibility. *Frontiers in human neuroscience, 13, 64.* Doi: https://doi.org/10.3389/fnhum.2019.00064

frontiers in Human Neuroscience

ORIGINAL RESEARCH
published: 25 February 2019
doi: 10.3389/fnhum.2019.00064

Alba, G., Vila, J., Rey, B., Montoya, P., & Muñoz, M. Á. (2019). The Relationship Between Heart Rate Variability and Electroencephalography Functional Connectivity Variability Is Associated with Cognitive Flexibility. *Frontiers in human neuroscience, 13, 64.* Doi: https://doi.org/10.3389/fnhum.2019.00064

The Relationship Between Heart Rate Variability and Electroencephalography Functional Connectivity Variability Is Associated With Cognitive Flexibility

*Guzmán Alba[1], Jaime Vila[1], Beatriz Rey[2], Pedro Montoya[3] and Miguel Ángel Muñoz[1]**

[1] Brain, Mind and Behavior Research Center, University of Granada, Granada, Spain, [2] Departamento de Ingeniería Gráfica, Universitat Politècnica de València, Valencia, Spain, [3] Research Institute of Health Sciences, University of Balearic Islands, Palma, Spain

The neurovisceral integration model proposes a neuronal network that is related to heart rate activity and cognitive performance. The aim of this study was to determine whether heart rate variability (HRV) and variability in electroencephalographic (EEG) functional connectivity in the resting state are related to cognitive flexibility. Thirty-eight right-handed students completed the CAMBIOS test, and their heart and EEG activity was recorded during 6 min in the resting state with their eyes open. We calculated correlations, partial correlations and multiple linear regressions among HRV indices, functional brain connectivity variability and CAMBIOS scores. Furthermore, the sample was divided into groups according to CAMBIOS performance, and one-way ANOVA was applied to evaluate group differences. Our results show direct and inverse correlations among cognitive flexibility, connectivity (positive and negative task networks) and heartbeat variability. Partial correlations and multiple linear regressions suggest that the relation between HRV and CAMBIOS performance is mediated by neuronal oscillations. ANOVA confirms that HRV and variability in functional brain connectivity is related to cognitive performance. In conclusion, the levels of brain signal variability might predict cognitive flexibility in a cognitive task, while HRV might predict cognitive flexibility only when it is mediated by neuronal oscillations.

Keywords: HRV, EEG, resting-state, sample entropy, variability of functional connectivity, cognitive flexibility

OPEN ACCESS

Edited by:
Sheng Li,
University of Texas Health Science Center at Houston, United States

Reviewed by:
Marzia De Lucia,
Lausanne University Hospital (CHUV), Switzerland
Giovanni Assenza,
Campus Bio-Medico University, Italy

****Correspondence:***
Miguel Ángel Muñoz
mamuoz@ugr.es

Received: *01 October 2018*
Accepted: *06 February 2019*
Published: *25 February 2019*

Citation:
Alba G, Vila J, Rey B, Montoya P and Muñoz MÁ (2019) The Relationship Between Heart Rate Variability and Electroencephalography Functional Connectivity Variability Is Associated With Cognitive Flexibility. Front. Hum. Neurosci. 13:64. doi: 10.3389/fnhum.2019.00064

INTRODUCTION

Cognitive flexibility refers to the ability to flexibly adapt processing to changing environmental information, to guide thought and behavior and to allow directed action toward a goal (Cañas et al., 2003; Geurts et al., 2009; Dennis and Vander Wal, 2010; Ionescu, 2012). Flexibility depends on strong executive control, particularly in terms of efficient shifting of attentional and cognitive resources to the processing of new information while inhibiting previous irrelevant information (Miyake et al., 2000). Research has shown a direct link between cognitive flexibility and the cardiovascular system through the autonomic vagal tone. A simple way of measuring

this relationship is to examine heart rate variability (HRV), a non-invasive measurement of the interactions between the autonomic nervous system (ANS) and central nervous system (CNS) based on the study of oscillations of the interval between heartbeats (Malik et al., 1996; Pumprla et al., 2002). The neurovisceral integration model (Thayer and Lane, 2009) proposes a neuronal network that relates heart rate activity and cognitive performance. This model assumes that the CNS and ANS are reciprocally interconnected such that information flows bidirectionally (Smith et al., 2017). Very compelling evidence indicates that prefrontal cortex activity is involved in the modulation of vagal efferent outflow to the heart, and HRV is an indicator of cardiac activity associated with cognitive flexibility in tasks involving attention, working memory and inhibitory control (Thayer et al., 2004; Saus et al., 2006; Hansen et al., 2009). The high-frequency component of HRV appears to be positively correlated with perseverative errors in the Wisconsin Card Sorting Test, as well as inhibition errors in the Color-Word Interference Test (Hovland et al., 2012). In a series of studies in which individuals were *a priori* stratified according to their resting-state levels of HRV, individuals with high HRV performed better on tasks involving executive function than those with low HRV (Hansen et al., 2009). Such findings indicate that individual differences in HRV are a useful predictor of cognitive flexibility (Gillie and Thayer, 2014).

Lately, brain signal variability has emerged as a valuable tool for investigating individual differences in cognitive performance (Yang et al., 2013; McDonough and Nashiro, 2014). The capacity of resting-state functional connectivity variability to predict cognitive performance with different methods and tasks has been explored (Mennes et al., 2010; Takeuchi et al., 2011; Mackey et al., 2013; Martínez et al., 2013; Thompson et al., 2016). These studies seem to indicate that executive functions are correlated with brain activity in the resting state (Fox et al., 2005, 2006; Seeley et al., 2007). Mennes et al. (2010) found a task-positive network that included frontal-cingulate-parietal areas during an Eriksen Flanker task. Fox et al. (2006) identified two brain networks in the resting state. One network consists of regions that are routinely positively correlated with cognitive task performance, and the other includes regions that are routinely negatively correlated. The presence of significant positive/negative correlations between a cerebral region and a task across participants suggests that at least some part of the cerebral response induced by a particular task is intrinsically represented in the brain (Mennes et al., 2010). Similarly, when variability is disrupted, the brain has little capacity to adapt to environmental conditions, resulting in neuropathological diseases such as epilepsy and attention-deficit/hyperactivity disorder (Mizuno et al., 2010; Catarino et al., 2011; Vakorin et al., 2011; Ramon and Holmes, 2013; Barttfeld et al., 2014; Alba et al., 2016; Chen et al., 2017).

Recently, relations between HRV and the endogenous dynamic of brain regions involved in autonomic control and emotional regulation during the resting state have been explored. These studies showed that high- and low-frequency components of HRV are strongly coupled with functional connectivity (Chang et al., 2013b; Jennings et al., 2016; Sakaki et al., 2016). However, these studies have not addressed the relation between the variability of functional connectivity and HRV or whether both factors might predict the outcomes of cognitive tasks. Palva et al. (2013) correlated the variability of functional connectivity using magneto-encephalography (MEG) and HRV during a stimulus detection task and during the resting-state period. Strong correlations were found between neuronal oscillations and task performance during the task and during the resting-state period. These results suggest that the variability of functional connectivity in the resting state is not specific to the task but is related to the performance of cognitive tasks. Moreover, this study found that HRV in both task and rest conditions predicted task performance.

In the present study, we investigated the association between electroencephalography (EEG) functional connectivity variability and HRV in the resting state and subsequent performance on a cognitive test. Normally, any EEG measure is estimated during the resting state by averaging its values in a certain number of EEG segments. This procedure assumes that resting-state EEG remains static during the recording period. Even in this case, recent evidence (see, e.g., Kitzbichler et al., 2009; Botcharova et al., 2014) clearly suggests that brain synchronization as assessed from neurophysiological signals is not constant, but during this time, it presents significant variability, which is disrupted in neuropathological conditions (Ramon and Holmes, 2013; Alba et al., 2016). Moreover, some studies suggest that the variability of functional connectivity in the resting state could predict cognitive performance (Liu et al., 2018). This association between variability and variations in mental state seems to oscillate at different frequency bands, such as theta or alpha (Chang et al., 2013a). Research on the variability of functional connectivity can unveil flexibility in the functional coordination between different neuronal systems and may improve our understanding of behavioral shifts and adaptive processes (Allen et al., 2014). In other words, how brain connectivity dynamics in the resting state might predict the outcome of cognitive tasks is of interest.

The aim of this study was to determine whether performance in a switch task is correlated with the interindividual variability of functional connectivity in the resting state and with HRV. Thus, we expect that better performance on the CAMBIOS switch test will be related to high variability of functional connectivity in the resting state. Furthermore, we expect that HRV and cognitive performance will be correlated. Because the literature regarding the relationship between HRV and cognitive performance shows contradictory results, we do not predict correlations or anticorrelations between these variables. Also, we hypothesize that the resting-state variability of functional connectivity (RSVFC) and HRV are correlated because the CNS and ANS are reciprocally interconnected. Moreover, to test whether fluctuations driven by the ANS play a role in the correlation between cerebral functional connectivity in the resting state and cognitive performance, we calculated the effect of HRV on correlations between performance in terms of CAMBIOS test scores and RSVFC using partial correlations. Following the previous results, we hypothesize that participants with better scores on the CAMBIOS test would show higher

RSVFC. Based on previous studies, we have no hypothesis regarding the HRV level (higher or lower) of participants with higher scores on the CAMBIOS test.

MATERIALS AND METHODS

Participants

Thirty-eight right-handed students (22 females and 16 males) participated in this study. All students attended the University of Granada (average age = 20.82 ± 9.5) and received extra credit in return for their participation. Participant exclusion criteria included cardiovascular problems, ongoing illicit substance use, mental health problems, or current medical or psychological treatment. We excluded four participants (2 females and 2 males) from the study due to technical issues with their recordings. Participants were recruited via information provided in university classrooms. All participants signed informed consent forms to participate in the study, which was approved by the ethics committee of University of Granada and carried out according to the recommendations of the Declaration of Helsinki.

Procedure

Data were compiled in an individual session that lasted approximately 45 min. Upon their arrival at the experimental session, participants received a brief explanation of the study before signing their informed consent, followed by a short interview to verify compliance with the inclusion criteria. Then, participants performed the CAMBIOS test, and they were moved to the recording room (quiet and dimly illuminated) and sat in a comfortable seat. Next, EEG and electrocardiography (EKG) electrodes were applied, and the experimental session started. Recordings were performed during a 3 min adaptation period and a 6 min resting-state period with eyes open. All participants were instructed to fix their eyes on a fixation cross to reduce ocular artifacts. Finally, a 3 min period to allow participants to return to the basal level was included. The instructions for the experimental conditions and fixation cross were presented with E-Prime 2.0 software (Psychology Software Tools) and a Canon LV-53 projector.

Cognitive Test

The CAMBIOS test (Seisdedos, 2004) evaluates cognitive flexibility. Cognitive flexibility can be described as open, organized, systematic behavior and the ability to quickly respond to classification stimuli. During the CAMBIOS test, participants determine whether there has been a change between three polygonal figures according to easily learned symbology. Participants had 7 min to complete the test. Two indices were used in analysis, errors (number of errors/total number of items) and hits (number of hits/total number of items).

Physiological Data Acquisition and Preprocessing

Physiological signals from EKG and EEG were continuously acquired using Ag/AgCl electrodes and two electro-oculogram channels with a 32-ch A.N.T. EEG System (Enschede, Netherlands). The sampling rate was accomplished at a frequency of 1024 Hz. Electrodes were mounted according to the 10/20 montage system, and a bilateral electro-oculogram was recorded from horizontal sites to monitor blinking and was referenced to ear lobes. All EEG channels were offline-referenced to the average of the electrodes, and impedance was maintained at <10 kOhm. Two-lead EKG was recorded using 8 mm Ag/AgCl surface electrodes placed over the wrists and ankles of participants and filtered with cut-offs above 5 Hz and below 35 Hz.

EEG preprocessing analysis was performed with the EEGLAB toolbox for MATLAB (Delorme and Makeig, 2004). The recordings were resampled to 512 Hz and filtered with a 0.01–40 Hz bandpass filter. Eye movement and blink artifacts were corrected using independent component analysis. EEG waveforms were segmented in epochs of 1 s duration (obtained a total of 360 epochs) for analyses, and artifact rejection methods consisted of exclusion of epochs with large amplitudes (over ± 100 μV). After artifact rejection was applied, the largest recording had 300 epochs, and the shortest recording had 180 epochs. The mean number of epochs rejected was 39.21, and the standard deviation was 34.20. To equalize the number of epochs between participants, we selected the first 180 epochs after rejection in all recordings. Because the literature indicates that cognitive performance is related to some frequency bands (Carrillo-de-la-Peña and García-Larrea, 2007; Cooper et al., 2015; Sadaghiani and Kleinschmidt, 2016), we explored the variability of EEG functional connectivity in the frequency domain at delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz).

HR was estimated from the R–R intervals from EKG filtering using the ECGLAB toolbox for MATLAB (de Carvalho et al., 2002). Cardiac autonomic activity was obtained from power spectral analysis of the R–R interval, named HRV by KARDIA software (Perakakis et al., 2010). We calculated the following HRV measures: high frequency (HF), low frequency (LF), very low frequency (VLF), RMSSD, and standard deviation of NN intervals (SDNN).

Variability in Resting-State Functional Connectivity

EEG variability functional connectivity analysis was conducted with a MATLAB self-programmed script. The procedure used to study RSVFC was as follows. First, coherence was calculated as the functional connectivity index (FC) in each frequency band (delta, theta, alpha and beta). This index measures the linear correlation between two EEG signals, x(t) and y(t), as a function of the frequency, f. Thus, coherence (C) is the ratio of the cross-power spectral density, *Sxy(f)*, between both signals and their individual power spectral densities, *Sxx(f)* and *Syy(f)*:

$$C_{xy}(f) = \frac{S_{xy}(f)}{\sqrt{S_{xx}(f)S_{yy}(f)}} \quad (1)$$

To reject spurious correlations between cortical sources, the imaginary part of coherence (IC) was extracted. The IC was

calculated in each EEG epoch between pairs of electrodes, yielding 435 links.

Finally, the variability of IC was calculated across 180 epochs in each frequency using the sample entropy algorithm (Richman and Moorman, 2000). The sample entropy of FC (SampEn-FC) allows us to obtain the variability of connectivity over time and the interdependencies between pairs of nodes (electrodes) in brain networks. SampEn is the negative logarithm of the conditional probability that two sequences will remain similar at the next point (2) where self-matches are not included in calculating the probability.

$$\mathrm{SampEn}(m, r, N) = -\ln\left[\frac{\mathrm{U}^{m+1}(r)}{U^{m}(r)}\right] \quad (2)$$

Where m is the embedded dimension, r is the tolerance value and N is the time series data. In the current work, $m = 2$ and $r = 0.15$*Standard Deviation.

Statistical Analysis

SampEn-FC, HRV, and CAMBIOS scores were initially checked for a normal distribution by using the Shapiro–Wilk test. Because these measurements significantly deviated from a normal distribution, correlations were assessed by using Spearman correlations.

To study how performance on a switching task is correlated with interindividual RSVFC and with HRV, we analyzed Spearman's correlations between CAMBIOS (Error and Hit scores) and HRV indices (HF, LF, VLF, RMSSD, and SDNN) and between CAMBIOS and SampEn-FC links in each frequency (delta, theta, alpha, and beta). Previous studies have demonstrated that the brain cognitive performance can be functionally divided into two networks: task-positive and task-negative networks (Jia et al., 2014). We built positive and negative networks in each frequency band. The positive network consisted of links with positive correlations between SampEn-FC and CAMBIOS scores. The negative network consisted of links with negative correlations between SampEn-FC and CAMBIOS scores. Finally, SampEn-FC means were obtained from the whole brain in each positive and negative network of all frequency bands, and partial correlations were calculated to measure the degree of association between the SampEn-FC means of the EEG networks, HRV and CAMBIOS scores.

To obtain further insight into the pattern of associations, multiple regression analyses were conducted, with EEG networks (in each frequency band) and HRV indices as predictors and CAMBIOS scores as the dependent variable. Eight separate regression analyses for each task network (positive and negative) and frequency band (delta, theta, alpha, and beta) were computed. A "stepwise" procedure was applied for the entry and removal of predictors. In this method, the predictor which explains the largest part of the variance of the dependent variable is the first to enter the model.

To examine the robustness of the results, we divided the sample into three subgroups according to CAMBIOS scores and carried out a one-way ANOVA to study differences in HRV indices and SampEn-FC. In all analyses involving repeated measures, the Greenhouse–Geisser epsilon correction was applied to control for violation of the sphericity assumption. *Post hoc* pairwise mean comparisons were performed by using Bonferroni correction with a level of significance set at 0.05. All analyses were performed with SPSS v.15.0 (SPSS, Inc., Chicago, IL, United States).

RESULTS

Correlations and Partial Correlations Between the CAMBIOS Test, HRV and SampEn-FCm

Table 1 shows the mean and standard deviation in CAMBIOS scores and HRV indices. The correlations between CAMBIOS and HRV indices revealed significant positive correlations between HF, LF, RMSSD, SDNN and the CAMBIOS Error subscore. No significant correlations between the CAMBIOS Hits subscore and HRV indices were found (**Figure 1**).

Correlation analysis between the SampEn-FC of pairs of electrodes and the Error subscore of the CAMBIOS test revealed two networks for each frequency band (delta, theta, alpha, and beta). The positive network was composed of links that were positively correlated with the Error subscore, and the negative network was composed of links that were negatively correlated with the Error subscore (**Figure 2**). The beta band showed more links correlated with the Error subscore (negative correlations 21/positive correlations 35), followed by theta (15/24), alpha (14/24), and delta (7/25) (**Table 2**). Because the aim of this research was to study the relation between HRV, SampEn-FC and performance, the Hits subscore correlation was not obtained because HRV indices were not correlated in the previous analysis.

Because previous studies indicated that executive functions are positively correlated with frontal connectivity (Fox et al., 2006; Seeley et al., 2007), SampEn-FC means (SampEn-FCm) were calculated by averaging the electrodes for the positive and negative networks obtained for each frequency band. Six regions of interest were obtained by grouping the following electrodes: frontal (Fp1, FPz, Fp2, F7, F3, Fz, F4, and F8), central (Fc5, Fc1, FCz, Fc2, Fc6, C3, Cz, and C4), temporal left (T7), temporal right (T8), parietal (Cp5, Cp1, CPz, Cp2, Cp6, P7, P3, Pz, P4, and P8), and occipital (O1 and O2). One-way ANOVA with repeated measures was used to compare differences in SampEn-FCm in each region in the positive and negative networks in each frequency band. No significant differences in functional connectivity variability were found between different regions in the positive [delta $F(3, 99) = 0.26$, $p > 0.05$; $\eta_p^2 = 0.01$; theta $F(4, 132) = 0.685$, $p > 0.05$; $\eta_p^2 = 0.02$; alpha $F(3, 99) = 0.506$, $p > 0.05$;

TABLE 1 | Means and standard deviations (SD) of CAMBIOS and HRV indices.

	Hits	Errors	HF	LF	VLF	RMSSD	SDNN
Mean	0.597	0.123	218.524	288.576	185.669	45.314	59.456
SD	0.205	0.095	206.622	256.571	164.945	22.212	18.911

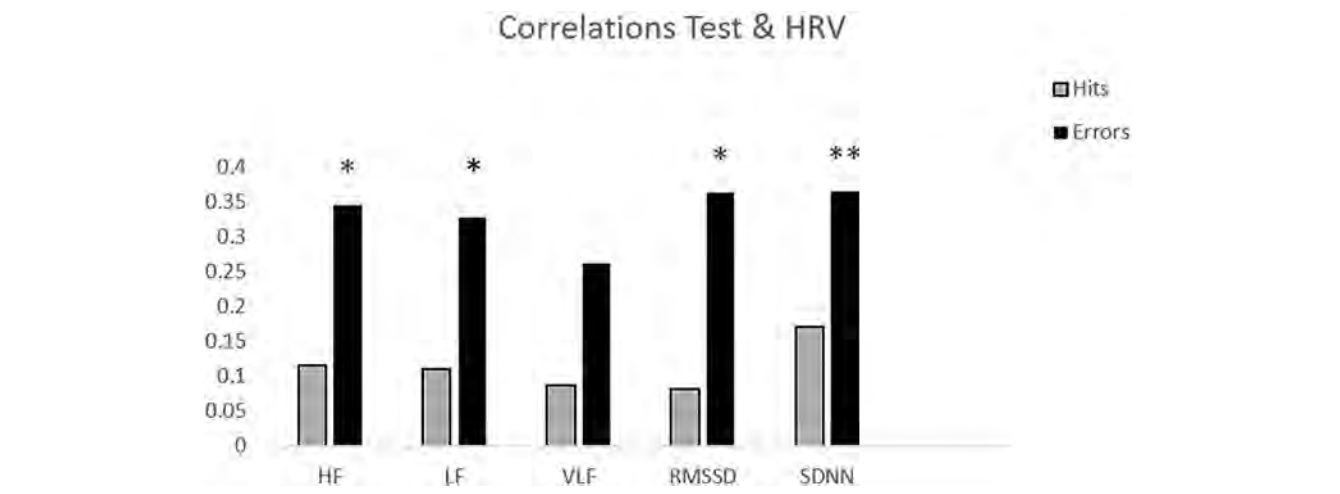

FIGURE 1 | Bar chart of the correlations between HRV measures and subscores on CAMBIOS (corrects and errors). $*p < 0.05$; $**p < 0.01$ (two-tailed).

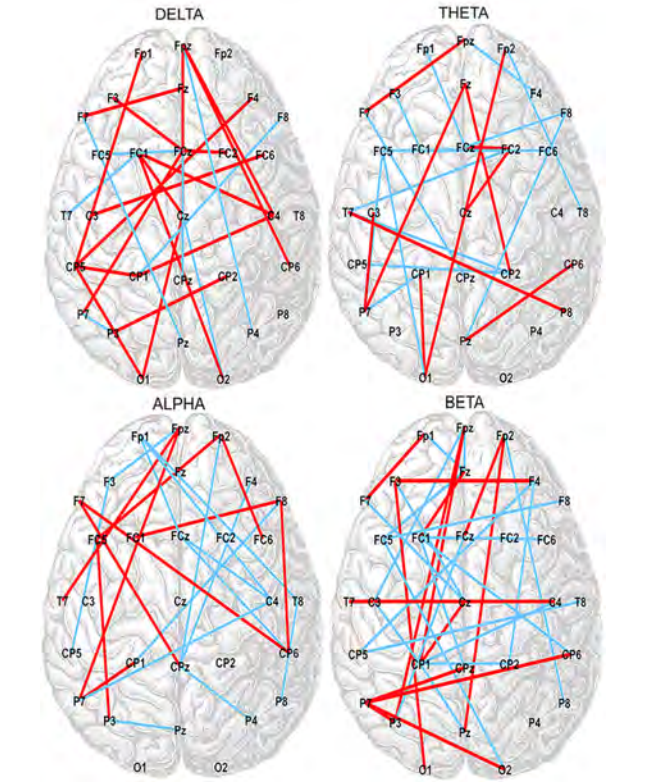

FIGURE 2 | Positive (red lines) and negative (blue lines) correlations between SampEn-FC and Error subscore on the CAMBIOS test for delta, theta, alpha, and beta frequency bands.

$\eta_p^2 = 0.02$; beta $F(4, 132) = 0.821$, $p > 0.05$; $\eta_p^2 = 0.02$] or negative network [delta $F(4, 132) = 1.67$, $p > 0.05$; $\eta_p^2 = 0.05$; theta $F(5, 165) = 1.74$, $p > 0.05$; $\eta_p^2 = 0.05$; alpha $F(3, 99) = 0.07$, $p > 0.05$; $\eta_p^2 = 0.002$; beta $F(4, 132) = 0.06$, $p > 0.05$; $\eta_p^2 = 0.003$].

Next, the SampEn-FCm of the whole brain was calculated from the positive and negative networks in each frequency band. In the positive network, the SampEn-FCm values were 2.531 in delta, 2.549 in theta, 2.538 in alpha, and 2.549 in beta. In the negative network, the SampEn-FCm values were 2.526 in delta, 2.578 in theta, 2.553 in alpha, and 2.523 in beta.

Figure 3 displays the Spearman correlations and partial correlations between HRV, SampEn-FCm and the Error subscore in all frequency bands. The SampEn-FCm values in the delta band and alpha band showed significant correlations with LF, SDNN and the Error subscore in the positive network (**Figure 3A**). The SampEn-FCm of the theta band correlated with RMSSD, while the Error subscore and SampEn-FCm of the beta band correlated with the Error subscore. In the negative network (**Figure 3B**), the SampEn-FCm values of the delta band and theta band correlated with SDNN and the Error subscore, that of the beta band correlated with HF, LF, SDNN and the Error subscore, and that of the alpha band correlated only with the Error subscore.

All frequency bands showed significant positive and negative correlations between SampEn-FCm and the Error subscore when HRV indices were partialled out. In contrast to results obtained for other frequency bands, partial correlations showed significant negative correlations between SampEn-FCm and SDNN when the CAMBIOS test was partialled out in the beta band.

In general, HRV indices and Error subscore correlations were weakened when the SampEn-FCm was partialled out. Similarly, HRV indices and SampEn-FCm correlations were weakened when the Error subscore was partialled out. However, SampEn-FCm and the Error subscore correlation did not decline when HRV indices were partialled out.

Multiple Linear Regressions

Table 3 displays the standardized beta weights resulting from the stepwise regression analyses. The positive network in the delta and alpha bands and the HRV indices used as predictors revealed a single model, in which SampEn-FCm directly predicted the

TABLE 2 | Correlations between the SampEn-FC of pairs of electrodes and the Error subscore.

Delta		Theta		Alpha		Beta	
Links	**Rho**	**Links**	**Rho**	**Links**	**Rho**	**Links**	**Rho**
Fp1-Cp5	0.348	Fp1-FCz	−0.365	Fp1-C4	−0.435	Fp1-F7	0.367
F7-Fz	0.351	Fp2-T8	−0.355	Fp1-FCz	−0.545	Fp1-Fz	−0.440
F7-Pz	−0.341	Fp2-O1	0.414	Fp1-T8	−0.455	Fp2-FCz	0.344
F3-FCz	0.438	F7-CPz	−0.358	Fp2-Fc5	0.415	Fp2-Pz	0.418
F4-Cp5	0.387	F7-FPz	0.452	Fp2-Fc6	0.403	Fp2-P8	−0.345
F8-Cp5	−0.352	F3-Fc1	−0.368	Fp2-CPz	−0.347	F7-Cz	−0.417
Fc5-FCz	−0.369	Fz-Cp2	0.362	F7-CPz	0.345	F3-F4	0.401
Fc1-Cz	0.478	Fz-P7	0.412	F7-Cp6	0.486	F3-Cz	−0.384
Fc1-C4	0.388	F4-FPz	−0.392	F3-Cp5	−0.385	F3-O1	0.359
Fc1-O2	0.349	F8-FCz	−0.455	F3-FPz	−0.523	Fz-Fc5	−0.496
Fc2-FCz	0.621	F8-Pz	−0.549	F4-CPz	−0.371	Fz-Fc1	0.342
Fc6-C3	0.451	Fc5-Fc2	−0.356	F8-Fc1	0.444	Fz-FPz	−0.386
Cz-O1	0.498	Fc5-Fc6	−0.373	F8-Cp1	−0.384	F4-Cp5	−0.409
Cz-FPz	0.435	Fc5-P7	−0.403	F8-Cp6	0.353	F4-Cp2	−0.435
Cz-O2	−0.349	Fc5-O1	−0.426	Fc5-P3	0.421	F8-Fc5	−0.393
C4-Cp1	0.370	Fc2-T7	−0.417	T7-FPz	0.381	Fc5-O2	−0.345
C4-FPz	0.431	Fc2-Cz	0.423	C4-FCz	−0.368	Fc1-Fc6	−0.400
FCz-CPz	−0.463	Fc2-FCz	0.358	C4-P7	−0.372	Fc1-CPz	−0.456
FCz-P7	0.355	T7-Cp2	−0.366	FCz-Cp6	−0.459	Fc1-Cp6	−0.421
Cp5-Cp1	0.403	T7-P8	0.504	T8-P8	−0.420	T7-Cz	0.375
Cp5-O1	0.386	Cp5-Cp2	−0.397	Cp1-P7	0.342	C3-Cz	−0.389
Cp2-P3	0.423	Cp1-P7	−0.421	CPz-P4	−0.343	C3-C4	0.469
Cp6-FPz	0.348	Cp1-O1	0.408	P7-FPz	0.426	C3-Cp1	−0.396
P7-P3	−0.375	Cp6-Pz	0.416	P3-Pz	−0.379	C3-FPZ	−0.376
P4-FPz	−0.415					C4-Cp1	−0.386
						FCz-P3	−0.342
						T8-Cp5	−0.373
						Cp1-Cp2	−0.448
						Cp1-Pz	−0.355
						Cp1-FPz	0.345
						CPz-P7	0.367
						Cp6-P7	0.381
						P7-P3	0.350
						P7-O2	0.382
						P3-FPz	0.374

number of errors in the CAMBIOS test. Moreover, the positive network in the theta and beta bands and the HRV indices used as predictors showed that SampEn-FCm and LF directly predicted the Errors subscore. The negative network in the theta, alpha and beta and the HRV indices used as predictors revealed a single model, in which SampEn-FCm inversely predicted the Errors subscore. Furthermore, the negative network in the delta band and the HRV indices used as predictors showed that SampEn-FCm inversely predicted the Errors subscore, while RMSSD directly predicted the Errors subscore.

Inter-Group Differences

To test differences in RSVFC networks and HRV between participants with high, medium and low performance in the switching task, we divided the sample into three subgroups according to the distribution of the sample in terms of CAMBIOS Error scores (low-, medium-, and high-error groups).

The ANOVA results for HRV indices revealed significant effects of group on LF [$F(2, 31) = 4.35$, $p < 0.05$; $\eta_p^2 = 0.219$] and SDNN [$F(2, 31) = 5.43$, $p < 0.01$; $\eta_p 2 = 0.260$]. Bonferroni tests comparing the CAMBIOS Error scores between the three groups showed significant differences between the low and high-error groups in both HRV indices (all $p < 0.05$). No significant differences were found between the medium-error group and the other two groups. **Figure 4A** depicts the HF, LF, RMSSD, and SDNN indices corresponding to each group of CAMBIOS Error score stimuli. As shown, the high-error group showed more LF and SDNN power than did the low-error group.

ANOVAs for SampEn-FC means across four frequency bands in the positive network yielded significant differences in delta [$F(2, 31) = 35.27$, $p < 0.001$; $\eta_p^2 = 0.695$], theta [$F(2, 31) = 15.81$, $p < 0.001$; $\eta p^2 = 0.505$], alpha [$F(2, 31) = 43.87$, $p < 0.001$; $\eta_p^2 = 0.739$] and beta [$F(2, 31) = 19.29$, $p < 0.001$; $\eta_p^2 = 0.554$]. As shown in **Figure 4B**, the Bonferroni test revealed that the high-error group had a higher SampEn-FC mean than the low-error group ($p < 0.001$).

Finally, ANOVAs for SampEn-FC means across the frequency bands in the negative network yielded significant differences in delta [$F(2,31) = 9.83, p < 0.001; \eta_p^2 = 0.388$], theta [$F(2,31) = 15.95$, $p < 0.001; \eta_p^2 = 0.507$], alpha [$F(2,31) = 33.18, p < 0.001; \eta_p^2 = 0.682$] and beta [$F(2, 31) = 46.74$, $p < 0.001$; $\eta_p^2 = 0.751$]. The *post hoc* comparations yielded significant differences between the high-error group and low-error group in terms of the SampEn-FC mean ($p < 0.001$; **Figure 4C**) and between the medium-error group and the low-error group ($p < 0.05$).

DISCUSSION

The aim of the present study was to determine whether individual functional connectivity variability in the resting state (RSVFC) and HRV predicted performance on a cognitive task. Our results confirm that HRV significantly correlated with performance on tasks that involved cognitive flexibility. Moreover, RSVFC correlated with performance on the tasks in all frequency bands. However, partial correlation showed that the correlation of heart rate fluctuations with cognitive flexibility was indirect and was mediated by functional connectivity variability, while the correlation between functional connectivity variability and task performance remained significant when the heart rate fluctuation index was partialled out. Finally, these results were confirmed when participants were divided into three subgroups according to their behavioral performance on the task. Significant differences were found between the high-performance and low-performance test subgroups on RSVFC, LF, and SDNN indices.

The CAMBIOS test assesses the ability to concentrate while attending to several changing conditions, e.g., the cognitive flexibility to determine if different changes are fulfilled and the speed of this process (Contreras et al., 2003). Our results revealed positive correlations between HRV (HF, LF, RMSSD, and SDNN) and the Error subscore of the CAMBIOS test and between CAMBIOS test performance and functional connectivity

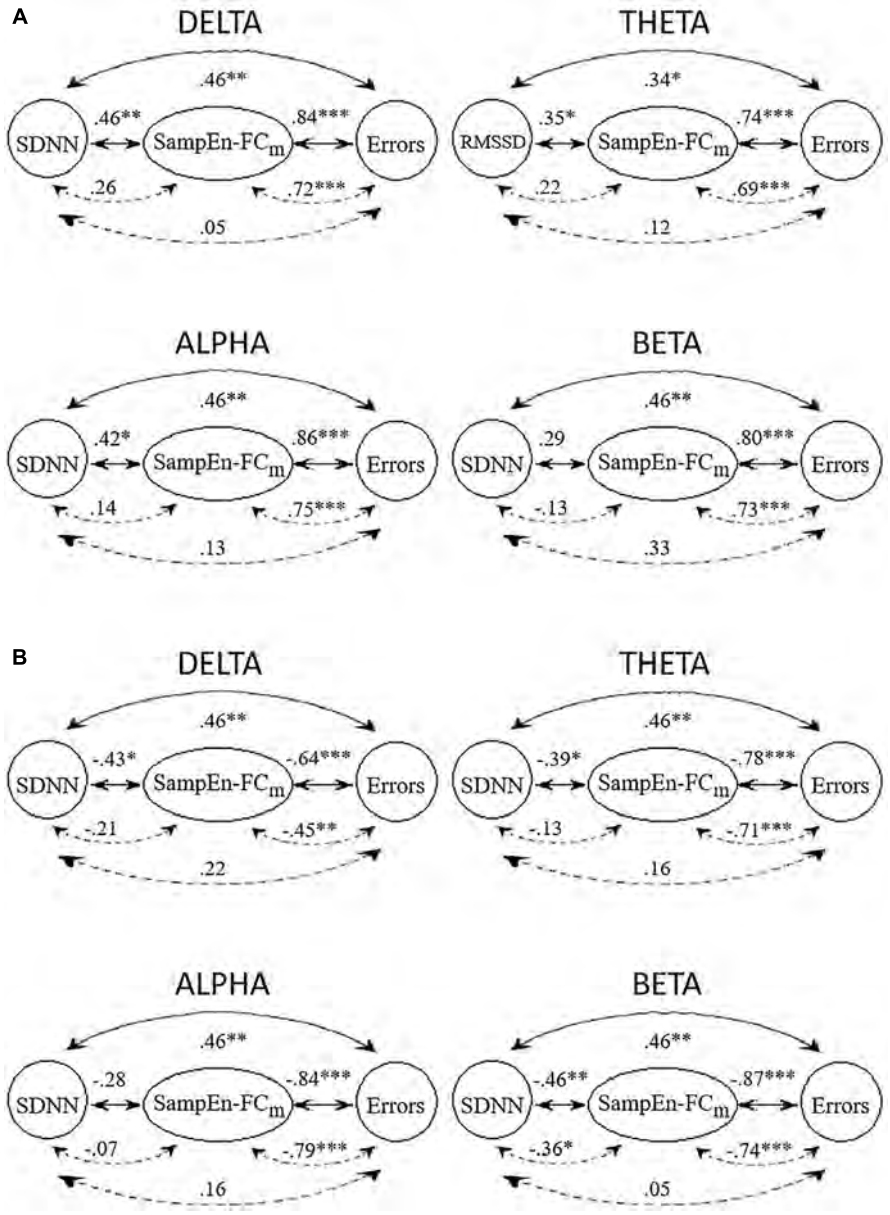

FIGURE 3 | Correlations (full lines) and partial correlations (broken lines) among HRV index with higher significant correlations with the SampEn-FCm of positive networks **(A)** and negative networks **(B)** and Error subscore in delta, theta, alpha, and beta frequency bands. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ (two-tailed).

variability in the resting state. These results are inconsistent with the classic assumption of an association between higher levels of cardiac vagal tone and cognitive performance (Albinet et al., 2010, 2016; Stenfors et al., 2016). Several studies found a positive correlation between higher levels of cardiac vagal tone and the number of errors on a cognitive task and between HRV indices and attentional function during both resting and task periods (Duschek et al., 2009; Hovland et al., 2012). Duschek et al. (2009) hypothesized that difficult tasks or tasks executed under time pressure demand higher energetic resources. Thus, the degree of central activation depends on the difficulty of the task, and the association between resting HRV and executive function depends on the requirements of the cognitive test. Therefore, the inverse association between resting HRV and CAMBIOS performance suggests that a pattern of cardiovascular adjustment, including enhanced sympathetic and reduced vagal cardiovascular influences, may induce an adaptive state associated with improved cognitive flexibility functioning.

The relationship between functional connectivity variability in the resting state and CAMBIOS test performance revealed two distinct networks; one network comprises regions that presented positive correlations between variability and the task Error subscore, while other regions exhibited negative correlations.

TABLE 3 | Regression analyses for the prediction of the Error subscore from the physiological parameters assessed during rest (standardized beta weights).

Positive network	Error subscore	Negative network	Error subscore
Delta		**Delta**	
SampEn-FCm	0.764***	SampEn-FCm	−0.518**
HF	0.095	HF	0.289
LF	0.017	LF	0.173
RMSSD	0.137	RMSSD	0.322*
SDNN	0.044	SDNN	0.217
Theta		**Theta**	
SampEn-FCm	0.742***	SampEn-FCm	−0.742***
HF	0.131	HF	0.177
LF	0.258*	LF	0.161
RMSSD	0.091	RMSSD	0.154
SDNN	0.171	SDNN	0.140
Alpha		**Alpha**	
SampEn-FCm	0.787***	SampEn-FCm	−0.817***
HF	0.168	HF	0.145
LF	0.069	LF	0.077
RMSSD	0.164	RMSSD	0.183
SDNN	0.082	SDNN	0.121
Beta		**Beta**	
SampEn-FCm	0.733***	SampEn-FCm	−0.779***
HF	0.207	HF	0.058
LF	0.249*	LF	0.035
RMSSD	0.215	RMSSD	0.117
SDNN	0.226	SDNN	0.001

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ (two-tailed).

No significant differences were found in functional connectivity variability between the electrode groups of interest (frontal, central, temporal left, temporal right, parietal, and occipital) in either network in each frequency band. Previous studies indicated more dynamic connectivity of the fronto-parietal localization in response to different frequency ranges during cognitive task performance, and this connectivity is related to better cognitive performance (González-Hernández et al., 2002; Fornito et al., 2012; Cole et al., 2013; Monti et al., 2014; Beatty et al., 2015; Vatansever et al., 2015). However, research on the dynamic connectivity between the fronto-parietal localization in the resting state with respect to the prediction of cognitive functioning yields mixed results. Both positive and negative correlations between resting-state dynamic connectivity and cognitive performance have been reported (Jia et al., 2014; Kucyi and Davis, 2014; Sadaghiani et al., 2015). Our results yielded no differences in variability between the electrode groups of interest and rhythms in resting states in relation to the performance task. Although this result could be due to the low spatial resolution of EEG, multiple brain regions are activated in parallel, and these regions do not generally display pure oscillations in resting conditions (Mantini et al., 2007; de Pasquale et al., 2010; Tagliazucchi et al., 2012). In fact, spontaneous brain activity in the resting state is organized in a finite set of spatiotemporal patterns that are linked to EEG brain rhythms (Mantini et al., 2007). Conversely, a combination of delta, theta, alpha, beta, and gamma rhythms are ascribed to brain networks during the resting state. This information leads us to think that high variability between cortical localization and rhythms could facilitate flexibility in adapting processing to changing tasks. The variability of functional connectivity is higher in healthy adults (showing better performance in cognitive tasks) than in older adults who show worse cognitive performance (McIntosh et al., 2008, 2010; Garrett et al., 2011), and default mode network connectivity (a network activated in the resting state Laufs et al., 2003; Raichle and Snyder, 2007) makes the greatest contribution to executive function/cognitive flexibility prediction (Liu et al., 2018). Our results suggest that the levels of variability in connectivity between localization are related to the effectiveness of performance and suggest beneficial effects of higher brain signal variability in general.

Very compelling evidence suggests that HRV is an indicator of the adaptation of the ANS to a variety of psychological and behavioral situations (Thayer et al., 2010; Zahn et al., 2016). Higher HRV is associated with performance on several cognitive tasks involving attention, working memory, and inhibitory control (Thayer et al., 2005; Duschek et al., 2009; Hovland et al., 2012). Similarly, direct correlations show that HRV or functional connectivity networks in the resting state are related to cognitive performance (Hansen et al., 2003; Saus et al., 2006; Chang et al., 2013b; Thompson et al., 2016). Our results revealed that HRV and RSVFC were related to the CAMBIOS performance, however, partial correlations revealed that RSVFC in all frequency ranges mediated the relationship between HRV and the cognitive test. Regression analyses indicated that RSVFC accounted for the largest portion of CAMBIOS performance variance in all frequencies. Although direct correlations among cognitive flexibility, neuronal and heartbeat variability are significant, partial correlations and multiple linear regressions suggest that the relation between heartbeat and cognitive performance is mediated by neuronal oscillations. Palva et al. (2013) found similar results using power-law form, long-range, temporal correlations in the resting state and during stimulus detection tasks. Moreover, neuronal networks that correlated with performance in the resting state were similar to networks during the task. Our results extend these findings to cognitive performance, suggesting that the levels of brain signal variability might predict cognitive flexibility in a cognitive task.

ANOVA confirmed that HRV and functional connectivity variability are associated with cognitive performance. The results yielded significant differences among the high-, medium- and low-Error subscore groups in LF and SDNN indices and RSVFC (positive and negative networks). Thus, participants with more errors on the CAMBIOS test showed more LF and SDNN, more variability in the positive network and less variability in the negative network in all frequency ranges. Other studies have compared resting HRV (Hansen et al., 2004; Albinet et al., 2010, 2016) and the variability of functional connectivity (Takeuchi et al., 2011; Martínez et al., 2013; Thompson et al., 2016) between groups with high and low cognitive performance using ANOVA. Higher resting HRV predicts good performance in cognitive tasks (Albinet et al., 2016; Stenfors et al., 2016). However, some studies suggest that the classic assumption of

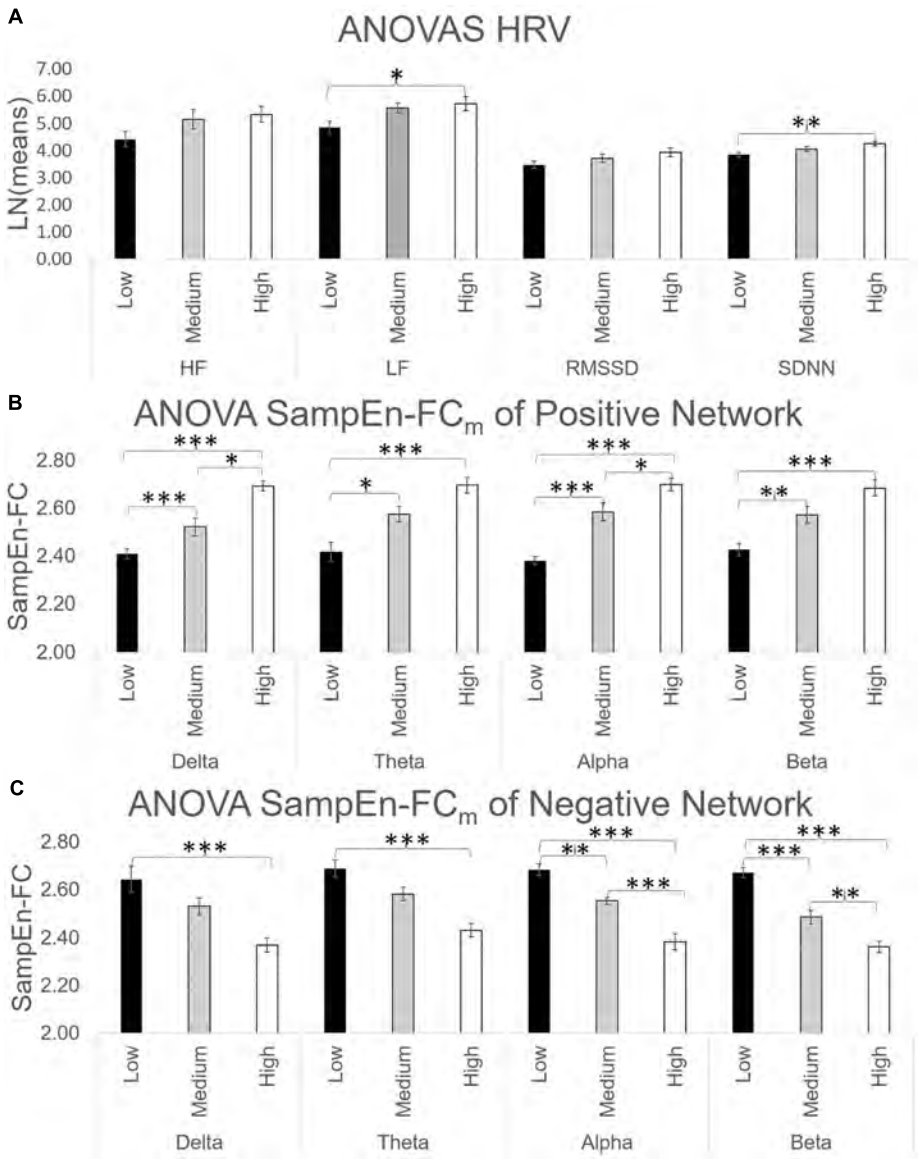

FIGURE 4 | (A) ANOVA of HF, LF, RMSSD, and SDNN indices. The HRV indices were log-transformed to equalize the scales. **(B)** ANOVA of SampEn-FCm of positive networks obtained in **Figure 2** for all frequency bands. **(C)** ANOVA of SampEn-FCm of negative networks obtained in **Figure 2** for all frequency bands. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ (two-tailed).

an association between higher resting levels of cardiac vagal tone and improved cognitive performance does not universally hold true. Thus, Hovland et al. (2012) found that HF-HRV in the resting state was positively correlated with the total errors and perseverative errors in the Wisconsin Card Sorting Test and with inhibition errors in the Color-Word Interference Test. Other studies have used batteries of cognitive tests, and they observed that not all tests of the battery correlated with HRV and the resting state (Jennings et al., 2015; Stenfors et al., 2016). The CAMBIOS test is a task with a high cognitive load that assesses the ability to handle a changing condition, similar to the Wisconsin Card Sorting Test, Color-Word Interference Test and Test D2. Duschek et al. (2009) hypothesized that the association between resting HRV and executive function performance may depend on the difficulty of the cognitive test when the brain is challenged. Therefore, more demanding tasks involve more cerebral resources, eliciting more heart rate activity.

In the future, replicating the current study using other cognitive tasks in which resting HRV has positive correlations with the studied hits would be interesting. For example, a continuous performance test or working memory test could be used because in these tasks, a high HRV group showed a faster mean reaction time, more correct responses and fewer errors than a low HRV group (Hansen et al., 2003, 2004). Partial correlations between HRV and these tasks when neuronal

oscillations are partialled out have not been studied. The current study could be replicated using different cognitive tasks if interconnections between the CNS and ANS are influenced by the type of task.

In this study, the analysis of EEG sources was not possible because 32 electrodes were insufficient for the accurate localization of EEG sources (Lantz et al., 2003). Future studies should include EEG systems with more electrodes and source localization analysis. Source localization methods allow quantitative prediction of the locations of EEG activity inside the brain. Thus, EEG source localization analysis is necessary for determining brain areas related to cognitive performance and heart rate oscillations with enhanced accuracy.

The neurovisceral model proposes that the relationship between the CNS and ANS is reciprocally interconnected such that information flows bidirectionally (Thayer and Lane, 2009; Smith et al., 2017). Our results seem to show that HRV, functional connectivity variability and cognitive flexibility are related between the CNS and ANS. Nevertheless, the relationship between HRV and cognitive performance is determined by the type of task and mediated by the functional connectivity variability of the brain. More studies using different cognitive tasks and paradigms are necessary to establish causal relations between these variables.

AUTHOR CONTRIBUTIONS

GA, JV, BR, PM, and MM contributed significantly to the design of the study. GA performed the data collection. GA and MM performed the data analysis and wrote most of the manuscript. and JV, BR, and PM critically revised important parts of the manuscript.

FUNDING

This work was supported by the Spanish Ministry of Economy and Competitiveness (PSI2014-57231-R). Research was funded by Grant Nos. PSI2014-57231-R and PSI2017-88388-C4-3-R from Spanish Ministry of Science. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have declared that no competing interests exist.

REFERENCES

Alba, G., Pereda, E., Mañas, S., Méndez, L. D., Duque, M. R., González, A., et al. (2016). The variability of EEG functional connectivity of young ADHD subjects in different resting states. *Clin. Neurophysiol.* 127, 1321–1330. doi: 10.1016/j.clinph.2015.09.134

Albinet, C. T., Abou-Dest, A., André, N., and Audiffren, M. (2016). Executive functions improvement following a 5-month aquaerobics program in older adults: role of cardiac vagal control in inhibition performance. *Biol. Psychol.* 115, 69–77. doi: 10.1016/j.biopsycho.2016.01.010

Albinet, C. T., Boucard, G., Bouquet, C. A., and Audiffren, M. (2010). Increased heart rate variability and executive performance after aerobic training in the elderly. *Eur. J. Appl. Physiol.* 109, 617–624. doi: 10.1007/s00421-010-1393-y

Allen, E. A., Damaraju, E., Plis, S. M., Erhardt, E. B., Eichele, T., and Calhoun, V. D. (2014). Tracking whole-brain connectivity dynamics in the resting state. *Cereb. Cortex* 24, 663–676. doi: 10.1093/cercor/bhs352

Barttfeld, P., Petroni, A., Báez, S., Urquina, H., Sigman, M., Cetkovich, M., et al. (2014). Functional connectivity and temporal variability of brain connections in adults with attention deficit/hyperactivity disorder and bipolar disorder. *Neuropsychobiology* 69, 65–75. doi: 10.1159/000356964

Beatty, E. L., Jobidon, M.-E., Bouak, F., Nakashima, A., Smith, I., Lam, Q., et al. (2015). Transfer of training from one working memory task to another: behavioural and neural evidence. *Front. Syst. Neurosci.* 9:86. doi: 10.3389/fnsys.2015.00086/abstract

Botcharova, M., Farmer, S. F., and Berthouze, L. (2014). Markers of criticality in phase synchronization. *Front. Syst. Neurosci.* 8:176. doi: 10.3389/fnsys.2014.00176/abstract

Cañas, J. J., Quesada, J. F., Antolí, A., and Fajardo, I. (2003). Cognitive flexibility and adaptability to environmental changes in dynamic complex problem solving tasks. *Ergonomics* 46, 482–501. doi: 10.1080/0014013031000061640

Carrillo-de-la-Peña, M. T., and García-Larrea, L. (2007). Right frontal event related EEG coherence (ERCoh) differentiates good from bad performers of the Wisconsin Card Sorting Test (WCST). *Neurophysiol. Clin.* 37, 63–75. doi: 10.1016/j.neucli.2007.02.002

Catarino, A., Churches, O., Baron-Cohen, S., Andrade, A., and Ring, H. (2011). Atypical EEG complexity in autism spectrum conditions: a multiscale entropy analysis. *Clin. Neurophysiol.* 122, 2375–2383. doi: 10.1016/j.clinph.2011.05.004

Chang, C., Liu, Z., Chen, M. C., Liu, X., and Duyn, J. H. (2013a). EEG correlates of time-varying BOLD functional connectivity. *Neuroimage* 72, 227–236. doi: 10.1016/j.neuroimage.2013.01.049

Chang, C., Metzger, C. D., Glover, G. H., Duyn, J. H., Heinze, H. J., and Walter, M. (2013b). Association between heart rate variability and fluctuations in resting-state functional connectivity. *Neuroimage* 68, 93–104. doi: 10.1016/j.neuroimage.2012.11.038

Chen, Y., Wang, W., Zhao, X., Sha, M., Liu, Y., Zhang, X., et al. (2017). Age-related decline in the variation of dynamic functional connectivity: a resting state analysis. *Front. Aging Neurosci.* 9:203. doi: 10.3389/fnagi.2017.00203

Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., and Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nat. Neurosci.* 16, 1348–1355. doi: 10.1234/12345678

Contreras, M. J., Colom, R., Hernández, J. M., and Santacreu, J. (2003). Is static spatial performance distinguishable from dynamic spatial performance? A latent-variable analysis. *J. Gen. Psychol.* 130, 277–288. doi: 10.1080/00221300309601159

Cooper, P. S., Wong, A. S. W., Fulham, W. R., Thienel, R., Mansfield, E., Michie, P. T., et al. (2015). Theta frontoparietal connectivity associated with proactive and reactive cognitive control processes. *Neuroimage* 108, 354–363. doi: 10.1016/j.neuroimage.2014.12.028

de Carvalho, J. L. A., Da Rocha, A. F., de Oliveira Nascimento, F. A., Neto, J. S., and Junqueira, L. F. (2002). "Development of a matlab software for analysis of heart rate variability," in *Proceedings of the 6th International Conference on Signal Processing*, Vol. 2 (Piscataway, NJ: IEEE), 1488–1491. doi: 10.1109/ICOSP.2002.1180076

de Pasquale, F., Della Penna, S., Snyder, A. Z., Lewis, C., Mantini, D., Marzetti, L., et al. (2010). Temporal dynamics of spontaneous MEG activity in brain networks. *Proc. Natl. Acad. Sci. U.S.A.* 107, 6040–6045. doi: 10.1073/pnas.0913863107

Delorme, A., and Makeig, S. (2004). EEGLAB: an open sorce toolbox for analysis of single-trail EEG dynamics including independent component anlaysis. *J. Neurosci. Methods* 134, 9–21. doi: 10.1016/j.jneumeth.2003.10.009

Dennis, J. P., and Vander Wal, J. S. (2010). The cognitive flexibility inventory: instrument development and estimates of reliability and validity. *Cogn. Ther. Res.* 34, 241–253. doi: 10.1007/s10608-009-9276-4

Duschek, S., Muckenthaler, M., Werner, N., and Reyes del Paso, G. A. (2009). Relationships between features of autonomic cardiovascular control and cognitive performance. *Biol. Psychol.* 81, 110–117. doi: 10.1016/j.biopsycho.2009.03.003

Fornito, A., Harrisona, B. J., Zaleskya, A., and Simonsd, J. S. (2012). Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. *Proc. Natl. Acad. Sci. U.S.A.* 109, 12788–12793. doi: 10.1073/pnas.1204185109

Fox, M. D., Corbetta, M., Snyder, A. Z., Vincent, J. L., and Raichle, M. E. (2006). Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc. Natl. Acad. Sci. U.S.A.* 103, 10046–10051. doi: 10.1073/pnas.0604187103

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., and Raichle, M. E. (2005). From the cover: the human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc. Natl. Acad. Sci. U.S.A.* 102, 9673–9678. doi: 10.1073/pnas.0504136102

Garrett, D. D., Kovacevic, N., McIntosh, A. R., and Grady, C. L. (2011). The importance of being variable. *J. Neurosci.* 31, 4496–4503. doi: 10.1523/JNEUROSCI.5641-10.2011

Geurts, H. M., Corbett, B., and Solomon, M. (2009). The paradox of cognitive flexibility in autism. *Trends Cogn. Sci.* 13, 74–82. doi: 10.1016/j.tics.2008.11.006

Gillie, B. L., and Thayer, J. F. (2014). Individual differences in resting heart rate variability and cognitive control in posttraumatic stress disorder. *Front. Psychol.* 5:758. doi: 10.3389/fpsyg.2014.00758/abstract

González-Hernández, J. A., Pita-Alcorta, C., Cedeno, I., Bosch-Bayard, J., Galán-Garcia, L., Scherbaum, W. A., et al. (2002). Wisconsin card sorting test synchronizes the prefrontal, temporal and posterior association cortex in different frequency ranges and extensions. *Hum. Brain Mapp.* 17, 37–47. doi: 10.1002/hbm.10051

Hansen, A. L., Johnsen, B. H., Sollers, J. J., Stenvik, K., and Thayer, J. F. (2004). Heart rate variability and its relation to prefrontal cognitive function: the effects of training and detraining. *Eur. J. Appl. Physiol.* 93, 263–272. doi: 10.1007/s00421-004-1208-0

Hansen, A. L., Johnsen, B. H., and Thayer, J. F. (2003). Vagal influence on working memory and attention. *Int. J. Psychophysiol.* 48, 263–274. doi: 10.1016/S0167-8760(03)00073-4

Hansen, A. L., Johnsen, B. H., and Thayer, J. F. (2009). Relationship between heart rate variability and cognitive function during threat of shock. *Anxiety Stress Coping* 22, 77–89. doi: 10.1080/10615800802272251

Hovland, A., Pallesen, S., Hammar, Å, Hansen, A. L., Thayer, J. F., Tarvainen, M. P., et al. (2012). The relationships among heart rate variability, executive functions, and clinical variables in patients with panic disorder. *Int. J. Psychophysiol.* 86, 269–275. doi: 10.1016/j.ijpsycho.2012.10.004

Ionescu, T. (2012). Exploring the nature of cognitive flexibility. *New Ideas Psychol.* 30, 190–200. doi: 10.1016/j.newideapsych.2011.11.001

Jennings, J. R., Allen, B., Gianaros, P. J., Thayer, J. F., and Manuck, S. B. (2015). Focusing neurovisceral integration: cognition, heart rate variability, and cerebral blood flow. *Psychophysiology* 52, 214–224. doi: 10.1111/psyp.12319

Jennings, J. R., Sheu, L. K., Kuan, D. C. H., Manuck, S. B., and Gianaros, P. J. (2016). Resting state connectivity of the medial prefrontal cortex covaries with individual differences in high-frequency heart rate variability. *Psychophysiology* 53, 444–454. doi: 10.1111/psyp.12586

Jia, H., Hu, X., and Deshpande, G. (2014). Behavioral relevance of the dynamics of the functional brain connectome. *Brain Connect.* 4, 741–759. doi: 10.1089/brain.2014.0300

Kitzbichler, M. G., Smith, M. L., Christensen, S. R., and Bullmore, E. (2009). Broadband criticality of human brain network synchronization. *PLoS Comput. Biol.* 5:e1000314. doi: 10.1371/journal.pcbi.1000314

Kucyi, A., and Davis, K. D. (2014). Dynamic functional connectivity of the default mode network tracks daydreaming. *Neuroimage* 100, 471–480. doi: 10.1016/j.neuroimage.2014.06.044

Lantz, G., Grave De Peralta, R., Spinelli, L., Seeck, M., and Michel, C. M. (2003). Epileptic source localization with high density EEG: how many electrodes are needed? *Clin. Neurophysiol.* 114, 63–69. doi: 10.1016/S1388-2457(02)00337-1

Laufs, H., Krakow, K., Sterzer, P., Eger, E., Beyerle, A., Salek-Haddadi, A., et al. (2003). Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. *Proc. Natl. Acad. Sci. U.S.A.* 100, 11053–11058. doi: 10.1073/pnas.1831638100

Liu, J., Liao, X., Xia, M., and He, Y. (2018). Chronnectome fingerprinting: identifying individuals and predicting higher cognitive functions using dynamic brain connectivity patterns. *Hum. Brain Mapp.* 39, 902–915. doi: 10.1002/hbm.23890

Mackey, A. P., Miller Singley, A. T., and Bunge, S. A. (2013). Intensive reasoning training alters patterns of brain connectivity at rest. *J. Neurosci.* 33, 4796–4803. doi: 10.1523/JNEUROSCI.4141-12.2013

Malik, M., Bigger, J. T., Camm, A. J., Kleiger, R. E., Malliani, A., Moss, A. J., et al. (1996). Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur. Hear J.* 17, 354–381. doi: 10.1093/oxfordjournals.eurheartj.a014868

Mantini, D., Perrucci, M. G., de Gratta, C., Romani, G. L., and Corbetta, M. (2007). Electrophysiological signatures of resting state networks in the human brain. *Proc. Natl. Acad. Sci. U.S.A.* 104:13170. doi: 10.1073/pnas.0700668104

Martínez, K., Solana, A. B., Burgaleta, M., Hernández-Tamames, J. A., Álvarez-Linera, J., Román, F. J., et al. (2013). Changes in resting-state functionally connected parietofrontal networks after videogame practice. *Hum. Brain Mapp.* 34, 3143–3157. doi: 10.1002/hbm.22129

McDonough, I. M., and Nashiro, K. (2014). Network complexity as a measure of information processing across resting-state networks: evidence from the human connectome project. *Front. Hum. Neurosci.* 8:409. doi: 10.3389/fnhum.2014.00409

McIntosh, A. R., Kovacevic, N., and Itier, R. J. (2008). Increased brain signal variability accompanies lower behavioral variability in development. *PLoS Comput. Biol.* 4:e1000106. doi: 10.1371/journal.pcbi.1000106

McIntosh, A. R., Kovacevic, N., Lippe, S., Garrett, D., Grady, C., and Jirsa, V. (2010). The development of a noisy brain. *Arch. Ital. Biol.* 148, 323–337. doi: 10.4449/aib.v148i3.1224

Mennes, M., Kelly, C., Zuo, X. N., Di Martino, A., Biswal, B. B., Castellanos, F. X., et al. (2010). Inter-individual differences in resting-state functional connectivity predict task-induced BOLD activity. *Neuroimage* 50, 1690–1701. doi: 10.1016/j.neuroimage.2010.01.002

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., and Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn. Psychol.* 41, 49–100. doi: 10.1006/cogp.1999.0734

Mizuno, T., Takahashi, T., Cho, R. Y., Kikuchi, M., Murata, T., Takahashi, K., et al. (2010). Assessment of EEG dynamical complexity in Alzheimer's disease using multiscale entropy. *Clin. Neurophysiol.* 121, 1438–1446. doi: 10.1016/j.clinph.2010.03.025

Monti, R. P., Hellyer, P., Sharp, D., Leech, R., Anagnostopoulos, C., and Montana, G. (2014). Estimating time-varying brain connectivity networks from functional MRI time series. *Neuroimage* 103, 427–443. doi: 10.1016/j.neuroimage.2014.07.033

Palva, J. M., Zhigalov, A., Hirvonen, J., Korhonen, O., Linkenkaer-Hansen, K., and Palva, S. (2013). Neuronal long-range temporal correlations and avalanche dynamics are correlated with behavioral scaling laws. *Proc. Natl. Acad. Sci. U.S.A.* 110, 3585–3590. doi: 10.1073/pnas.1216855110

Perakakis, P., Joffily, M., Taylor, M., Guerra, P., and Vila, J. (2010). KARDIA: a matlab software for the analysis of cardiac interbeat intervals. *Comput. Methods Progr.* 98, 83–89. doi: 10.1016/j.cmpb.2009.10.002

Pumprla, J., Howorka, K., Groves, D., Chester, M., and Nolan, J. (2002). Functional assessment of heart rate variability: physiological basis and practical applications. *Int. J. Cardiol.* 84, 1–14. doi: 10.1016/S0167-5273(02)00057-8

Raichle, M. E., and Snyder, A. Z. (2007). A default mode of brain function: a brief history of an evolving idea. *Neuroimage* 37, 1083–1090. doi: 10.1016/j.neuroimage.2007.02.041

Ramon, C., and Holmes, M. D. (2013). Noninvasive localization of epileptic sites from stable phase synchronization patterns on different days derived from short duration interictal scalp dEEG. *Brain Topogr.* 26, 1–8. doi: 10.1007/s10548-012-0236-z

Richman, J. S., and Moorman, J. R. (2000). Physiological time-series analysis using approximate entropy and sample entropy. *Am. J. Physiol. Hear Circ. Physiol.* 278, H2039–H2049. doi: 10.1152/ajpheart.2000.278.6.H2039

Sadaghiani, S., and Kleinschmidt, A. (2016). Brain networks and α-oscillations: structural and functional foundations of cognitive control. *Trends Cogn. Sci.* 20, 805–817. doi: 10.1016/j.tics.2016.09.004

Sadaghiani, S., Poline, J.-B., Kleinschmidt, A., and D'Esposito, M. (2015). Ongoing dynamics in large-scale functional connectivity predict perception. *Proc. Natl. Acad. Sci. U.S.A.* 112, 8463–8468. doi: 10.1073/pnas.1420687112

Sakaki, M., Yoo, H. J., Nga, L., Lee, T. H., Thayer, J. F., and Mather, M. (2016). Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. *Neuroimage* 139, 44–52. doi: 10.1016/j.neuroimage.2016.05.076

Saus, E.-R., Johnsen, B. H., Eid, J., Riisem, P. K., Andersen, R., and Thayer, J. F. (2006). The effect of brief situational awareness training in a police shootingsimulator: an experimentalstudy. *Mil. Psychol.* 18, 3–22. doi: 10.1207/s15327876mp1803s_2

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., et al. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci.* 27, 2349–2356. doi: 10.1523/JNEUROSCI.5587-06.2007

Seisdedos, N. (2004). *CAMBIOS Test de Flexibilidad Cognitiva*. Madrid: TEA Ediciones.

Smith, R., Thayer, J. F., Khalsa, S. S., and Lane, R. D. (2017). The hierarchical basis of neurovisceral integration. *Neurosci. Biobehav. Rev.* 75, 274–296. doi: 10.1016/j.neubiorev.2017.02.003

Stenfors, C. U. D., Hanson, L. M., Theorell, T., and Osika, W. S. (2016). Executive cognitive functioning and cardiovascular autonomic regulation in a population-based sample of working adults. *Front. Psychol.* 7:1536. doi: 10.3389/fpsyg.2016.01536

Tagliazucchi, E., Balenzuela, P., Fraiman, D., and Chialvo, D. R. (2012). Criticality in large-scale brain fmri dynamics unveiled by a novel point process analysis. *Front. Physiol.* 3:15. doi: 10.3389/fphys.2012.00015

Takeuchi, H., Taki, Y., Hashizume, H., Sassa, Y., Nagase, T., Nouchi, R., et al. (2011). Effects of training of processing speed on neural systems. *J. Neurosci.* 31, 12139–12148. doi: 10.1523/JNEUROSCI.2948-11.2011

Thayer, J. F., Hansen, A. L., and Johnsen, B. H. (2010). "The non-invasive assessment of autonomic influences on the heart using impedance cardiography and heart rate variability," in *Handbook of Behavioral Medicine* (New York, NY: Springer), 723–740. doi: 10.1007/978-0-387-09488-5_47

Thayer, J. F., Hansen, A. L., Sollers, I. I. I. J. J., and Johnsen, B. H. (2005). "Heart rate variability as an index of prefrontal neural function in military settings," in *Proceedings of the Biomonitoring for Physiological and Cognitive Performance During Military Operations* (Bellingham: SPIE) doi: 10.1117/12.604420

Thayer, J. F., and Lane, R. D. (2009). Claude bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. *Neurosci. Biobehav. Rev.* 33, 81–88. doi: 10.1016/j.neubiorev.2008.08.004

Thayer, J. F., Ruiz-Padial, E., Hansen, A. L., and Johnsen, B. H. (2004). Autonomic nervous system activity and its relationship to attention and working memory. *Int. J. Psychophysiol.* 54, 19–19.

Thompson, T. W., Waskom, M. L., and Gabrieli, J. D. (2016). Intensive working memory training produces functional changes in large-scale frontoparietal networks. *J. Cogn. Neurosci.* 28, 575–588. doi: 10.1162/jocn_a_00916

Vakorin, V. A., Lippe, S., and McIntosh, A. R. (2011). Variability of brain signals processed locally transforms into higher connectivity with brain development. *J. Neurosci.* 31, 6405–6413. doi: 10.1523/JNEUROSCI.3153-10.2011

Vatansever, D., Menon, D. K., Manktelow, A. E., Sahakian, B. J., and Stamatakis, E. A. (2015). Default mode network connectivity during task execution. *Neuroimage* 122, 96–104. doi: 10.1016/j.neuroimage.2015.07.053

Yang, A. C., Huang, C. C., Yeh, H. L., Liu, M. E., Hong, C. J., Tu, P. C., et al. (2013). Complexity of spontaneous BOLD activity in default mode network is correlated with cognitive function in normal male elderly: a multiscale entropy analysis. *Neurobiol. Aging* 34, 428–438. doi: 10.1016/j.neurobiolaging.2012.05.004

Zahn, D., Adams, J., Krohn, J., Wenzel, M., Mann, C. G., Gomille, L. K., et al. (2016). Heart rate variability and self-control–a meta-analysis. *Biol. Psychol.* 115, 9–26. doi: 10.1016/j.biopsycho.2015.12.007

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ESTUDIO 2

Alba, G., Vila, J., Miranda, J.G.V., Montoya, P. & Muñoz, M. A. (2021) Tonic pain reduces the autonomic responses and EEG functional connectivity elicited by affective stimuli. *The Journal of Pain*. (En revisión)

Alba, G., Vila, J., Miranda, J.G.V., Montoya, P. & Muñoz, M. A. (2021) Tonic pain reduces the autonomic responses and EEG functional connectivity elicited by affective stimuli. *The Journal of Pain*. (En revisión)

Tonic pain reduces the autonomic responses and electroencephalographic functional connectivity elicited by affective stimuli

Guzmán Alba[1], Jaime Vila.[1], José G. V. Miranda[2], Pedro Montoya[3] & Miguel A. Muñoz[1]

1 Brain, Mind and Behavior Research Center at University of Granada (CIMCYC-UGR), Spain

2 Institute of Physics, Laboratory of Biosystems, Federal University of Bahia, Salvador, Bahia, Brazil

3 Research Institute of Health Sciences (IUNICS), University of Balearic Islands, Palma, Spain

Running title: Pain reduces affective autonomic responses & EEG-FC

Disclosures

This work was supported by the Spanish Ministry of Economy and Competitiveness (PSI2014-57231-R) and Counseling Economy, Knowledge, Business and Universities of the Regional Government of Andalusia (B-SEJ-028-UGR18). The authors declare that the research was conducted in the absence of any professional, commercial or financial relationships that could be construed as a potential conflict of interest.

Corresponding Author: Prof. Dr. Miguel Ángel Muñoz, University of Granada Granada, Mind, Brain and Behavior Research Center (CIMCYC), Campus de la Cartuja SN, Granada, Spain.
Phone: (+34) 958-249542

Email: mamuoz@ugr.es

Number of tables: 1

Number of figures: 4

Abstract: The influence of pain over attentional processing and how affective stimuli modulate pain is well known. However, the influence of pain over attentional processing of affective stimuli has been less studied. In this study was investigated the physiological responses related with this effect of pain. Forty participants (20 men and 20 women) received tonic painful and non-painful thermal stimulation when they were viewing blocks of pleasant, unpleasant, or neutral images. Galvanic skin response (GSR), electrocardiogram and electroencephalographic (EEG) functional connectivity in delta, theta, alpha, and beta bands were recorded, and participants had to rate the unpleasantness of pain at the end of each block. Autonomic responses in no pain condition followed the typical physiological pattern; affective images evoked the largest GSR and more cardiac deceleration than neutral ones. Pain changed this pattern, increasing GSR to neutral images and accelerating the cardiac response to affective images. In addition, pain increased EEG functional connectivity of frontal and central regions in delta and theta bands when participants viewed affective images. Pain decreased the connectivity of right central region in alpha band with pleasant images. Our findings suggest that tonic pain induced attentional biases and reduced the attentional processing of affective stimuli, altering the emotional experience of pain.

Perspective: Present results give new physiological information about the influence of pain over attentional processing of affective stimuli. This work hypothesized that the physiological changes caused by the interactions between attention and pain could explain the emotional dysregulation observed in chronic pain.

Keywords: Pain, Emotion, Attention, Galvanic Skin Response, Heart Rate, EEG functional connectivity

1. Introduction

Threating stimuli capture attentional resources, priming defensive actions whereas appetitive stimuli capture attentional resource priming approach behaviours [13,14,42,74]. Consistent with this idea, evidence from behavioural and neurobiological studies suggests that pain-related information captures attentional resources in both healthy persons and chronic pain patients [20,54,57,65]. Numerous studies have investigated how pain can affect attentional resources dedicated to the processing of a secondary task. These findings suggest that tasks that require control over attentional deployment are the most affected by pain [11,50]. Other studies have focused on the importance of emotion over pain. In general, pleasant context reduce pain responses, and unpleasant ones increase them [43,63,78,79]. Previous evidence shows that skin conductance response (SCR) and heart rate (HR) acceleration elicited by painful electrical shocks are higher during unpleasant picture viewing compared with pleasant images [58,59,78,79]. The functional connectivity patterns shows that frontal area connectivity subserves the extraordinary sensitivity of the pain to affective context [56,64].

Interestingly, these studies have focused on the influence of pain over attentional processing or how affective stimuli modulate pain perception. Much less is known about how pain influences the attentional processing of affective stimuli. Hints for a possible influence of pain on affective processing come from the study of chronic pain patients. Rossello et al. [62] found that patients with fibromyalgia showed deficits in affective processing in virtual environments compared with healthy controls. These differences were interpreted as a manifestation of impaired attentional components and inhibition of affective information processing. Other studies have shown similar results: chronic pain patients reduce engagement and attentional resources to emotional stimuli [21,25,48,49,60]. However, these results could be a consequence of depression

and anxiety, which occur together with chronic pain [5,68]. Investigating the effect of pain over emotion in healthy populations would allow us to understand the attentional deficits in the processing of affective information present in chronic pain patients without the effects of other affective disorders. In this sense, Wieser et al. [77] found that tonic pain reduces attentional processing of facial expressions in healthy volunteers, it could indicate that pain reduces attentional processing to affective stimuli.

In this study, we investigated the effect of tonic pain over attentional processing of affective stimuli, focusing on autonomic responses and brain functional connectivity. Autonomic and central responses have been widely studied in motivational attention to images [12,24]. In general, physiological results demonstrate that viewing relevant and arousing images garners more attention and elicits a higher SCR and more HR deceleration than neutral images [12]. In relation to brain activity, EEG functional connectivity suggests that motivational stimuli captures attentional resources [29], enhancement of connectivity of prefrontal electrodes in both cerebral hemispheres in beta and theta bands [45]. We expect that tonic pain will reduce the attentional processing of affective images and that physiological measures will reflect the reduction of this attention. Because the literature on the EEG affective brain network functional connectivity presents heterogeneous results, we do not predict which affective networks will be affected by tonic heat pain stimulation.

2. Materials and methods

2.1 Participants

Sample size was determined using G*Power, which indicated that N = 40 was required to detect all relevant physiological effects at a medium effect size ($f = 0.25$, α error $= 0.05$,

power = 0.98, and assumed correlation of repeated measures = 0.4). Forty right-handed students (20 females and 20 males) participated in the study. They were all students at the University of Granada (average age = 19.86 ± 1.839) and received extra credit in return for their participation. Participant exclusion criteria included chronic pain, cardiovascular problems, ongoing illicit substance use, reporting mental health problems, or undergoing medical or psychological treatment. Two participants (2 males) were excluded from the study due to troubles in recordings. The participants were recruited via information provided in university classrooms. All subjects signed informed consent forms to participate in the study, which was approved by the ethics committee of the University of Granada and was performed according to the recommendations of the Declaration of Helsinki.

2.2 Quantitative sensory testing

Heat stimulation was administered with a computer-controlled thermode of a 4 x 4-cm Peltier plate and adjusted for each participant individually. Assessment of heat pain tolerance consisted of the evaluation of increasing temperatures starting at 37°C until participants considered the heat to be unbearable. The sequence of the pain assessment was as follows. First, participants were instructed to keep the index finger of their left hand in contact with the thermode for 5 s. Then, participants had to rate the current unpleasantness of the temperature using a 0–10 Visual Analogue Scale (VAS; 0 representing 'no unpleasant temperature', 5 representing 'starting to be an unpleasant temperature' and 10 representing 'the unpleasantness of the temperature is unbearable'). Sequentially, the next temperature (1°C warmer than the previous temperature) was delivered and evaluated. Each heat pain tolerance measurement was performed thrice, and the average value was adopted as the subject's heat pain tolerance. The heat-pain stimulation of each

participant was calculated as 60% of the heat pain tolerance [.6 x (average heat pain tolerance-37°C) + 37°C].

2.3 Affect induction

Sixty digital images that evoked positive, negative, and neutral emotions were chosen from the Spanish validation of the International Affective Picture System (IAPS; [46,47,75]. For each of the three emotional conditions, a set of 20 different images was selected. The 'positive set' included erotic scenes and sports images (IAPS numbers: 4652, 4658, 4668, 4669, 4670, 4672, 4676, 4681, 8178, 8185, 8186, 8193, 8251, 8300, 8341, 8370, 8400, 8490, 8496, and 8499). The 'negative set' included images of mutilation and human and animal attacks (IAPS numbers: 1050, 1113, 2811, 3064, 3100, 3170, 3400, 3550, 6212, 6250, 6263, 6313, 6410, 6550, 6560, 6570.1, 9040, 9120, 9187, and 9400). The 'neutral set' included images of mushrooms and household objects (5530, 5531, 5532, 5533, 5534, 7001, 7002, 7003, 7004, 7006, 7009, 7010, 7012, 7020, 7025, 7030, 7031, 7032, 7035, and 7040). To control for the effects of arousal, we selected pleasant and unpleasant slides with similar arousal ratings but markedly different valence ratings. In contrast, we selected neutral slides with intermediate valence and low arousal.

2.4 Procedure

Data were compiled in an individual session that lasted approximately 90 min. On their arrival at the experimental session, participants received a brief explanation of the study before signing their informed consent followed by a short interview to verify compliance with inclusion criteria. Immediately after consenting to the procedure, participants completed several questionnaires to characterize the sample in relation to psychological variables, such as state anxiety (State Anxiety Inventory (STAI) [69]), the subject's mood state (Positive and Negative

Affect Schedule (PANAS) [76]), and manual dominance (Edinburgh Handedness Inventory [53]). Then, participants were moved to a quiet and dimly illuminated room and sat in a comfortable seat where they performed the quantitative sensory test (explained in section 2.3). Subsequently, SCR, ECG and EEG electrodes were applied, and the experimental session started.

Before the experimental task started, participants were instructed to keep their index finger of their left hand in contact with the thermode during all task times, and they had to pay attention to the images that were going to appear on the wall. The task (see Fig. 1) consisted of 2 baselines of 3 min each and 8 affective blocks (pleasant, unpleasant pain, neutral, black screen pain, unpleasant, pleasant pain, black screen and neutral pain) of 2 min each. The presentation order of affective blocks was counterbalanced in four different orders. The task was divided into two parts with a baseline and 4 different affective blocks, 2 without pain and 2 with pain. The period between the two parts involved a 5-min rest period. Pleasant, unpleasant and neutral blocks were composed of 20 images of IAPS of 6 s each that were continuously presented. The temporal interval (ITI) between blocks was random, oscillating between 6-24 s, and involved a black screen. Over 24 s, the temperature increased from 37°C to the heat-pain stimulation point calculated previously. The temperature ramping started in the last 12 s of the ITI and completed in the first 12 s of the blocks. At the end of each affective block, participants evaluated unpleasantness in relation to temperature with a 0-10 Visual Analogue Scale (VAS). In the blocks with heat pain, when this evaluation had finished, the temperature returned to baseline (37°C). After completion of the task, the participants evaluated the emotional dimensions (valence and arousal) of each picture using a computerized version of the SAM scale [41].

INSERT FIGURE 1 HERE

2.5 Physiological data acquisition and preprocessing

Physiological signals from ECG and SCR were continuously acquired using PowerLab 4/25T equipment (ADInstruments, Australia) and LabChart 5 software (ADInstruments, Australia). The EEG was continuously acquired using the Geodesic Sensor Net connected to a DC-coupled amplifier (Net Amp 400, Electrical Geodesics, Inc.) and Net Station 4.5 software (Electrical Geodesics, Eugene, Oregon). The sample rate of all physiological signals was accomplished at a frequency of 1000 Hz.

ECG raw signals were recorded using the lead I configuration (positive and negative sensors were placed on the collarbones, and the ground sensor was placed on the right ankle) and filtered with a 1- to 35-Hz bandpass filter. The cardiac period (i.e., the R- R interval) was measured in milliseconds, visually inspected and corrected using an ECG beat detection software program [3]. Sequentially, the cardiac period was transformed into heart rate (HR) in beats per minute using KARDIA software [55]. Finally, for each trial, the weighted average of the HR every 6 s was obtained. Eleven participants were excluded from the HR analysis due to artefacts in the ECG. SCR was recorded with two electrodes placed in the hypothenar eminence of the left hand. The SCR in microSiemens was first averaged every 6 s for each block of 2 min. To eliminate basal levels of SCR, block data were transformed into differential scores by subtracting the average SCR during 3 s prior to each block. Four participants were excluded from the SC analyses due to artefacts.

The EEG was recorded from 58 electrodes with reference to the vertex (Cz). Impedance was maintained at <50 kOhm. EEG preprocessing analysis was calculated with the EEGLAB toolbox of MATLAB [22]. EEG was re-referenced offline to the average of electrodes and filtered

with the 0.01-Hz high pass filter, 40-Hz low pass filter and 50-Hz Notch filter. EEG waveforms were segmented in epochs of 100-ms duration (1200 per block) with a baseline correction of 10 ms prior to each epoch. Those epochs with amplitudes greater than ±70 μV were excluded, retaining between 601 and 935 epochs per block. To equalize the number of epochs between blocks and participants, we randomly selected 601 epochs in all recordings. EEG data from two participants were completely discarded due to technical problems during data acquisition.

2.6 Functional connectivity

The Motif-Synchronization (MS) method allows the dynamic study of EEG functional connectivity by counting the simultaneous appearance of predefined patterns or motifs between two time series [61]. Using the time varying graph (TVG) approach [9,70], this method allows the construction of EEG networks based on synchronisations between pairs of electrodes (links of network) with a high temporal resolution and over time. Thus, a weighted network is obtained where the weight of each edge represents the number of times that a pair of electrodes has remained synchronized over time.

First, we calculated the edge weight between pairs of electrodes for each frequency band: delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz). The functional connectivity networks were constructed using a time-varying graph structure [9,70], and then the EEG time series were analysed using a sliding time window of 100 ms with 1-ms steps. Thus, we obtained a synchronization matrix between pairs of electrodes (58x58 matrix) for each time window. To reduce spurious correlations, a threshold was selected from the synchronization between electrodes of the adjacent matrix obtained by shuffling all data points from the EEG signal. A .7 synchronization value means that 70% of the motif fluctuation patterns from both electrode EEG

signals are the same. The threshold was defined as the value at which a chance lower than or equal to .1% of times was noted in the adjacent matrix over time. Thus, synchronization values between electrodes greater or equal to .7 were selected as significant from the correlation matrix, and the node degree was summed over time. The edge weight was normalized by dividing it by the maximum edge weight value of the trial. To reduce the number of comparisons in statistical analysis, weight node degrees were grouped into regions corresponding to anatomical brain lobes where electrodes were placed [37]: left frontal (Fp1, AF3, F1, F3, F5, F7 and F9), right frontal (Fp2, AF4, F2, F4, F6, F8 and F10), left central (FC1, FC3, FC5, C1, C3 and C5), right central (FC2, FC4, FC6, C2, C4 and C6), left temporal (FT7, TP7, T7, T9 and CP5), right temporal (FT8, TP8, T8, T10 and CP6), left parietal (CP1, P1, P3, P5, P7 and P9), right parietal (CP2, P2, P4, P6, P8 and P10), left occipital (PO3 and O1) and right occipital (PO4 and O2). Finally, we calculated the average edge weight for each region with itself and the other nine regions.

2.7 Statistical analysis

Analysis of the self-reported Valence/Arousal ratings was analysed separately using one-way repeated measures analysis of variance (ANOVA) using Emotion (pleasant, unpleasant and neutral category) as a single repeated measures factor. Analysis of VAS scores consisted of a 3x2 repeated measures analysis of variance (ANOVA) using Emotion and Pain (no pain/pain) as within-subject factors.

Analysis of the SCR and HR response to affective blocks consisted of a 3x2x17 repeated measures analysis of variance (ANOVA) using Emotion and Pain and Time (17 bins of 6 s each one) as within-subject factors.

Functional connectivity analysis was performed for the frequency bands delta, theta, alpha and beta. Analysis consisted of 3x2x10 repeated measures analysis of variance (ANOVA) using Emotion, Pain and Links as within-subject factors for each scalp region (left frontal, right frontal, left central, right central, left temporal, right temporal, left parietal, right parietal, left occipital and right occipital).

In all analyses, the Greenhouse-Geisser epsilon correction was applied to control for violation of the sphericity assumption. The results are reported with the original degrees of freedom and the corrected p-values. When significant effects were found, post hoc analyses were performed using Bonferroni correction with the level of significance set at .05. Partial eta squared (η_p^2) was used as the effect size for F tests.

3. Results

3.1 Subjective measures

Figure 2 presents the means of the subjective response to affective images (pleasant, unpleasant, and neutral) from each block in valence and arousal ratings and unpleasantness of temperature (VAS ratings). The ANOVA revealed significant effects of Emotion for both the valence ($F[2,57]=449.43$, $p < .001$, $\eta_p^2=.94$) and arousal ($F[2,57]=461.92$, $p< .001$, $\eta_p^2=.94$) dimensions. Post hoc comparisons indicated that valence ratings for pleasant images were significantly increased compared with neutral images and unpleasant images (all $p< .001$), whereas valence ratings for unpleasant images were significantly reduced compared with those for neutral images ($p< .001$) (Fig. 2A). Unpleasant and pleasant images were rated as more arousing than neutral images ($p < .001$) (Fig. 2B).

The 3x2 repeated measures ANOVA of VAS scores revealed significant main effects in Emotion ($F[2,74]=3.54$, $p< .05$, $\eta_p^2=.09$) and Pain ($F[1,37]=191.78$, $p< .001$, $\eta_p^2=.88$). The Bonferroni test showed no significant differences in the Emotion factor but revealed that the unpleasantness of temperature was higher during the pain condition compared with the no pain condition ($p < .001$; Fig. 2C). No significant Emotion x Pain interaction effect was found.

INSERT FIGURE 2 HERE

3.2 Peripheral measures

Figure 3 presents autonomic responses during pain and no pain stimulation. The 3x2x17 repeated measures ANOVA on SCR yielded significant effects of Time ($F[16,560]=40.04$, $p< .001$, $\eta_p^2=.53$), Emotion x Pain ($F[2,70]=4.68$, $p< .05$, $\eta_p^2=.12$) and Emotion x Pain x Time ($F[32,1120]=3.70$, $p< .01$, $\eta_p^2=.10$). Other main or interaction effects were not significant.

The main effect of Time simply indicated that the SCR changed over time. The post hoc test of the Emotion x Pain interaction revealed that neutral-pain evoked more SCR than neutral-no pain ($p<.05$). No significant differences between Pain conditions were found in other affective categories (all p-values > .05). Regarding each pain condition, a significant difference was only found between neutral-no pain compared with unpleasant-no pain blocks ($p < .05$), and a trend was found between neutral-no pain compared with pleasant-no pain ($p=.08$). Finally, post hoc analyses of Emotion x Pain x Time revealed that neutral-pain evoked more SCR than the neutral-no pain condition for all time intervals (all p-values <.05), and unpleasant-pain evoked more SCR than unpleasant-no pain in time 1 ($p<.05$).

The 3x2x17 repeated measures (ANOVA) on HR response yielded significant differences in Time ($F[16,448]=3.31$, $p< .01$, $\eta_p^2=.10$), Pain ($F[1,28]=7.21$, $p< .05$, $\eta_p^2=.21$) and Emotion x

Pain ($F[2,56]=5.70$, $p< .01$, $\eta_p^2=.17$). The main effect of Time simply indicated that the HR response changed over time. Pain indicated that HR was increased in the pain condition compared with the no pain condition regardless of the Emotion condition. The post-hoc test of Emotion x Pain revealed that the neutral-no pain block evoked more HR acceleration than the pleasant-no pain and unpleasant-no pain blocks (all p-values < .05). Furthermore, HR acceleration was increased in pleasant and unpleasant pain conditions compared with their respective no pain conditions (all p-values< .05).

INSERT FIGURE 3 HERE

3.3 Regional functional connectivity

To provide clarity, only significant results related with pain are reported; Emotion effects are reported in Supplementary Materials. Table 1 shows the results of 3x2x10 (ANOVA) Emotion x Pain x Links analysis in the delta band (0.5-4 Hz) in each scalp region. Significant effects were yielded for Links on all Scalp Regions, indicating that the edge weight between regions was different (all p-values< .001). ANOVA yielded a significant effect of Emotion in the right occipital and right posterior regions ($p<.05$; see Supplementary Materials, Table A). Likewise, significant effects were yielded for Emotion x Links in the left frontal, right frontal, right central, left temporal, right temporal, left parietal, right parietal, left occipital and right occipital regions (all p-values< .05; see Supplementary Materials, Table A).

Significant effects of Pain were noted in the **right central** ($F[1,37]=8.16$, $p< .01$, $\eta_p^2=.18$) and in **right parietal regions** ($F[1,37]=4.69$, $p< .05$, $\eta_p^2=.11$); pain condition increased the edge weight of the right central and right parietal regions with all regions and with themselves compared with no pain. A significant interaction effect was found for Emotion x Pain interaction in the **right**

parietal region (F[2,74]=3.36, p< .05, η_p^2=.08). A follow-up post hoc test revealed that the edge weight of the right parietal region with the rest of the scalp region was greater in the pain condition compared with no pain in pleasant blocks. Significant interaction effects were found for Emotion x Pain x Links in the **right frontal, left central and right central regions** (p-values<.05; see Table 1). The post-hoc test indicated that Pain increases the edge weight between the **right frontal** and the right central region for the unpleasant blocks. The edge weight between the **left central** and left frontal regions was greater for Pain in unpleasant blocks, whereas the edge weight between the **left central** and right central regions and the right parietal region was lower in Pain in unpleasant blocks. The functional connectivity of the **left central region** with the right parietal and right occipital regions was greater for Pain in pleasant blocks. Likewise, the edge weight between the **right central** region with the left occipital and right occipital regions was greater in Pain in pleasant blocks (Figure 4). Supplementary Materials Table E shows post-hoc test regarding each pain condition.

INSERT TABLE 1 HERE

INSERT FIGURE 4 HERE

The 3x2x10 (ANOVA) applied to the functional connectivity in the theta band (4-8 Hz) yielded significant effects of Links on all Scalp Regions. The main effects of Links on all scalp regions simply indicated that edge weight between regions was different (all p-values< .001). ANOVA yielded significant effects for Emotion in the left frontal, right frontal, left central and left temporal regions (all p-values< .05; see Supplementary Materials, Table B). Likewise, significant effects were yielded for Emotion x Links in the left frontal, left occipital and right occipital regions (all p-values< .05; see Supplementary Materials, Table B). There was a

significant effect of Pain in the **right central region** ($F[1,37]=8.57$, $p< .01$, $\eta_p^2=.19$); pain condition increased the edge weight of the right central region with all regions and with itself compared with no pain. Significant interaction effects were found for Emotion x Pain x Links in the **right frontal and right central regions** (see Table 1). Follow-up post hoc comparisons revealed that the edge weight of the **right frontal region** with the right central region was greater in the pain condition compared with no pain in unpleasant and neutral blocks. Likewise, the edge weight between the **right frontal region** with the left occipital and right occipital regions and the **right central region** with the left parietal and left occipital regions were greater in pain condition compared with no pain in pleasant blocks (Figure 4). Supplementary Materials Table E shows post-hoc test regarding each pain condition.

The 3x2x10 (ANOVA) applied to the functional connectivity in the alpha band (8-13 Hz) yielded significant main effects of Links on all Scalp regions. ANOVA yielded significant effects for Emotion in the right frontal, right central, left parietal and right parietal regions (all p-values< .05; see Supplementary Materials, Table C). Likewise, significant effects were yielded for Emotion x Links in the left frontal, right frontal and left temporal regions (all p-values< .05; see Supplementary Materials, Table C). A significant effect was found for Emotion x Pain x Links in the **right central region** ($F[18,666]=2.37$, $p< .05$, $\eta_p^2=.06$). Follow-up post hoc comparisons indicated that edge weight of the **right central** region with the right frontal region was greater in pain condition compared with no pain in the neutral blocks. Conversely, the edge weight between the **right central** and right frontal regions was lower in the pain condition compared with no pain in the pleasant blocks (Figure 4). Supplementary Materials Table E shows post-hoc test regarding each pain condition.

Finally, 3x2x10 (ANOVA) applied to the functional connectivity in the beta band (13-30 Hz) yielded significant main effects of Links on all Scalp regions. ANOVA yielded significant effects for Emotion in the left frontal, right frontal, left central, right central, left temporal and left parietal regions (all p-values< .05; see Supplementary Materials, Table D). There was a significant effect of Emotion x Links in the **left frontal region** (p< .05; see Supplementary Materials, Table D). No significant differences were found in others factors.

4. Discussion

The aim of the present study was to investigate how pain affects the processing of emotional information to understand the effects of chronic pain in patients. Galvanic skin, heart rate and EEG functional connectivity responses in delta, theta, alpha and beta were recorded while healthy volunteers viewed pleasant, unpleasant and neutral images with pain and without pain. The participants reported higher levels of discomfort in the pain condition compared with the no pain condition. As expected, GSR were reduced in the neutral images compared with the pleasant and unpleasant images when pain was not present. HR was accelerated in the neutral images compared with the pleasant and unpleasant conditions in the no pain condition. However, pain evoked an increased GSR in the neutral images compared with no pain. Moreover, HR was accelerated in the pleasant and unpleasant images when pain was present. In relation to functional connectivity analysis, pain increased the connectivity of the frontal, central and parietal regions in the theta and delta bands. In general, an opposite pattern was observed in the alpha band when pain was present, decreases in connectivity in frontal brain regions. These results suggest that pain is a motivational relevant stimulus, which captures the attentional resources damping emotional processing and the affective response.

Evaluation of the unpleasantness of temperature (VAS scores) indicated that temperature only was considered unpleasant during pain conditions. Unpleasantness of temperature was not influenced by the affective content of stimuli, although the images were evaluated as pleasant or unpleasant with high arousal and neutral with low arousal. Some studies indicate that painful stimuli can be influenced by affective stimuli with more arousal than pain [58,59,78]. However, unpleasantness of temperature is influenced by the affective valence of a secondary stimulus (images) when temperature is slight but not when temperature is severe and painful [32]. In our study, the mean level of temperature applied in the experimental session was 47.3°C, which may overwhelm unpleasant levels and prevent pain from being influenced by emotional stimuli.

As expected, the SCR and HR responses in the no pain condition follow the typical physiological patterns found in affective images [12,80]. More arousing stimuli evoked the largest SCR and most pronounced cardiac deceleration, whereas modest SCR and pronounced cardiac acceleration were evoked by the least arousing stimuli. These responses have been interpreted as reflecting sustained attention in favour of motivational stimuli [12]; stimuli with higher levels of activation (threat, mutilations, and erotica stimuli) are relevant stimuli that capture attention and prompt heightened orienting and information intake [30] compared with neutral stimuli (mushrooms and household objects). When tonic pain was present, this physiological pattern disappeared; neutral images evoked the largest GSR and the same cardiac acceleration when pain was delivered, reaching levels similar to more arousing pleasant and unpleasant images. The lack of differences between affective categories when tonic pain was present could indicate that attentional resources are involved in processing arousing and noxious stimuli, blocking emotional stimuli processing at the moment [48,49,60].

Overall, changes in functional connectivity were observed in the right hemisphere for affective images, which is consistent with the dominance of the right hemisphere over the left for processing emotions [31,35,36]. Moreover, when pain was presented, images showed increased functional connectivity in the delta and theta frequencies compared with no pain in the frontal, central and parietal regions. A wide group of studies have demonstrated that the activity of the delta and theta bands in the frontocentral region is positively correlated with attention to affective stimuli [6,7,40]. Delta oscillations are involved in attentional and decision-making tasks as well as perception and emotional processing [28,39,40]. In our study, pain evoked an increased synchronization between the frontal and central regions in the delta band in the unpleasant images. Additionally, pain evoked an increased delta synchronization between the central, occipital and parietal regions in the pleasant block. In the theta band, pain condition increases connectivity between frontocentral regions with occipital and parietal regions in affective images. Increases in theta power in these regions of the cortex are associated with orientational responses [15,16,18] and the mechanisms of attention to activating affective stimuli [1,8,82]. Frontal network in these frequency bands is related with motivated attention and state of alertness to biologically relevant stimuli [6]. Our results seem to indicate that when tonic pain is sufficiently intense and persistent, it competes for attentional resources with affective images. These findings support the idea that tonic pain is a motivational stimulus that kidnaps attentional resources dedicated to processing emotional information [21,62,71]. This neural network may reflect the great information exchange between the somatosensory area and the frontal and parietal areas and occipital areas related to pain salience [33,51,67]. The somatosensory area is a critical component of the nociceptive pathway, receiving and processing afference information about the body location and the intensity of nociceptive stimuli [73]. Localizing pain within the body should significantly influence

attentional focus to processing pain information. Consistent with this interpretation, a recent study using fMRI recording demonstrated that pain increases central connectivity with the salience network with greater pain intensity increases associated with greater shifts in these connectivity patterns [10,38]. Other studies have indicated that the theta and delta bands increase connectivity mainly over frontal and central brain areas with higher pain perceived in both healthy volunteers and chronic pain patients [17,26,27,34,44]. This notion could also explain the increase in theta connectivity between the central and frontal regions in neutral blocks with pain. Thus, an increase in theta central connectivity might indicate that tonic pain increased pain-related processing independently of the type of affective context.

Synchronization in the alpha band was observed in the pain condition in the centrofrontal regions in the neutral images block, while desynchronization in the pain condition was observed in the centrofrontal regions in the pleasant condition. It has been hypothesized that alpha oscillations reflect an attention suppression mechanism in which brain regions processing relevant information exhibit decreased alpha power [4,19,23]. Thus, an inverse relationship exists between alpha power in frontal and central areas and motivated attention to affective stimuli. Several studies show that affective stimuli reduce alpha power over central and frontal areas compared with neutral stimuli [6,66,72]. Recently, it has been observed suppression of alpha power and increases in connectivity between central areas and the medial prefrontal cortex during pain stimulation [52]. Considering these findings, the increased alpha connectivity in the centrofrontal region in pain compared with the no pain condition on neutral blocks could reflect that tonic pain captures attention and reduces attentional resources to other less-activating stimuli. The results observed in pleasant conditions are difficult to explain. It is possible that the decrease in alpha central

connectivity indicates that pleasant images collect more attentional resources alone than when presented with tonic pain [81].

This is study jointly provides autonomic and EEG functional connectivity results about how tonic pain affects affective processing. We observed that when pain is a tonic stimulus, peripheral and central changes are consistent with the bottom-up mechanism, which produces an involuntary demand for attention by pain. Thus, when pain is tonic stimuli-induced attentional biases, reducing the emotional experience. Van Damme et al. [21] and Van Ryckeghem and Crombez [65] emphasized that pain occurring during the pursuit of a target captures attention, hindering the processing of the target. This finding could explain the affective disturbances and emotional dysregulation observed in chronic pain states, showing that depression and anxiety that occur together with chronic pain could be a consequence of persistence of pain.

It should be noted that functional connectivity differences in all bands occurred in pleasant blocks, whereas those in unpleasant blocks were scarce. It has been hypothesised the existence of two affective networks [2]: a pleasant network characterized mainly by connectivity between cortical areas and an unpleasant network characterized mainly by connectivity between subcortical areas. In our study, the lack of changes in connectivity between the unpleasant block and the unpleasant-pain block could be due to the technical limitations present in our EEG recordings. In the future, replicating the current study using fMRI could shed light about subcortical brain connectivity in unpleasant stimuli. We compared passive affective picture viewing without pain with passive affective picture viewing with pain, and we assumed that tonic pain captures the attentional resources dedicated to affective processing. However, affective picture viewing is not an attentional task per se. Replicating the present study using an affective attentional task, could help to separate the attentional contributions of pain on affective visual processing. Another

limitation is that the pain stimulation was only delivered on the left hand. Thus, functional connectivity changes in the right hemisphere could be explained by pain stimulation on the left hand and not be dominance of the right hemisphere in the processing of emotions.

References

[1] Aftanas LI, Reva N V., Varlamov AA, Pavlov S V., Makhnev VP. Analysis of evoked EEG synchronization and desynchronization in conditions of emotional activation in humans: Temporal and topographic characteristics. Neurosci Behav Physiol 2004;34:859–867. doi: 10.1023/B:NEAB.0000038139.39812.eb [2] Aldhafeeri FM, Mackenzie I, Kay T, Alghamdi J, Sluming V. Regional brain responses to pleasant and unpleasant IAPS pictures: Different networks. Neurosci Lett 2012;512:94–98. doi:10.1016/j.neulet.2012.01.064.

[3] Azevedo De Carvalho JL, Da Rocha AF, De Oliveira Nascimento FA, Neto JS, Junqueira LF. Development of a matlab software for analysis of heart rate variability. Int Conf Signal Process Proceedings, ICSP 2002;2:1488–1491. doi: 10.1109/ICOSP.2002.1180076

[4] Bagherzadeh Y, Baldauf D, Pantazis D, Desimone R. Alpha Synchrony and the Neurofeedback Control of Spatial Attention. Neuron 2020;105:577-587.e5. doi:10.1016/j.neuron.2019.11.001.

[5] Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med 2003;163:2433–2445. doi: 10.1001/archinte.163.20.2433

[6] Balconi M, Brambilla E, Falbo L. Appetitive vs. defensive responses to emotional cues. Autonomic measures and brain oscillation modulation. Brain Res 2009;1296:72–84. doi:10.1016/j.brainres.2009.08.056.

[7] Balconi M, Brambilla E, Falbo L. BIS/BAS, cortical oscillations and coherence in response to emotional cues. Brain Res Bull 2009;80:151–157. doi:

10.1016/j.brainresbull.2009.07.001

[8] Balconi M, Vanutelli ME. Empathy in negative and positive interpersonal interactions. What is the relationship between central (EEG, fNIRS) and peripheral (autonomic) neurophysiological responses? Adv Cogn Psychol 2017;13:105–120. doi: 10.5709/acp-0211-0

[9] Basu P, Bar-Noy A, Ramanathan R, Johnson MP. Modeling and Analysis of Time-Varying Graphs. 2010:1–11. Available: http://arxiv.org/abs/1012.0260.

[10] Bauer M, Oostenveld R, Peeters M, Fries P. Tactile spatial attention enhances gamma-band activity in somatosensory cortex and reduces low-frequency activity in parieto-occipital areas. J Neurosci 2006;26:490–501. doi: 10.1523/JNEUROSCI.5228-04.2006

[11] Berryman C, Stanton TR, Bowering KJ, Tabor A, McFarlane A, Moseley GL. Do people with chronic pain have impaired executive function? A meta-analytical review. Clin Psychol Rev 2014;34:563–579. doi:10.1016/j.cpr.2014.08.003.

[12] Bradley MM. Natural selective attention: Orienting and emotion. Psychophysiology 2009;46:1–11. doi: 10.1111/j.1469-8986.2008.00702.x

[13] Bradley MM, Codispoti M, Cuthbert BN, Lang PJ. Emotion and Motivation I: Defensive and Appetitive Reactions in Picture Processing. Emotion 2001;1:276–298. doi: 10.1037/1528-3542.1.3.276

[14] Carretié L. Exogenous (automatic) attention to emotional stimuli: a review. 2014 p. doi: 10.3758/s13415-014-0270-2

[15] Cavanagh JF, Frank MJ. Frontal theta as a mechanism for cognitive control. Trends Cogn

Sci 2014;18:414–421. doi:10.1016/j.tics.2014.04.012.

[16] Cavanagh JF, Zambrano-Vazquez L, Allen JJB. Theta lingua franca: A common mid-frontal substrate for action monitoring processes. Psychophysiology 2012;49:220–238. doi: 10.1111/j.1469-8986.2011.01293.x

[17] Chen ACN, Rappelsberger P, Filz O. Topology of EEG coherence changes may reflect differential neural network activation in cold and pain perception. Brain Topogr 1998;11:125–132. doi: 10.1023/A:1022254505510

[18] Clayton MS, Yeung N, Cohen Kadosh R. The roles of cortical oscillations in sustained attention. Trends Cogn Sci 2015;19:188–195. doi:10.1016/j.tics.2015.02.004.

[19] Clayton MS, Yeung N, Kadosh RC. Electrical stimulation of alpha oscillations stabilizes performance on visual attention tasks. J Exp Psychol Gen 2019;148:203–220. doi: 10.1037/xge0000502

[20] Crombez G, Van Ryckeghem DML, Eccleston C, Van Damme S. Attentional bias to pain-related information: A meta-analysis. Pain 2013;154:497–510. doi:10.1016/j.pain.2012.11.013.

[21] van Damme S, Legrain V, Vogt J, Crombez G. Keeping pain in mind: A motivational account of attention to pain. Neurosci Biobehav Rev 2010;34:204–213. doi: 10.1016/j.neubiorev.2009.01.005

[22] Delorme A, Makeig S. EEGLAB: an open sorce toolbox for analysis of single-trail EEG dynamics including independent component anlaysis. J Neurosci Methods 2004;134:9–21. doi: 10.1016/j.jneumeth.2003.10.009

[23] Feng W, Störmer VS, Martinez A, McDonald JJ, Hillyard SA. Involuntary orienting of attention to a sound desynchronizes the occipital alpha rhythm and improves visual perception. Neuroimage 2017;150:318–328. doi:10.1016/j.neuroimage.2017.02.033.

[24] Gable PA, Poole BD. Influence of trait behavioral inhibition and behavioral approach motivation systems on the LPP and frontal asymmetry to anger pictures. Soc Cogn Affect Neurosci 2014;9:182–190. doi: 10.1093/scan/nss130

[25] Giel KE, Paganini S, Schank I, Enck P, Zipfel S, Junne F. Processing of emotional faces in patients with chronic pain disorder: An eye-tracking study. Front Psychiatry 2018;9. doi: 10.3389/fpsyt.2018.00063

[26] González-Roldán AM, Cifre I, Sitges C, Montoya P. Altered dynamic of EEG oscillations in fibromyalgia patients at rest. Pain Med (United States) 2016;17:1058–1068. doi: 10.1093/pm/pnw023

[27] Gram M, Erlenwein J, Petzke F, Falla D, Przemeck M, Emons MI, Reuster M, Olesen SS, Drewes AM. The cortical responses to evoked clinical pain in patients with hip osteoarthritis. PLoS One 2017;12:1–13. doi: 10.1371/journal.pone.0186400

[28] Güntekin B, Başar E. Review of evoked and event-related delta responses in the human brain. Int J Psychophysiol 2016;103:43–52. doi: 10.1016/j.ijpsycho.2015.02.001

[29] Güntekin B, Femir B, Gölbaşi BT, Tülay E, Başar E. Affective pictures processing is reflected by an increased long-distance EEG connectivity. Cogn Neurodyn 2017;11:355–367. doi: 10.1007/s11571-017-9439-z

[30] Hajcak G, Foti D. Significance?& Significance! Empirical, methodological, and

theoretical connections between the late positive potential and P300 as neural responses to stimulus significance: An integrative review. Psychophysiology 2020;57:1–15. doi: 10.1111/psyp.13570

[31] Holtgraves T, Felton A. Hemispheric asymmetry in the processing of negative and positive words: A divided field study. Cogn Emot 2011;25:691–699. doi: 10.1080/02699931.2010.493758

[32] Horn C, Blischke Y, Kunz M, Lautenbacher S. Does pain necessarily have an affective component? Negative evidence from blink reflex experiments. Pain Res Manag 2012;17:15–24. doi: 10.1155/2012/478019

[33] Hu L, Peng W, Valentini E, Zhang Z, Hu Y. Functional features of nociceptive-induced suppression of alpha band electroencephalographic oscillations. J Pain 2013;14:89–99. doi: 10.1016/j.jpain.2012.10.008

[34] Huishi Zhang C, Sohrabpour A, Lu Y, He B. Spectral and spatial changes of brain rhythmic activity in response to the sustained thermal pain stimulation. Hum Brain Mapp 2016;37:2976–2991. doi: 10.1002/hbm.23220

[35] Itkes O, Mashal N. Processing negative valence of word pairs that include a positive word. Cogn Emot 2016;30:1180–1187. doi: 10.1080/02699931.2015.1039934

[36] Jończyk R. Hemispheric asymmetry of emotion words in a non-native mind: A divided visual field study. Laterality 2015;20:326–347. doi: 10.1080/1357650X.2014.966108

[37] Kamarajan C, Pandey AK, Chorlian DB, Manz N, Stimus AT, Bauer LO, Hesselbrock VM, Schuckit MA, Kuperman S, Kramer J, Porjesz B. Reward processing deficits and

impulsivity in high-risk offspring of alcoholics: A study of event-related potentials during a monetary gambling task. Int J Psychophysiol 2015;98:182–200. doi:10.1016/j.ijpsycho.2015.09.005.

[38] Kim J, Mawla I, Kong J, Lee J, Gerber J, Ortiz A, Kim H, Chan ST, Loggia ML, Wasan AD, Edwards RR, Gollub RL, Rosen BR, Napadow V. Somatotopically specific primary somatosensory connectivity to salience and default mode networks encodes clinical pain. Pain 2019;160:1594–1605. doi: 10.1097/j.pain.0000000000001541

[39] Klados MA, Frantzidis C, Vivas AB, Papadelis C, Lithari C, Pappas C, Bamidis PD. A framework combining delta event-related oscillations (EROs) and synchronisation effects (ERD/ERS) to study emotional processing. Comput Intell Neurosci 2009;2009. doi: 10.1155/2009/549419

[40] Knyazev GG, Slobodskoj-Plusnin JY, Bocharov A V. Event-related delta and theta synchronization during explicit and implicit emotion processing. Neuroscience 2009;164:1588–1600. doi:10.1016/j.neuroscience.2009.09.057.

[41] Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): Instruction manual and affective ratings. Cent Res psychophysiology, Univ Florida 1999.

[42] Lang PJ, Bradley MM, Cuthbert BN. Motivated attention: Affect, activation, and action. Atten orienting Sens Motiv Process 1997;97:135.

[43] Lee Y, Uchiyama M. The Effect of Humorous Stimuli on Alleviating Pain during Mammography: A Preliminary Study. Health (Irvine Calif) 2015;07:659–664. doi: 10.4236/health.2015.76078

[44] Levitt J, Choo HJ, Smith KA, LeBlanc BW, Saab CY. Electroencephalographic frontal synchrony and caudal asynchrony during painful hand immersion in cold water. Brain Res Bull 2017;130:75–80. doi: 10.1016/j.brainresbull.2016.12.011

[45] Miskovic V, Schmidt LA. Cross-regional cortical synchronization during affective image viewing. Brain Res 2010;1362:102–111. doi:10.1016/j.brainres.2010.09.102.

[46] Moltó J, Montañés S, Poy Gil R, Segarra Cabedo P, Pastor Verchili M, Tormo Irún M, Ramírez Uclés I, Hernández M, Sánchez M, Fernández Santaella M, Vila Castellar J. Un método para el estudio experimental de las emociones: el International Affective Picture System (IAPS). Adaptación española. Rev Psicol Gen y Apl Rev la Fed Española Asoc Psicol 1999;52:55–87.

[47] Moltó J, Segarra P, López R, Esteller À, Fonfría A, Pastor MC, Poy R. Adaptación española del "International Affective Picture System" (IAPS). Tercera parte. An Psicol 2013;29:965–984. doi: 10.6018/analesps.29.3.153591

[48] Montoro CI, Duschek S, de Guevara CML, del Paso GAR. Patterns of cerebral blood flow modulation during painful stimulation in fibromyalgia: A transcranial Doppler sonography study. Pain Med (United States) 2016;17:2256–2267. doi: 10.1093/pm/pnw082

[49] Montoya P, Sitges C, García-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. doi: 10.1097/01.psy.0000188401.55394.18

[50] Moore DJ, Keogh E, Eccleston C. The interruptive effect of pain on attention. Q J Exp Psychol 2012;65:565–586. doi: 10.1080/17470218.2011.626865

[51] Nani A, Manuello J, Mancuso L, Liloia D, Costa T, Cauda F. The neural correlates of consciousness and attention: Two sister processes of the brain. Front Neurosci 2019;13. doi: 10.3389/fnins.2019.01169

[52] Nickel MM, Ta Dinh S, May ES, Tiemann L, Hohn VD, Gross J, Ploner M. Neural oscillations and connectivity characterizing the state of tonic experimental pain in humans. Hum Brain Mapp 2020;41:17–29. doi: 10.1002/hbm.24784

[53] Oldfield RC, others. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113.

[54] Peláez I, Ferrera D, Barjola P, Fernandes R, Mercado F. Subliminal emotional pictures are capable of modulating early cerebral responses to pain in fibromyalgia. PLoS One 2019;14:1–24. doi: 10.1371/journal.pone.0217909

[55] Perakakis P, Joffily M, Taylor M, Guerra P, Vila J. KARDIA: A Matlab software for the analysis of cardiac interbeat intervals. Comput Methods Programs Biomed 2010;98:83–89. doi:10.1016/j.cmpb.2009.10.002.

[56] Ploner M, Lee MC, Wiech K, Bingel U, Tracey I. Flexible Cerebral Connectivity Patterns Subserve Contextual Modulations of Pain. Cereb Cortex 2011;21:719–726. doi: 10.1093/cercor/bhq146

[57] Priebe JA, Messingschlager M, Lautenbacher S. Gaze behaviour when monitoring pain faces: An eye-tracking study. Eur J Pain (United Kingdom) 2015;19:817–825. doi: 10.1002/ejp.608

[58] Rhudy JL, Williams AE, McCabe KM, Rambo PL, Russell JL. Emotional modulation of

spinal nociception and pain: The impact of predictable noxious stimulation. Pain 2006;126:221–233. doi: 10.1016/j.pain.2006.06.027

[59] Rhudy JL, Williams AE, Mccabe KM, Russell JL, Maynard LJ. Emotional control of nociceptive reactions (ECON): Do affective valence and arousal play a role ? Pain 2008;136:250–261. doi: 10.1016/j.pain.2007.06.031

[60] Roa Romero Y, Straube T, Nitsch A, Miltner WHR, Weiss T. Interaction between stimulus intensity and perceptual load in the attentional control of pain. Pain 2013;154:135–140. doi:10.1016/j.pain.2012.10.003.

[61] Rosário RS, Cardoso PT, Muñoz MA, Montoya P, Miranda JGV. Motif-Synchronization: A new method for analysis of dynamic brain networks with EEG. Phys A Stat Mech its Appl 2015;439:7–19. doi:10.1016/j.physa.2015.07.018.

[62] Rosselló F, Muñoz MA, Duschek S, Montoya P. Affective Modulation of Brain and Autonomic Responses in Patients with Fibromyalgia. Psychosom Med 2015;77:721–732. doi: 10.1097/PSY.0000000000000217

[63] Roy M, Lebuis A, Hugueville L, Peretz I, Rainville P. Spinal modulation of nociception by music. Eur J Pain (United Kingdom) 2012;16:870–877. doi: 10.1002/j.1532-2149.2011.00030.x

[64] Roy M, Piché M, Chen J-I, Peretz I, Rainville P. Cerebral and spinal modulation of pain by emotions. Proc Natl Acad Sci 2009;106:20900–20905. doi:10.1073/pnas.0904706106.

[65] van Ryckeghem D, Crombez G. Pain and attention: Toward a motivational account. Motivational Perspectives on Chronic Pain: Theory, Research, and Practice.2018. pp.

211–246. doi: 10.1093/oso/9780190627898.003.0006

[66] Schubring D, Schupp HT. Affective picture processing: Alpha- and lower beta-band desynchronization reflects emotional arousal. Psychophysiology 2019;56:1–13. doi: 10.1111/psyp.13386

[67] Shen W, Tu Y, Gollub RL, Ortiz A, Napadow V, Yu S, Wilson G, Park J, Lang C, Jung M, Gerber J, Mawla I, Chan ST, Wasan AD, Edwards RR, Kaptchuk T, Li S, Rosen B, Kong J. Visual network alterations in brain functional connectivity in chronic low back pain: A resting state functional connectivity and machine learning study. NeuroImage Clin 2019;22:101775. doi:10.1016/j.nicl.2019.101775.

[68] Sheng J, Liu S, Wang Y, Cui R, Zhang X. The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. Neural Plast 2017;2017. doi: 10.1155/2017/9724371

[69] Spielberger CD, Gorsuch RL, Lushene RE. The State-Trait Anxiety Inventory (STAI) Test Manual for Form X, 1970. Palo Alto Consult Psychol Press (Italian Transl Ed by Lazzari R Pancheri P, 1980, Florence, Organ Spec n.d.

[70] Tang J, Scellato S, Musolesi M, Mascolo C, Latora V. Small-world behavior in time-varying graphs. Phys Rev E 2010;81:55101. doi:10.1103/PhysRevE.81.055101.

[71] Torta DM, Legrain V, Mouraux A, Valentini E. Attention to pain! A neurocognitive perspective on attentional modulation of pain in neuroimaging studies. Cortex 2017;89:120–134. doi: 10.1016/j.cortex.2017.01.010

[72] Uusberg A, Uibo H, Kreegipuu K, Allik J. EEG alpha and cortical inhibition in affective

attention. Int J Psychophysiol 2013;89:26–36. doi:10.1016/j.ijpsycho.2013.04.020.

[73] Vierck CJ, Whitsel BL, Favorov O V, Brown AW, Tommerdahl M. Role of primary somatosensory cortex in the coding of pain. PAIN® 2013;154:334–344. doi: 10.1016/j.pain.2012.10.021

[74] Vila J, Guerra P, Muñoz MÁ, Vico C, Viedma-del Jesús MI, Delgado LC, Perakakis P, Kley E, Mata JL, Rodríguez S. Cardiac defense: From attention to action. Int J Psychophysiol 2007;66:169–182. doi: 10.1016/j.ijpsycho.2007.07.004

[75] Vila J, Sanchez M, Ramirez I, Fernandez MC, Cobos P, Rodriguez S, Munoz MA, Tormo MP, Herrero M, Segarra P, Pastor MC, Poy R. El Sistema Internacional De Imágenes Afectivas (Iasp): Adaptación Espanola . Segunda Parte. Rev Pslcol Gral y Aplic 2001;54:635·657.

[76] Watson D, Clark LA. The PANAS-X: Manual for the positive and negative affect schedule-expanded form. 1999 p. doi:10.17077/48vt-m4t2.

[77] Wieser MJ, Gerdes ABM, Greiner R, Reicherts P, Pauli P. Tonic pain grabs attention, but leaves the processing of facial expressions intact-Evidence from event-related brain potentials. Biol Psychol 2012;90:242–248. doi: 10.1016/j.biopsycho.2012.03.019

[78] Williams AE, Rhudy JL. Emotional modulation of autonomic responses to painful trigeminal stimulation ☆. Int J Psychophysiol 2009;71:242–247. doi:10.1016/j.ijpsycho.2008.10.004.

[79] Williams AE, Rhudy JL. Motivational Priming Predicts How Noxious Unconditioned Stimuli Influence Affective Reactions to Emotional Pictures. 2012;3:883–891.

doi:10.4236/psych.2012.310133.

[80] Wilson KA, James GA, Kilts CD, Bush KA. Combining Physiological and Neuroimaging Measures to Predict Affect Processing Induced by Affectively Valent Image Stimuli. Sci Rep 2020;10:1–10. doi:10.1038/s41598-020-66109-3.

[81] Wu X, Zheng W, Member BLS. Identifying Functional Brain Connectivity Patterns for EEG-Based Emotion Recognition. 2019 9th Int IEEE/EMBS Conf Neural Eng 2019:235–238. doi: 10.1109/NER.2019.8717035

[82] Zhang W, Li X, Liu X, Duan X, Wang D, Shen J. Distraction reduces theta synchronization in emotion regulation during adolescence. Neurosci Lett 2013;550:81–86. doi:10.1016/j.neulet.2013.05.070.

Tables and figures

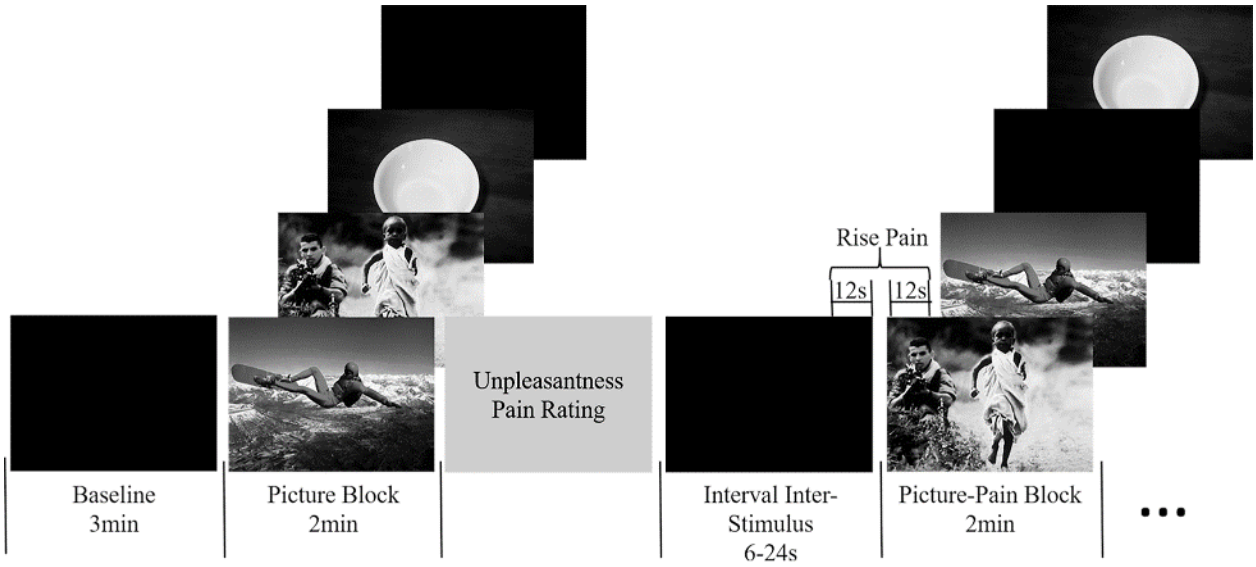

Fig. 1. Experimental procedure. One baseline of 3 min occurred before the task period. During the task, participants viewed 3 affective blocks (pleasant, unpleasant and neutral) and one black screen block for 2 min each. Pain stimuli were delivered in the half of the blocks and 12 s after the blocks started. Each block was followed by one unpleasantness pain rating and 6-24 s of ITI. This procedure was repeated after 5 min of rest.

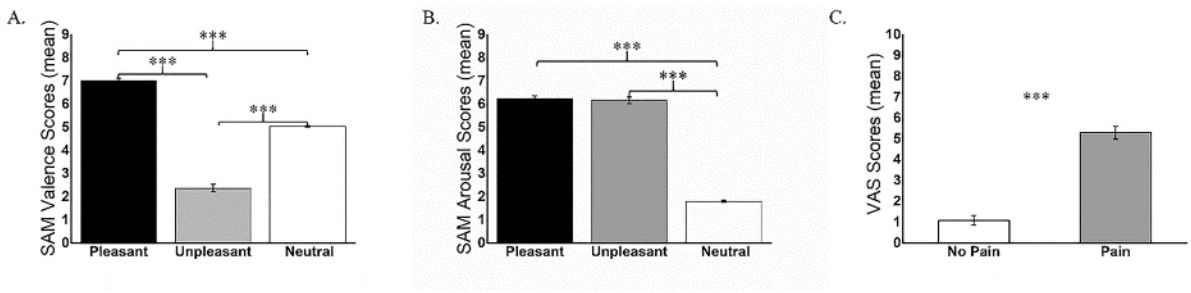

Fig. 2. A. Means of SAM valence scores for pleasant, unpleasant and neutral images. **B.** Means of SAM arousal scores for pleasant, unpleasant and neutral images. **C.** Means of unpleasantness pain ratings for no pain and pain stimulation. ***p<.001

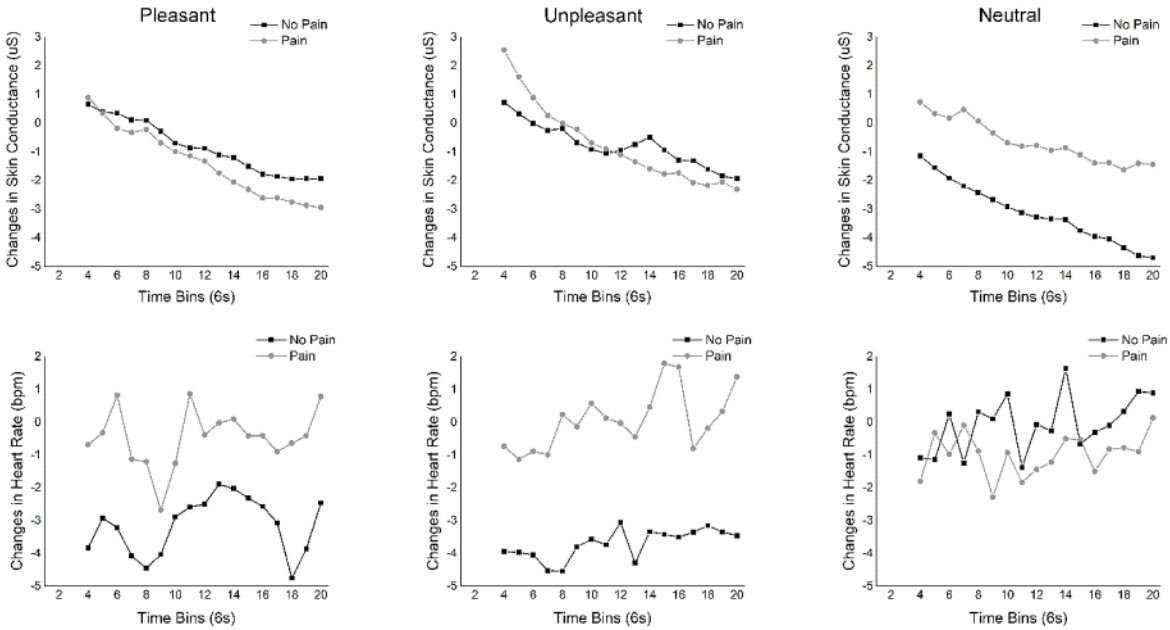

Fig. 3. Time bins (6 s) of changes in skin conductance and heart rate for pleasant, unpleasant and neutral images during no pain and pain stimulation.

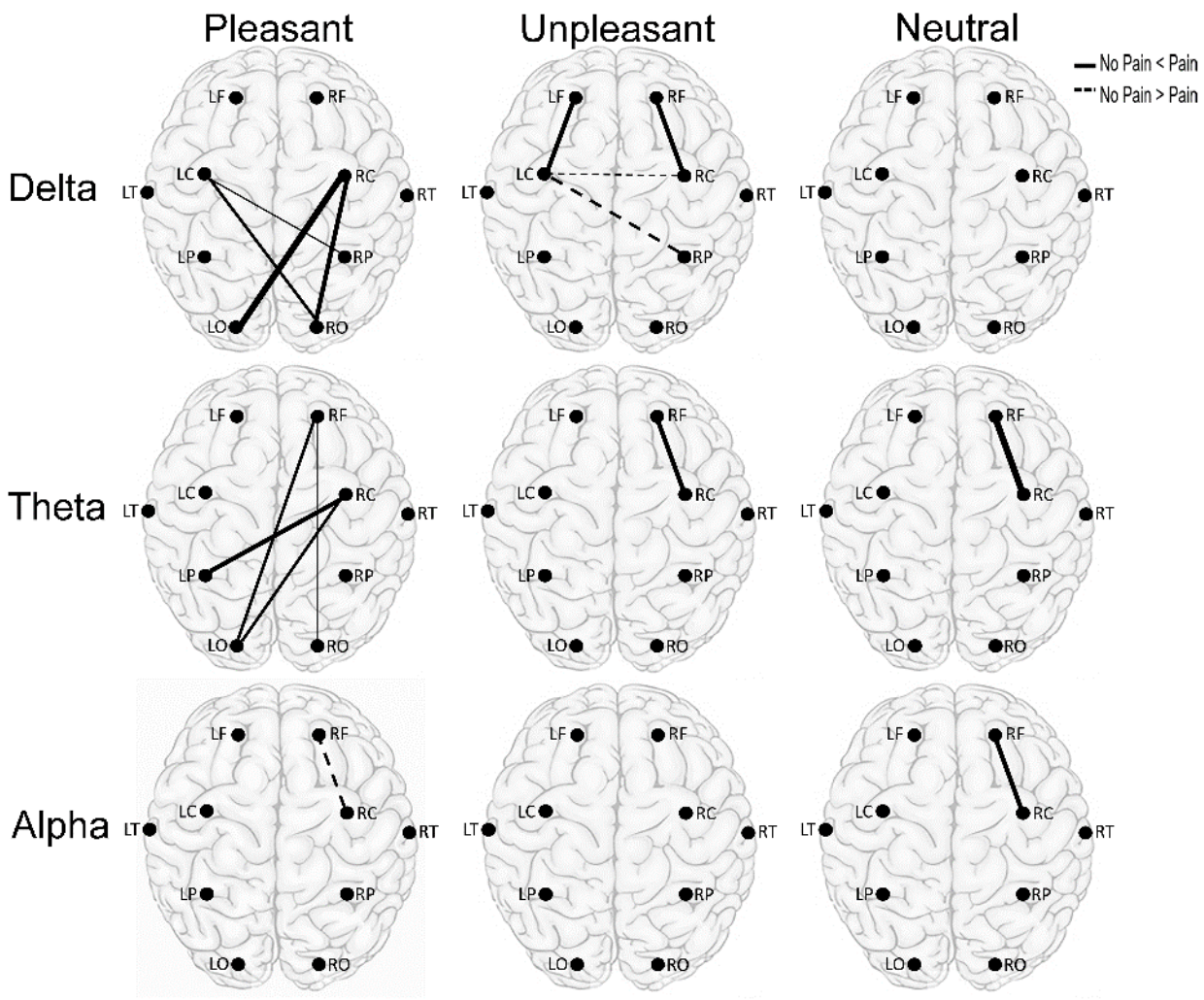

Fig. 4. Regional networks of significant differences between no pain and pain stimulation for pleasant, unpleasant and neutral (columns) conditions in delta, theta and alpha bands (rows).

Table 1. Regional functional connectivity Somatosensory condition (2) x affective category (3) x links (10) repeated measures AN
with Greenhouse-Geisser correction of weight degree between EEG electrodes groups in each frequency band. * p < .05; ** p < .0
RF=Right Frontal; LC=Left Central; RC=Right Central; LT=Left Temporal; RT=Right Temporal; LP=Left Parietal; RP=Righ
RO=Right Occipital

Frequencies Bands	Regions	Pain	η_p^2	Emotion x Pain	η_p^2	Emotion x Pain x Link	η_p^2	Pair	Pai
Delta 0.5-4 Hz	**RF**	F(1,37)=2.80	.07	F(2,74)=.09	.00	F(18,666)=2.41*	.06	RF-RC	UNP (
	LC	F(1,37)=.45	.02	F(2,74)=1.23	.03	F(18,666)=2.43*	.06	LC-LF	UNP (
								LC-RC	UNP (
								LC-RP	PLE (
									UNP(
								LC-RO	PLE (
	RC	**F(1,37)=8.16****	.18	F(2,74)=.09	.00	F(18,666)=2.75*	.07		**NoPa**
								RC-LO	PLE (.
								RC-RO	PLE (
	RP	**F(1,37)=4.68***	.11	**F(2,74)=3.36***	.08	F(18,999)=1.11	.02		**NoP**
									PLE(.4
Theta 4-8 Hz	**RF**	F(1,37)=2.01	.05	F(2,74)=1.17	.03	F(18,666)=3.26**	.06		
								RF-RC	UNP (
									NEU (.
								RF-LO	PLE (.
								RF-RO	PLE (
	RC	**F(1,37)=8.57***	.19	F(2,74)=.18	.01	F(18,666)=2.67*	.07		**NoPa**
								RC-LP	PLE (
								RC-LO	PLE (.
Alpha 8-13 Hz	**RC**	F(1,37)=.76	.02	F(2,74)=.85	.02	F(18,666)=2.38*	.06		
								RC-RF	NEU (
									PLE (.

Supplementary Materials

Table A. Regional functional connectivity Emotion (3) x Pain (2) x Links (10) repeated measures ANOVA significant F-Test results with Greenhouse-Geisser correction of edge weight between EEG electrodes groups in Delta frequency band. * p < .05; ** p < .01; ***p<.001. LF=Left Frontal; RF=Right Frontal; LC=Left Central; RC=Right Central; LT=Left Temporal; RT=Right Temporal; LP=Left Parietal; RP=Right Parietal; LO=Left Occipital; RO=Right Occipital

Regions	Emotion	η_p^2	Emotion x Link	η_p^2	Pair	Pairs Comparisons (Mean±SD)
LF	F(2,74)=2.85	.07	F(18,666)=2.46*	.06		
					LF-LF	PLE (.70 ± .05) < NEU (.71 ± .06)
					LF-RC	PLE (.41 ± .03) > NEU (.40 ± .03)
					LF-RT	PLE (.36 ± .02) > UNP (.36 ± .02)
					LF-LO	UNP (.29 ± .03) < NEU (.30 ± .02)
RF	F(2,74)=2.13	.06	F(18,666)=2.59*	.07		
					RF-LC	PLE (.41 ± .03) > NEU (.40 ± .03)
					RF-RT	PLE (.52 ± .03) < NEU (.53 ± .03)
					RF-RP	UNP (.37 ± .02) < NEU (.38 ± .02)
					RF-RO	UNP (.29 ± .02) < NEU (.30 ± .02)
RC	F(2,74)=2.57	.07	F(18,666)=2.76*	.07		
					RC-RC	PLE (.74 ± .05) < NEU (.74 ± .05)
					RC-LT	PLE (.33 ± .03) > UNP (.32 ± .03)
					RC-RP	UNP (.52 ± .03) < NEU (.52 ± .04)
LT	F(2,74)=1.04	.03	F(18,666)=2.25*	.06		
RT	F(2,74)=2.37	.06	F(18,666)=2.65*	.07		
					RT-LO	PLE (.44 ± .02) > NEU (.44 ± .03)
LP	F(2,74)=.35	.01	F(18,666)=2.60*	.07		
					LP-RP	UNP (.50 ± .02) > NEU (.49 ± .02)
					LP-RO	UNP (.61 ± .04) > NEU (.60 ± .04)
RP	**F(2,74)=3.36***	.08	F(18,666)=3.18**	.07		
					RP-LO	PLE (.62 ± .04) > NEU (.61 ± .03) UNP (.62 ± .03) > NEU (.61 ± .03)
LO	F(2,74)=2.86	.07	F(18,666)=3.49**	.09		
					LO-LC	PLE (.39 ± .03) < NEU (.40 ± .03)
					LO-LO	UNP (.82 ± .07) > NEU (.81 ± .08)
					LO-RO	UNP (.81 ± .05) > NEU (.80 ± .05)
RO	**F(2,74)=4.53***	.11	F(18,666)=2.67*	.07		**UNP (.52 ± .02) > NEU (.51 ± .02)**
					RO-RO	UNP (.83 ± .08) > NEU (.82 ± .08)

Table B. Regional functional connectivity Emotion (3) x Pain (2) x Links (10) repeated measures ANOVA significant F-Test results with Greenhouse-Geisser correction of edge weight between EEG electrodes groups in theta frequency band. * $p < .05$; ** $p < .01$; ***$p<.001$. LF=Left Frontal; RF=Right Frontal; LC=Left Central; RC=Right Central; LT=Left Temporal; RT=Right Temporal; LP=Left Parietal; RP=Right Parietal; LO=Left Occipital; RO=Right Occipital

Regions	Emotion	η_p^2	Emotion x Link	η_p^2	Pair	Pairs Comparisons (Mean±SD)
LF	**F(2,74)=13.62*** **	.27	F(18,666)=2.12*	.06		**PLE (.49 ± .01) < NEU (.50 ± .02)**
						UNP (.49 ± .02) < NEU (.50 ± .02)
					LF-LF	PLE (.78 ± .06) < NEU (.79 ± .06)
						UNP (.79 ± .05) < NEU (.79 ± .06)
					LF-RF	UNP (.61 ± .05) < NEU (.61 ± .05)
					LF-LC	PLE (.67 ± .05) < NEU (.67 ± .05)
						PLE (.67 ± .05) < UNP (.67 ± .04)
					LF-LT	PLE (.59 ± .04) < NEU (.60 ± .04)
					LF-LO	PLE (.33 ± .03) < NEU (.33 ± .03)
RF	**F(2,74)=13.60*** **	.27	F(18,666)=1.15	.03		**PLE (.49 ± .01) < NEU (.50 ± .02)**
LC	**F(2,74)=10.46*** **	.22	F(18,666)=1.57	.04		**PLE (.52 ± .01) < NEU (.52 ± .02)**
						UNP (.52 ± .01) < NEU (.52 ± .02)
LT	**F(2,74)=6.34** **	.15	F(18,666)=1.33	.04		**PLE (.53 ± .01) < NEU (.53 ± .02)**
						UNP (.53 ± .01) < NEU (.53 ± .02)
LO	F(2,74)=.97	.03	F(18,666)=3.38**	.07		
					LO-LC	UNP (.44 ± .03) < NEU (.45 ± .03)
					LO-RC	PLE (.37 ± .03) < NEU (.38 ± .03)
					LO-LT	UNP (.55 ± .03) < NEU (.55 ± .03)
					LO-RO	PLE (.86 ± .04) > NEU (.85 ± .04)
RO	F(2,74)=.24	.01	F(18,666)=2.18*	.06		
					RO-LC	PLE (.38 ± .03) < NEU (.38 ± .03)

Table C. Regional functional connectivity Emotion (3) x Pain (2) x Links (10) repeated measures ANOVA significant F-Test results with Greenhouse-Geisser correction of edge weight between EEG electrodes groups in alpha frequency band. * $p < .05$; ** $p < .01$; ***$p<.001$. LF=Left Frontal; RF=Right Frontal; LC=Left Central; RC=Right Central; LT=Left Temporal; RT=Right Temporal; LP=Left Parietal; RP=Right Parietal; LO=Left Occipital; RO=Right Occipital

Regions	Emotion	η_p^2	Emotion x Link	η_p^2	Pair	Pairs Comparisons (Mean±SD)
LF	F(2,74)=1.08	.03	F(18,666)=4.11***	.10		
					LF-LF	PLE (.84 ± .05) < NEU (.85 ± .05)
						UNP (.84 ± .04) < NEU (.85 ± .05)
					LF-RF	PLE (.72 ± .04) > UNP (.72 ± .04)
						UNP (.72 ± .04) < NEU (.73 ± .05)
					LF-RP	PLE (.56 ± .03) > NEU (.55 ± .04)
RF	**F(2,74)=3.49***	.09	F(18,666)=2.99*	.08		
					RF-RF	PLE (.84 ± .04) < NEU (.84 ± .04)
						UNP (.83 ± .04) < NEU (.84 ± .04)
					RF-LP	PLE (.56 ± .04) > NEU (.55 ± .04)
					RF-RP	PLE (.63 ± .03) > UNP (.6 3± .03)
						PLE (.63 ± .03) > NEU (.62 ± .03)
RC	**F(2,74)=3.92***	.10	F(18,666)=1.07	.03		**PLE (.68 ± .03) > NEU (.68 ± .03)**
LT	F(2,74)=2.17	.06	F(18,666)=2.37*	.06		
					LT-RC	PLE (.58 ± .03) > NEU (.58 ± .03)
						UNP (.58 ± .03) > NEU (.58 ± .03)
LP	**F(2,74)=4.50***	.11	F(18,666)=1.00	.03		**PLE (.71 ± .03) > NEU (.70 ± .03)**
RP	**F(2,74)=3.23***	.08	F(18,666)=1.25	.03		

Table D. Regional functional connectivity Emotion (3) x Pain (2) x Links (10) repeated measures ANOVA significant F-Test results with Greenhouse-Geisser correction of edge weight between EEG electrodes groups in Beta frequency band. * p < .05; ** p < .01; ***p<.001. LF=Left Frontal; RF=Right Frontal; LC=Left Central; RC=Right Central; LT=Left Temporal; RT=Right Temporal; LP=Left Parietal; RP=Right Parietal; LO=Left Occipital; RO=Right Occipital

Regions	Emotion	η_p^2	Emotion x Link	η_p^2	Pair	Pairs Comparisons (Mean±SD)
LF	**F(2,74)=10.01*** **	.21	F(18,666)=2.33*	.06		**PLE (.53 ± .02) < NEU (.54 ± .02)**
						UNP (.53 ± .02) < NEU (.54 ± .02)
					LF-LF	PLE (.65 ± .06) < NEU (.66 ± .06)
						UNP (.65 ± .06) < NEU (.66 ± .06)
					LF-RF	UNP (.52 ± .01) < NEU (.52 ± .01)
					LF-LC	UNP (.56 ± .03) < NEU (.57 ± .04)
					LF-RC	UNP (.51 ± .02) < NEU (.52 ± .02)
					LF-LT	UNP (.53 ± .02) < NEU (.53 ± .02)
					LF-LP	UNP (.49 ± .02) < NEU (.50 ± .03)
RF	**F(2,74)=5.01***	.12	F(18,666)=1.22	.03		**UNP (.53 ± .02) < NEU (.54 ± .03)**
LC	**F(2,74)=6.65****	.15	F(18,666)=.88	.02		**PLE (.55 ± .03) < NEU (.56 ± .03)**
RC	**F(2,74)=4.03***	.10	F(18,666)=.88	.02		
LT	**F(2,74)=4.44***	.11	F(18,666)=.98	.03		**UNP (.53 ± .03) < NEU (.54 ± .03)**
LP	**F(2,74)=6.41****	.15	F(18,666)=1.21	.03		**PLE (.56 ± .03) < NEU (.56 ± .03)**
						UNP (.56 ± .03) < NEU (.56 ± .03)

Table E. Regional functional connectivity Emotion (3) x Pain (2) x Links (10) repeated measures ANOVA significant F-Test results with Greenhouse-Geisser correction of weight degree between EEG electrodes groups in each frequency band. * p < .05; ** p < .01; ***p<.001. LF=Left Frontal; RF=Right Frontal; LC=Left Central; RC=Right Central; LT=Left Temporal; RT=Right Temporal; LP=Left Parietal; RP=Right Parietal; LO=Left Occipital; RO=Right Occipital

Frequencies Bands		Pair of Regions	Pairs Comparisons (Mean±SD)
Delta 0.5-4 Hz	**No Pain**	RF-LC	PLE (.41 ± .03) > NEU (.40 ± .04)*
		RF-RP	UNP (.37 ± .02) < NEU (.38 ± .02)*
		LC-RP	PLE (.32 ± .03) < UNP (.33 ± .03)*
		LC-LO	PLE (.39 ± .04) < NEU (.40 ± .03)*
		LC-RO	PLE (.34 ± .04) < NEU (.35 ± .03)*
		RC-RP	UNP (.51 ± .03) < NEU (.52 ± .04)*
	Pain	RF-RC	PLE (.58 ± .06) < UNP (.60 ± .06)**
			PLE (.58 ± .06) < NEU (.60 ± .06)*
		RF-RT	PLE (.52 ± .03) < NEU (.53 ± .04)*
		LC-LF	PLE (.58 ± .04) < UNP (.59 ± .05)*
Theta 4-8 Hz	**No Pain**	RF-LP	PLE (.31 ± .04) < NEU (.32 ± .04)*
		RF-LO	PLE (.30 ± .03) < UNP (.31 ± .03)*
			PLE (.30 ± .03) < NEU (.31 ± .03)**
		RC-LP	PLE (.35 ± .05) < UNP (.36 ± .04)*
			PLE (.35 ± .05) < NEU (.36 ±.05)*
		RC-LO	PLE (.37 ± .03) < UNP (.38 ± .03)**
			PLE (.37 ± .03) < NEU (.38 ± .03)**
	Pain	RF-RF	PLE (.77 ± .05) < NEU (.79 ± .06)**
			UNP (.78 ± .05) < NEU (.79 ± .06)*
		RF-RC	PLE (.67 ± .05) < NEU (.68 ± .06)*
		RF-RT	PLE (.59 ± .04) < NEU (.60 ± .04)**
		RC-LT	PLE (.36 ± .04) > NEU (.36 ± .04)*
Alpha 8-13 Hz	**No Pain**	RC-RF	PLE (.78 ± .04) > NEU (.77 ± .04)*
		RC-RT	PLE (.77 ± .05) > NEU (.76 ± .05)*
	Pain	RC-LC	PLE (.64 ± .04) > NEU (.63 ± .05)*
		RC-LT	PLE (.58 ± .03) > NEU (.58 ± .04)*

ESTUDIO 3

Alba, G., Terrasa, J.L., Montoya, P., Vila, J., & Muñoz, M. A. (2021) Network Physiology changes after sensorimotor rhythm neurofeedback training: a pilot study. *Neuromodulation.* (En revisión)

Alba, G., Terrasa, J.L., Montoya, P., Vila, J., & Muñoz, M. A. (2021) Network Physiology changes after sensorimotor rhythm neurofeedback training: a pilot study. *Neuromodulation.* (En revisión)

Network Physiology changes after sensorimotor rhythm neurofeedback training: a pilot study

Running title: Network Physiology changes after SMR training

Alba, G.[1], Terrasa, J. L.[2]., Montoya, P[2]., Vila, J.[1], & Muñoz, M. A.[1]

1 Brain, Mind and Behavior Research Center at University of Granada (CIMCYC-UGR), Spain

2 Research Institute of Health Sciences (IUNICS), University of Balearic Islands, Palma, Spain

This work was supported by the Spanish Ministry of Economy and Competitiveness (PSI2014-57231-R).

The authors declare that the research was conducted in the absence of any professional, commercial or financial relationships that could be construed as a potential conflict of interest.

Corresponding Author: Prof. Dr. Miguel Ángel Muñoz, University of Granada Granada, Mind, Brain and Behavior Research Center (CIMCYC), Campus de la Cartuja SN, Granada, Spain. Phone: (+34) 958-249542

Email: mamuoz@ugr.es

Number of tables: 1

Number of figures: 3

Abstract

Objectives

Previous research has found that neurofeedback can induce long-term changes in brain functional connectivity and peripheral activity. However, the influence of neurofeedback on the connectivity between different physiological systems is unknown. We analyze the electroencephalography (EEG) connectivity and EEG-heart rate (HR) connectivity before and after the neurofeedback training.

Materials and Methods

Seventeen patients with a diagnosis of fibromyalgia were divided in two groups: sensorimotor rhythm (SMR) training and fake training (SHAM). Training consisted in six sessions to learn to synchronize and to desynchronize the SMR (12-15 Hz) power at left sensory-motor related electrodes. Before the first training (Pre-resting state) and sixth training (Post-resting state), an open-eyes resting state EEG and electrocardiography were recorded.

Results

The analyses of the task performance revealed that only some participants of the SMR training group were able to achieve a success rate above 50%. Thus, SMR participants were divided in: Good SMR responders and Bad SMR responders. Good responders showed reduced connectivity between central areas with frontal, central, occipital and heart activity after SMR neurofeedback training. While, SHAM group showed increases in EEG functional connectivity and bad SMR responders showed both decreases and increases. The physiological changes of Good SMR responders were related with a decrease of pain in these patients.

Conclusions

Neurofeedback training led to changes in the network physiology connectivity between Central Nervous System and Cardiac System. Our results are modest, but they seem to indicate that neurofeedback training is a promising tool for a better understanding of the interactions between the different systems of the organism.

INTRODUCTION

Brain is a complex network of dynamic connections between local and distant brain areas[1]. Interregional neural communication is thought to be accompanied by a synchronization of oscillations between different brain regions[2]. This synchronization can be analyzed by mean of functional connectivity, which is a measure of the statistical dependency between activity in different brain regions. In recent years, investigations in the field of functional connectivity have been extended from brain regional relations to integration with peripheral systems[3,4]. This approach proposes the analysis of the interactions between different physiological signals (for example: electromyography, electrocardiography (EKG), electroencephalography (EEG), electrodermal activity…) as a biomarker of neuropathological and mental states[3,5–7]. The underlying rationale is that the organisms consist of an integrated network, where multi-component systems continuously interact through various feedback mechanisms to optimize its function[3]. In this line, it has been demonstrated that central functional connectivity is related with cardiovascular homeostasis at rest[8–11]. However, to our knowledge, there are no studies about the synergistic effects from manage a node from of physiological systems over other physiological systems.

Neurofeedback (NFB) is a non-invasive technique which allows to learn to self-regulate brain activity by showing visual or acoustic information about certain parameters of cortical activity[12–14]. An increasing number of studies have demonstrated that neurofeedback is a potential non-pharmacological treatment for the management of several neuropathological conditions, such as chronic pain diseases[15–20]. Many studies

have shown both structural[21] and functional[22] changes in brain networks after neurofeedback training[23–26]. Moreover, the influence of neurofeeback training is not limited to neural activations related to the single trained channel, but changes the functional connectivity involving other brain areas, extending throughout the brain[27]. For example, it has been found that neurofeedback training in sensorimotor rhythm (SMR, 12–15 Hz) in C3 and C4 decrease functional connectivity between frontal and temporal electrodes[28]. Similarly, neurofeedback training in somatosensory areas in fibromyalgia patients showed an increase in functional magnetic resonance imaging (fMRI) connectivity between somatosensory and motor-related areas in resting state associated with reduction of subjective pain[29].

If we consider that the human body has a complex interconnected network physiology, acting on one of these individual systems should lead to changes in the dynamics of other physiological systems and reorganize the physiologic network characteristics. Thus, heart rate variability (HRV) has been related with cerebral blood flow in medial prefrontal cortex and amygdala[30,31] and SMR neurofeedback training with increased HRV and decreased HR[32,33]. However, these studies consider that central nervous system and cardiac system are two independent systems that correlate but they are not considerate as two nodes interconnected which belongs to the same network. The goal of the present study was to analyse changes in EEG and heart activity functional connectivity in response to SMR neurofeedback training in fibromyalgia patients. We also analysed the relation between EEG and EKG activity considering them as nodes of the same network, before and after the neurofeedback training.

MATERIALS AND METHODS

Participants

Clinical and others physiological variables of the present study were previously published by our group[29]. Seventeen right-handed female patients (aged 54.94 ± 10.11) with a diagnosis of fibromyalgia were recruited from the Asociación Granadina de Fibromialgia (AGRAFIM) in Granada (Spain). The diagnosis of fibromyalgia was confirmed following the American Rheumatology College Criteria[34]. Exclusion criteria were: fibromyalgia diagnosis of less than 1 year, pregnancy, vision or auditory deficits, and neurological or psychiatric diseases (except depression). Thirteen of the seventeen fibromyalgia patients had a diagnosed and medicated disorders were accepted in the study. During the experiment, participants were asked to avoid the use of any other non-pharmacology therapy. The study was conducted in accordance with the Declaration of Helsinki (1991) and approved by the Ethics Committee of the Balearic Islands (Spain). Written informed consents were obtained from the participants after the experimental procedure explanation.

Procedure

The patients were sequentially assigned to either a SMR neurofeedback training (SMR, n = 9) or a control group that received false feedback during the training (SHAM, n = 8). All participants underwent a medical and psychological interview, including assessment of mood state (depression, anxiety) and level of pain experienced. Neurofeedback training program consisted in 6 session divided in 3 sessions per week during 2 weeks. Before the first training session (Pre-resting state) and to the start of the sixth training session (Post-resting state), an open-eyes resting state EEG and EKG were recorded during 7 minutes.

The EEG neurofeedback task is described in detail elsewhere[29]. Briefly, the goal of the task was to move a ball and impact in a target localized in the right or in the left of computer screen using the Cursor Task module of BCI2000 platform[35]. The participants learned to synchronize (by increasing power amplitude) and to desynchronize (by decreasing power amplitude) the SMR at sensory-motor related electrodes (C3, CP1, and CP5) to move the ball to target. The number of trials in which the ball hit the target (percentage of hits) was collected as task performance index. The greater the power variation, the greater the performance index was. In the first and the sixth training session both SMR and SHAM groups received real feedback on their performance. In the remaining four training sessions, only the SMR group received real feedback on the SMR power variations, while the SHAM group received random feedback. For the latter, the movement of the ball was manipulated to reach the target only in 50% of the trials.

First and sixth training session consisted in a SMR training of 100 trials (50 trials with the target displayed on each side of the screen) presented in random order with an interval between the 15s trials; both SMR and SHAM groups received real feedback on their performance. The remaining four training sessions consisted of four runs with 20 trials (10 trials with the target displayed on each side of the screen) presented in random order within each run and with an interval between trials of 6s. In these neurofeedback training sessions, only the SMR group received real feedback on the SMR power variations, while the SHAM group received random feedback. For the latter, the movement of the ball was manipulated to reach the target only in 50% of the trials (25% right, 25% left).

Physiological Data Acquisition and Preprocessing

In this paper, functional connectivity results will be presented only. The EEG during neurofeedback and others variables were presented in a previous paper[29]. Physiological signals during resting state were continuously acquired using Ag/AgCl electrodes with a 64-ch QuickAmp amplifier (Brain Products GmbH, Munich, Germany). EEG electrodes were mounted according to the 10/20 montage system and their impedance was maintained at <10 kOhm and sampling rate was of 1000 Hz. The EKG was recorded with one electrode located on left side of back (near to the heart). Both physiological signals were online-referenced to AFz electrode. EEG preprocessing analysis was performed with the EEGLAB toolbox for MATLAB[36]. The recordings were filtered offline with the 0.1-Hz high pass filter, 70-Hz low pass filter. All channels were offline-referenced to the average of the electrodes. EEG waveforms were segmented in epochs of 2 s duration (obtained a total of 210 epochs) for analyses. Nine from sixty-three EEG channels (FPz, AF7, AF8, FT9, FT10, F5, F6, TP7 and TP8) were removed by artifacts (±70 μV amplitude criterion and visual inspection). After artifact rejection was applied, the largest recording had 210 epochs, and the shortest recording had 180 epochs. The mean number of epochs rejected was 12.76, and the standard deviation was 10.92. To equalize the number of epochs between participants, we selected the first 180 epochs after rejection in all recordings.

EKG signal was filtered offline with the 5-Hz high pass filter, 45-Hz low pass filter. R–R intervals were extracted from EKG filtered using the ECGLAB toolbox for MATLAB[37]. Then, the Kardia software[38] was used to obtain the weighted average of the HR every 2 s, obtained a total of 210 HR values.

Functional connectivity Central-EEG

Functional connectivity analysis was conducted with a MATLAB self-programmed script. Firstly, the power spectral density of EEG signals was estimated with Welch's averaged periodogram method using a Hamming window that has 500-point Fast Fourier transformation and without overlapping. Then coherence was calculated as the functional connectivity index in SMR. This index measures the linear correlation between two EEG signals, x(t) and y(t), as a function of the frequency, f. Thus, coherence is the ratio of the crosspower spectral density, Sxy(f), between both signals and their individual power spectral densities, Sxx(f) and Syy(f):

$$K_{xy}(f) = \frac{S_{xy}(f)}{\sqrt{S_{xx}(f)S_{yy}(f)}}$$

To reject spurious correlations between cortical sources, the imaginary part of coherence (iCOH) was calculated in each EEG epoch between central electrodes (Fc5, Fc3, Fc1, Fc2, Fc4, Fc6, C5, C3, C1, Cz, C2, C4, C6, Cp5, Cp3, Cp1, Cpz, Cp2, Cp4, Cp6) and the rest of EEG electrodes. The mean of iCOH across the time was obtained for each link of the Central-EEG network. We decide to use both right and left hemispheres electrodes in central areas because low spatial resolution of EEG and the fact that the use neurofeedback training over C3, CP1 and CP5 electrodes shows contralateral desynchronization and ipsilateral synchronization over central areas

Functional connectivity Central-Heart

This analysis was conducted with a self-programmed MATLAB script. The SMR power was calculated in each EEG epoch as the sum of power spectral densities between 12 and 15 Hz in central electrodes. Length of HR time series was equalized to SMR power time series eliminated the epochs rejected during EEG preprocessing. Both time series

were z transformed to improve normality and stabilize the variance. Finally, Pearson correlations were done between HR and SMR power of central electrodes.

Statistical Analysis

After the initial statistical analyses, we observed that participants in the SMR group as a whole could not achieve an average performance above the random level. Therefore, we decided to subdivide the SMR group in good responders (who achieved a mean performance level above 50% of success during all the sessions) and bad responders (who achieved a mean performance level under 50% of success during all the sessions). Thus, the study was finally conducted with three groups: Good SMR-responders (n = 4) with 67.76% ± 15.97 of successful trials (mean of the six sessions), Bad SMR-responders (n = 5) with 48.31% ± 7.26 of successful trials and SHAM group (n = 8). The task performance (percentage of success) for each group through the six sessions are shown in Figure 1.

INSERT FIGURE 1

Statistical analyses were carried out using IBM SPSS Statistics v.23. For repeated measures analyses, normal distributions of the used variables were tested and Greenhouse–Geisser epsilon corrections were applied to control for violation of the sphericity assumption. When significant effects were found, post hoc analyses were performed using Bonferroni correction. Physiological and network measures consisted in 3 x 2 repeated measures analysis of variance (ANOVA) with Group (SHAM, Good SMR-responders and Bad SMR-responders) as between subject factor and Resting State Session (Pre-resting state and Post-resting state) as within subject factor.

RESULTS

Functional connectivity Central-EEG

A 3 x 2 repeated measures ANOVA on iCOH was realized for each link between central electrodes and the rest of EEG electrodes. For clarity, only significant results related with group by season will be report while main effects of, *Resting State Session* or *Group* will be not reported. Table 1 displays the *F*s and partial etas of Group x Resting State Session interactions in Central-EEG and Central-heart connectivity.

Bonferroni post hoc tests between groups, revealed that Good SMR-responders presented higher iCOH on 5 links (Fc2Fp1, Fc4P4, Fc2F7, Fc1Fz and Fc2Fz) compared with SHAM group in Pre-resting state session. In Post-resting state session, Good SMR-responders had lower iCOH on Fc1F8 link compared with Bad SMR-responders. Bad SMR-responders presented higher iCOH on 8 links (CzFp1, C1F3, Fc1F8, C1Fz, CzF1, CzAF4, CpzF1 and C1AF3) and lower iCOH on 2 links (Fc5F2 and Fc5AF3) compared with SHAM group in Post-resting state session.

P*ost hoc* analysis of the interaction comparing Pre and Post resting state session on each group yielded significant differences in 42 links in Good SMR-responders, 30 links in Bad SMR-responders and only 11 links SHAM group (Figure 2). In summary, Good SMR-responders decreased iCOH on central-frontal, central-central, central-parietal and central-occipital links in Post-resting state session. Bad SMR-responders presented a random patron of increases and decreases between central, frontal and occipital links in Post-resting state session. Finally, SHAM group mainly increased iCOH on some central-frontal, central-central, central-parietal and central-occipital links in Post-

resting state session. Thus, neurofeedback training changed resting EEG functional connectivity more than SHAH training condition and good performance in SMR-modulation was related with a decrease of iCOH after the training.

INSERT TABLE 1

INSERT FIGURE 2

Functional connectivity Central-Heart

The functional connectivity between SMR power in central electrodes and heart activity reached significant Group x Resting State Session interactions in Fc5, Fc4, C6 and Cp6 electrodes (Table 1). Bonferroni *post hoc* tests yielded that Good SMR-responders decreased their connectivity in Fc5HR, Fc4HR and C6HR links in Post-resting state session (Figure 3). However, Bad SMR-responders increased their connectivity on Cp6HR in Post-Resting State Session. SHAM group showed no significant differences in functional connectivity between central electrodes and heart activity.

INSERT FIGURE 3

Bonferroni *post hoc* tests between groups, showed that Good SMR-responders presented higher Central-HR connectivity of SMR power on Fc5HR and Cp6HR compared with Bad SMR-responders in Pre-resting state session. Moreover, Good SMR-responders showed higher HR-SMR power connectivity on Fc5HR compared with SHAM group. No significant differences between groups in Pre-resting state session in Fc4HR and C6HR, nor differences between groups in Post-resting state session were found.

DISCUSSION

The aim of the present study was to examine changes on network physiology after a SMR neurofeedback training. A sample of fibromyalgia patients were enrolled in a neurofeedback training based in synchronization and desynchronization of SMR (12-15 Hz) over central areas. Participants were randomly assigned to a SMR training group or to a SHAM group. The analyses of the task performance during the six sessions revealed that only some participants of the SMR training group were able to achieve a success rate above 50%. Thus, SMR participants were divided into those who performed the task above the chance level (Good SMR responders), and those who performed the task at the chance level (Bad SMR responders). Good responders showed reduced connectivity between central areas with frontal, central, occipital and heart activity after SMR neurofeedback training. However, SHAM group showed increases in EEG functional connectivity while bad SMR responders showed both decreases and increases. In relation to connectivity between Central SMR activity and heart activity, Good SMR responders decreased their connectivity in Fc5HR, Fc4HR and C6HR links after neurofeedback training, while Bad SMR-responders increased functional connectivity on Cp6HR in after neurofeedback training. Results showed that SMR neurofeedback training reduced functional connectivity between central electrodes (situated over motor and sensory areas), EEG and heart activity electrodes. Moreover, functional connectivity changes remained stable during the resting-state evaluation. Our findings provide new evidence that neurofeedback can induce long-term changes on brain functional connectivity and that acting on one of these individual systems can lead to changes in the dynamics of other physiological systems[24–26].

Good SMR-responders were able to successfully synchronize and desynchronize SMR through the sessions. The neural correlate of this successful training was a decrease of functional connectivity of central with frontal, parietal, occipital and with itself nodes in SMR when comparing Pre and Post resting state sessions. On the other hand, bad SMR-responders showed an unclear pattern of increases and decreases in EEG functional connectivity of central with frontal and occipital nodes and with itself in SMR when comparing Pre and Post resting state sessions. In contrast, SHAM group showed an increased functional connectivity of central with frontal, parietal and occipital nodes comparing Pre and Post resting state sessions, though these changes only affected eleven links. It is well known that chronic pain patients show overactivation in frequency ranges between 12 to 15 hz over central areas in resting state[39–42], as well as strengthened connectivity of somatosensory regions with brain regions involved in pain processing[43–45]. Moreover, previous studies suggest that SMR neurofeedback training reduce the coherence of central electrodes with other EEG areas[46,47]. Thus, such as was reported in Terrasa et al., (2020), our results seem to indicate that a decrease of SMR connectivity with the rest of the electrodes could be related with neurofeedback training effectiveness in pain relief[15,18,48,49]. Moreover, neurofeedback SMR training and pain relief could be related with the learning of an EEG pattern characterized by reduced connectivity between central areas and areas related with pain processing, while that EEG pattern characterized by random connectivity could reflect neurofeedback training learning difficulties.

As far as we know, there are no previous studies testing how neurofeedback training could modulate the connectivity between central and peripheral systems,

considering heart activity another node more. It is well known that heart rate has an effect on EEG activity[31,50]. For example, Prinsloo et al. (2011)[51] observed that HRV biofeedback training induces higher theta/beta ratios in the frontal, central and parietal areas. Similarly, neurofeedback training of HRV increases levels of SMR in central localizations, and SMR neurofeedback training produces decrease of HR[32,33]. Thompson and Thompson (2009) support the existing of neural synergy between physiological systems, which propose that neurofeedback done at Cz it will affect not just activity at central region but whole physiological networks (in both central and automatic neural systems). The current study is the first to show that neurofeedback in central areas could induce long-term changes on connectivity, not only at functional connectivity of EEG but also at heart activity. Good SMR-responders decreased the connectivity between three central electrodes (Fc5, Fc4 and C6) and HR after training; while Bad SMR-responders increased the connectivity between Cp6 electrode and HR. Some studies indicate that there is a close integration of brain areas related with pain processing and neuronal network involved in cardiovascular regulation[52–56]. Moreover, a recent study evidenced that altered primary somatosensory cortex connectivity of fibromyalgia patients are related with heart activity[57]. Investigation of the somatic aspects of chronic pain patients have demonstrated that the autonomic state of fibromyalgia patients is characterized by increased sympathetic and decreased parasympathetic tone at resting state[58–60] with concurrent higher heart activity than heathy voluntaries. Our result showed that after a neurofeedback training, the functional connectivity between central localization and heart rate was diminish in Good SMR responders. Nevertheless, the connectivity changes on Fc5HR and Cp6HR should be taken with caution because theses links presented differences between groups in the Pre

resting state session. Thus, physiological network could be shaped by experience driven modulation of SMR neurofeedback and training could cause long-term changes between physiological systems.

The design of the current study presents two shortcomings and, therefore, its findings should be taken with caution. First and most important, the sample size was small (the statistical power was 50.98% considering f = .25, α error = .05 and correlation of repeated measures = .4) and this makes the findings only preliminary. Second, the fact that all participants took regular medication during neurofeedback training could have biased the results, so their possible effects on the connectivity changes observed in this study should be further explored.

In summary, the present study revealed that neurofeedback training based on the synchronization and the desynchronization of the SMR led to changes in the network physiology connectivity between Central Nervous System and Cardiac System. Our results are modest, but they seem to indicate that neurofeedback training is a promising tool for a better understanding of the interactions between the different systems of the organism, allowing to act in physiological network.

REFERENCES

1. Varela F, Lachaux J-P, Rodriguez E, Martinerie J. The brainweb: Phase synchronization and large-scale integration. *Nat Rev Neurosci*. 2001;2(4):229-239. doi:10.1038/35067550

2. Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn Sci*. 2005;9(10):474-480.

doi:10.1016/j.tics.2005.08.011

3. Bartsch RP, Liu KKL, Bashan A, Ivanov PC. Network Physiology: How Organ Systems Dynamically Interact. Perc M, ed. *PLoS One*. 2015;10(11):e0142143. doi:10.1371/journal.pone.0142143

4. Ivanov PCH, Liu KKL, Bartsch RP. Focus on the emerging new fields of network physiology and network medicine. *New J Phys*. 2016;18(10):100201. doi:10.1088/1367-2630/18/10/100201

5. Schulz S, Haueisen J, Bär K-J, Voss A. Multivariate assessment of the central-cardiorespiratory network structure in neuropathological disease. *Physiol Meas*. 2018;39(7):074004. doi:10.1088/1361-6579/aace9b

6. Gould van Praag CD, Garfinkel SN, Sparasci O, et al. Mind-wandering and alterations to default mode network connectivity when listening to naturalistic versus artificial sounds. *Sci Rep*. 2017;7(1):45273. doi:10.1038/srep45273

7. Liu KKL, Bartsch RP, Lin A, Mantegna RN, Ivanov PC. Plasticity of brain wave network interactions and evolution across physiologic states. *Front Neural Circuits*. 2015;9(OCTOBER):1-15. doi:10.3389/fncir.2015.00062

8. Alba G, Vila J, Rey B, Montoya P, Muñoz MÁ. The Relationship Between Heart Rate Variability and Electroencephalography Functional Connectivity Variability Is Associated With Cognitive Flexibility. *Front Hum Neurosci*. 2019;13(February):1-12. doi:10.3389/fnhum.2019.00064

9. Ding K, Tarumi T, Wang C, Vernino S, Zhang R, Zhu DC. Central autonomic

network functional connectivity: correlation with baroreflex function and cardiovascular variability in older adults. *Brain Struct Funct*. 2020;225(5):1575-1585. doi:10.1007/s00429-020-02075-w

10. Sakaki M, Yoo HJ, Nga L, Lee TH, Thayer JF, Mather M. Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. *Neuroimage*. 2016;139:44-52. doi:10.1016/j.neuroimage.2016.05.076

11. Chand T, Li M, Jamalabadi H, et al. Heart Rate Variability as an Index of Differential Brain Dynamics at Rest and After Acute Stress Induction. *Front Neurosci*. 2020;14(July). doi:10.3389/fnins.2020.00645

12. Gruzelier JH. EEG-neurofeedback for optimising performance. I: A review of cognitive and affective outcome in healthy participants. *Neurosci Biobehav Rev*. 2014;44:124-141. doi:10.1016/j.neubiorev.2013.09.015

13. Enriquez-Geppert S, Huster RJ, Herrmann CS. EEG-Neurofeedback as a Tool to Modulate Cognition and Behavior: A Review Tutorial. *Front Hum Neurosci*. 2017;11(February):1-19. doi:10.3389/fnhum.2017.00051

14. Thibault RT, MacPherson A, Lifshitz M, Roth RR, Raz A. Neurofeedback with fMRI: A critical systematic review. *Neuroimage*. 2018;172(December 2017):786-807. doi:10.1016/j.neuroimage.2017.12.071

15. Caro XJ, Winter EF. EEG Biofeedback Treatment Improves Certain Attention and Somatic Symptoms in Fibromyalgia: A Pilot Study. *Appl Psychophysiol Biofeedback*. 2011;36(3):193-200. doi:10.1007/s10484-011-9159-9

16. Jensen MP, Hakimian S, Sherlin LH, Fregni F. New Insights Into Neuromodulatory Approaches for the Treatment of Pain. *J Pain*. 2008;9(3):193-199. doi:10.1016/j.jpain.2007.11.003

17. Jensen MP, Day MA, Miró J. Neuromodulatory treatments for chronic pain: efficacy and mechanisms. *Nat Rev Neurol*. 2014;10(3):167-178. doi:10.1038/nrneurol.2014.12

18. Kayıran S, Dursun E, Dursun N, Ermutlu N, Karamürsel S. Neurofeedback Intervention in Fibromyalgia Syndrome; a Randomized, Controlled, Rater Blind Clinical Trial. *Appl Psychophysiol Biofeedback*. 2010;35(4):293-302. doi:10.1007/s10484-010-9135-9

19. Mayaud L, Wu H, Barthélemy Q, et al. Alpha-phase synchrony EEG training for multi-resistant chronic low back pain patients: an open-label pilot study. *Eur Spine J*. 2019;28(11):2487-2501. doi:10.1007/s00586-019-06051-9

20. Vučković A, Altaleb MKH, Fraser M, McGeady C, Purcell M. EEG Correlates of Self-Managed Neurofeedback Treatment of Central Neuropathic Pain in Chronic Spinal Cord Injury. *Front Neurosci*. 2019;13(JUL):1-17. doi:10.3389/fnins.2019.00762

21. Ghaziri J, Tucholka A, Larue V, et al. Neurofeedback Training Induces Changes in White and Gray Matter. *Clin EEG Neurosci*. 2013;44(4):265-272. doi:10.1177/1550059413476031

22. Ros T, Théberge J, Frewen PA, et al. Mind over chatter: Plastic up-regulation of the fMRI salience network directly after EEG neurofeedback. *Neuroimage*.

2013;65:324-335. doi:10.1016/j.neuroimage.2012.09.046

23. Amano K, Shibata K, Kawato M, Sasaki Y, Watanabe T. Learning to Associate Orientation with Color in Early Visual Areas by Associative Decoded fMRI Neurofeedback. *Curr Biol*. 2016;26(14):1861-1866. doi:10.1016/j.cub.2016.05.014

24. Rance M, Walsh C, Sukhodolsky DG, et al. Time course of clinical change following neurofeedback. *Neuroimage*. 2018;181(December 2017):807-813. doi:10.1016/j.neuroimage.2018.05.001

25. Ramot M, Kimmich S, Gonzalez-Castillo J, et al. Direct modulation of aberrant brain network connectivity through real-time NeuroFeedback. *Elife*. 2017;6:1-23. doi:10.7554/eLife.28974

26. Robineau F, Meskaldji DE, Koush Y, et al. Maintenance of Voluntary Self-regulation Learned through Real-Time fMRI Neurofeedback. *Front Hum Neurosci*. 2017;11(March):1-8. doi:10.3389/fnhum.2017.00131

27. Thompson M, Thompson L. Systems theory of neural synergy: Neuroanatomical underpinnings of effective intervention using neurofeedback plus biofeedback. *J Neurother*. 2009;13(1):72-74.

28. Cheng MY, Wang KP, Hung CL, et al. Higher power of sensorimotor rhythm is associated with better performance in skilled air-pistol shooters. *Psychol Sport Exerc*. 2017;32:47-53. doi:10.1016/j.psychsport.2017.05.007

29. Terrasa JL, Barros-Loscertales A, Montoya P, Muñoz MA. Self-Regulation of SMR Power Led to an Enhancement of Functional Connectivity of Somatomotor

Cortices in Fibromyalgia Patients. *Front Neurosci*. 2020;14(March):1-14. doi:10.3389/fnins.2020.00236

30. Thayer JF, Åhs F, Fredrikson M, Sollers JJ, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev*. 2012;36(2):747-756. doi:10.1016/j.neubiorev.2011.11.009

31. Thompson M, Thompson L. Current Practice of Neurofeedback: Where We Are and How We Got There. *Biofeedback*. 2016;44(4):181-205. doi:10.5298/1081-5937-44.4.02

32. Reid A, Nihon S, Thompson L, Thompson M. The Effects of Heart Rate Variability Training on Sensorimotor Rhythm: A Pilot Study. *J Neurother*. 2013;17(1):43-48. doi:10.1080/10874208.2013.759020

33. Balt K, Du Toit P, Smith M, van Rensburg C. The The Effect of Infraslow Frequency Neurofeedback on Autonomic Nervous System Function in Adults with Anxiety and Related Diseases. *NeuroRegulation*. 2020;7(2):64-74. doi:10.15540/nr.7.2.64

34. Wolfe F, Häuser W. Fibromyalgia diagnosis and diagnostic criteria. *Ann Med*. 2011;43(7):495-502. doi:10.3109/07853890.2011.595734

35. Schalk G, McFarland DJ, Hinterberger T, Birbaumer N, Wolpaw JR. BCI2000: A General-Purpose Brain-Computer Interface (BCI) System. *IEEE Trans Biomed Eng*. 2004;51(6):1034-1043. doi:10.1109/TBME.2004.827072

36. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods*. 2004;134(1):9-21. doi:10.1016/j.jneumeth.2003.10.009

37. de Carvalho JLA, da Rocha AF, de Oliveira Nascimento FA, Neto JS, Junqueira LF. Development of a Matlab software for analysis of heart rate variability. In: *6th International Conference on Signal Processing, 2002.* Vol 2. IEEE; 2002:1488-1491. doi:10.1109/ICOSP.2002.1180076

38. Perakakis P, Joffily M, Taylor M, Guerra P, Vila J. KARDIA: A Matlab software for the analysis of cardiac interbeat intervals. *Comput Methods Programs Biomed*. 2010;98(1):83-89. doi:10.1016/j.cmpb.2009.10.002

39. Kim JA, Bosma RL, Hemington KS, et al. Neuropathic pain and pain interference are linked to alpha-band slowing and reduced beta-band magnetoencephalography activity within the dynamic pain connectome in patients with multiple sclerosis. *Pain*. 2019;160(1):187-197. doi:10.1097/j.pain.0000000000001391

40. Stern J, Jeanmonod D, Sarnthein J. Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients. *Neuroimage*. 2006;31(2):721-731. doi:10.1016/j.neuroimage.2005.12.042

41. Sarnthein J, Stern J, Aufenberg C, Rousson V, Jeanmonod D. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. *Brain*. 2006;129(1):55-64. doi:10.1093/brain/awh631

42. Wang W en, Roy A, Misra G, et al. Altered neural oscillations within and between

sensorimotor cortex and parietal cortex in chronic jaw pain. *NeuroImage Clin*. 2019;24(July):101964. doi:10.1016/j.nicl.2019.101964

43. Cifre I, Sitges C, Fraiman D, et al. Disrupted Functional Connectivity of the Pain Network in Fibromyalgia. *Psychosom Med*. 2012;74(1):55-62. doi:10.1097/PSY.0b013e3182408f04

44. Flodin P, Martinsen S, Löfgren M, Bileviciute-Ljungar I, Kosek E, Fransson P. Fibromyalgia Is Associated with Decreased Connectivity Between Pain- and Sensorimotor Brain Areas. *Brain Connect*. 2014;4(8):587-594. doi:10.1089/brain.2014.0274

45. Ichesco E, Schmidt-Wilcke T, Bhavsar R, et al. Altered Resting State Connectivity of the Insular Cortex in Individuals With Fibromyalgia. *J Pain*. 2014;15(8):815-826.e1. doi:10.1016/j.jpain.2014.04.007

46. Kober SE, Witte M, Stangl M, Väljamäe A, Neuper C, Wood G. Shutting down sensorimotor interference unblocks the networks for stimulus processing: An SMR neurofeedback training study. *Clin Neurophysiol*. 2015;126(1):82-95. doi:10.1016/j.clinph.2014.03.031

47. Reichert JL, Kober SE, Neuper C, Wood G. Resting-state sensorimotor rhythm (SMR) power predicts the ability to up-regulate SMR in an EEG-instrumental conditioning paradigm. *Clin Neurophysiol*. 2015;126(11):2068-2077. doi:10.1016/j.clinph.2014.09.032

48. Mueller HH, Donaldson CCS, Nelson D V., Layman M. Treatment of fibromyalgia incorporating EEG-Driven stimulation: A clinical outcomes study. *J Clin Psychol*.

2001;57(7):933-952. doi:10.1002/jclp.1060

49. Kravitz HM, Esty ML, Katz RS, Fawcett J. Treatment of Fibromyalgia Syndrome Using Low-Intensity Neurofeedback with the Flexyx Neurotherapy System: A Randomized Controlled Clinical Trial. *J Neurother*. 2006;10(2-3):41-58. doi:10.1300/J184v10n02_03

50. Sherlin L, Muench F, Wyckoff S. Respiratory Sinus Arrhythmia Feedback in a Stressed Population Exposed to a Brief Stressor Demonstrated by Quantitative EEG and sLORETA. *Appl Psychophysiol Biofeedback*. 2010;35(3):219-228. doi:10.1007/s10484-010-9132-z

51. Prinsloo GE, Rauch HGL, Lambert MI, Muench F, Noakes TD, Derman WE. The effect of short duration heart rate variability (HRV) biofeedback on cognitive performance during laboratory induced cognitive stress. *Appl Cogn Psychol*. 2011;25(5):792-801. doi:10.1002/acp.1750

52. Edwards L, Ring C, McIntyre D, Carroll D. Modulation of the human nociceptive flexion reflex across the cardiac cycle. *Psychophysiology*. 2001;38(4):S0048577201001202. doi:10.1017/S0048577201001202

53. Edwards L, McIntyre D, Carroll D, Ring C, Martin U. The human nociceptive flexion reflex threshold is higher during systole than diastole. *Psychophysiology*. 2002;39(5):678-681. doi:10.1017/S0048577202011770

54. Edwards L, Inui K, Ring C, Wang X, Kakigi R. Pain-related evoked potentials are modulated across the cardiac cycle. *Pain*. 2008;137(3):488-494. doi:10.1016/j.pain.2007.10.010

55. Martins AQ, Ring C, McIntyre D, Edwards L, Martin U. Effects of unpredictable stimulation on pain and nociception across the cardiac cycle. *Pain*. 2009;147(1-3):84-90. doi:10.1016/j.pain.2009.08.016

56. Shao S, Shen K, Wilder-Smith EPV, Li X. Effect of pain perception on the heartbeat evoked potential. *Clin Neurophysiol*. 2011;122(9):1838-1845. doi:10.1016/j.clinph.2011.02.014

57. Kim J, Loggia ML, Cahalan CM, et al. The Somatosensory Link in Fibromyalgia: Functional Connectivity of the Primary Somatosensory Cortex Is Altered by Sustained Pain and Is Associated With Clinical/Autonomic Dysfunction. *Arthritis Rheumatol*. 2015;67(5):1395-1405. doi:10.1002/art.39043

58. Meeus M, Goubert D, De Backer F, et al. Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: A systematic review. *Semin Arthritis Rheum*. 2013;43(2):279-287. doi:10.1016/j.semarthrit.2013.03.004

59. Reyes del Paso GA, Garrido S, Pulgar Á, Martín-Vázquez M, Duschek S. Aberrances in Autonomic Cardiovascular Regulation in Fibromyalgia Syndrome and Their Relevance for Clinical Pain Reports. *Psychosom Med*. 2010;72(5):462-470. doi:10.1097/PSY.0b013e3181da91f1

60. Tracy LM, Ioannou L, Baker KS, Gibson SJ, Georgiou-Karistianis N, Giummarra MJ. Meta-analytic evidence for decreased heart rate variability in chronic pain implicating parasympathetic nervous system dysregulation. *Pain*. 2016;157(1):7-29. doi:10.1097/j.pain.0000000000000360

Figures & Tables

Table 1. Significant F-Test results and partial etas of 3 x 2 repeated measures ANOVAs for each node of Network Physiology.					
Fp1Cz	F(2,14)=9.61**	η_p^2=.58	Fp1Fc1	F(2,14)=4.52*	η_p^2=.39
Fp1Fc2	F(2,14)=7.87**	η_p^2=.53	Fp1Fc3	F(2,14)=4.12*	η_p^2=.37
Fp1C5	F(2,14)=7.69**	η_p^2=.52	Fp2C5	F(2,14)=8.18**	η_p^2=.54
F3C4	F(2,14)=4.12*	η_p^2=.37	F3Cz	F(2,14)=5.29*	η_p^2=.43
F3Fc1	F(2,14)=4.83*	η_p^2=.41	F3Fc2	F(2,14)=5.15*	η_p^2=.42
F3Cp2	F(2,14)=4.95*	η_p^2=.41	F3C1	F(2,14)=5.56*	η_p^2=.44
F3C2	F(2,14)=4.11*	η_p^2=.37	F4C5	F(2,14)=6.16*	η_p^2=.47
C3Fz	F(2,14)=4.07*	η_p^2=.37	C3Fc2	F(2,14)=3.75*	η_p^2=.35
C4O1	F(2,14)=4.57*	η_p^2=.40	C4Fz	F(2,14)=6.30*	η_p^2=.47
C4Fc1	F(2,14)=6.82**	η_p^2=.49	C4Cp5	F(2,14)=4.99*	η_p^2=.42
C4F1	F(2,14)=4.95*	η_p^2=.41	C4Fc3	F(2,14)=6.21*	η_p^2=.47
C4Cp3	F(2,14)=5.11*	η_p^2=.42	P4Cz	F(2,14)=4.16*	η_p^2=.37
P4Fc1	F(2,14)=5.75*	η_p^2=.45	P4Fc2	F(2,14)=7.29**	η_p^2=.51
O2Fc1	F(2,14)=3.96*	η_p^2=.36	O2Fc3	F(2,14)=5.55*	η_p^2=.44
F7Fc1	F(2,14)=4.10*	η_p^2=.37	F7Fc2	F(2,14)=3.80*	η_p^2=.35
F8Fc1	F(2,14)=5.24*	η_p^2=.43	P7Fc2	F(2,14)=3.89*	η_p^2=.36
P8Fc3	F(2,14)=4.23*	η_p^2=.38	FzCz	F(2,14)=4.12*	η_p^2=.37
FzFc1	F(2,14)=7.72**	η_p^2=.53	FzFc2	F(2,14)=4.78*	η_p^2=.41
FzCp2	F(2,14)=6.67**	η_p^2=.49	FzCp6	F(2,14)=4.13*	η_p^2=.37
FzC1	F(2,14)=6.07*	η_p^2=.46	FzC2	F(2,14)=4.64*	η_p^2=.40
FzCp4	F(2,14)=4.21*	η_p^2=.38	FzC5	F(2,14)=8.74**	η_p^2=.56
CzOz	F(2,14)=4.18*	η_p^2=.37	CzPoz	F(2,14)=4.98*	η_p^2=.42
CzF1	F(2,14)=3.90*	η_p^2=.36	CzAF4	F(2,14)=7.34**	η_p^2=.51
CzPo7	F(2,14)=3.87*	η_p^2=.36	PzC5	F(2,14)=5.02*	η_p^2=.42
OzFc1	F(2,14)=4.91*	η_p^2=.41	OzFc2	F(2,14)=4.87*	η_p^2=.41
Fc1Fc2	F(2,14)=5.02*	η_p^2=.42	Fc1Cp2	F(2,14)=4.32*	η_p^2=.38
Fc1Poz	F(2,14)=7.37**	η_p^2=.51	Fc1AF3	F(2,14)=4.01*	η_p^2=.36
Fc1AF4	F(2,14)=4.60*	η_p^2=.40	Fc2C1	F(2,14)=4.01*	η_p^2=.36
Fc2AF3	F(2,14)=5.13*	η_p^2=.42	Fc2Cp4	F(2,14)=5.07*	η_p^2=.42
Fc2Po8	F(2,14)=4.47*	η_p^2=.39	Cp2Po3	F(2,14)=3.78*	η_p^2=.35
Fc5F2	F(2,14)=3.80*	η_p^2=.35	Fc5AF3	F(2,14)=4.82*	η_p^2=.41
Fc5HR	F(2,14)=4.10*	η_p^2=.37	Cp5AF3	F(2,14)=8.10**	η_p^2=.54
Cp5Cp4	F(2,14)=4.09*	η_p^2=.37	Cp5Po4	F(2,14)=4.20*	η_p^2=.38
Cp6Po3	F(2,14)=4.59*	η_p^2=.40	Cp6Po4	F(2,14)=4.40*	η_p^2=.39
Cp6Ft7	F(2,14)=3.75*	η_p^2=.35	Cp6HR	F(2,14)=4.50*	η_p^2=.39
F1Fc3	F(2,14)=6.11*	η_p^2=.47	F1C5	F(2,14)=5.69*	η_p^2=.45
F1Cpz	F(2,14)=4.74*	η_p^2=.40	F2C5	F(2,14)=3.94*	η_p^2=.36
C1AF3	F(2,14)=5.96*	η_p^2=.46	C2AF3	F(2,14)=4.54*	η_p^2=.39
P1C5	F(2,14)=4.91*	η_p^2=.41	AF3Fc3	F(2,14)=6.24*	η_p^2=.47
AF4Fc3	F(2,14)=3.86*	η_p^2=.36	AF4C5	F(2,14)=5.10*	η_p^2=.42
Fc3Po8	F(2,14)=4.79*	η_p^2=.41	Fc4HR	F(2,14)=4.13*	η_p^2=.37
Cp3C5	F(2,14)=5.08*	η_p^2=.42	Cp4Po3	F(2,14)=6.78**	η_p^2=.49
Po3C6	F(2,14)=9**	η_p^2=.56	C6HR	F(2,14)=4.73*	η_p^2=.40

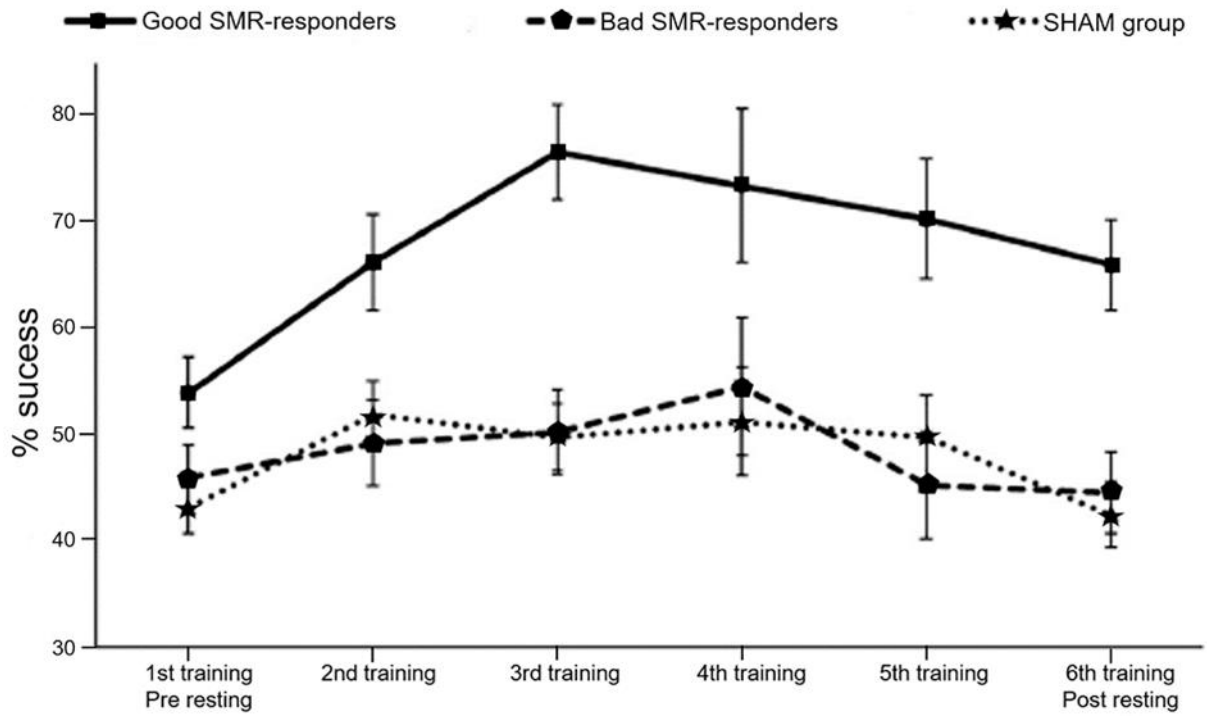

Figure 1. Percentage of success of each group across training sessions.

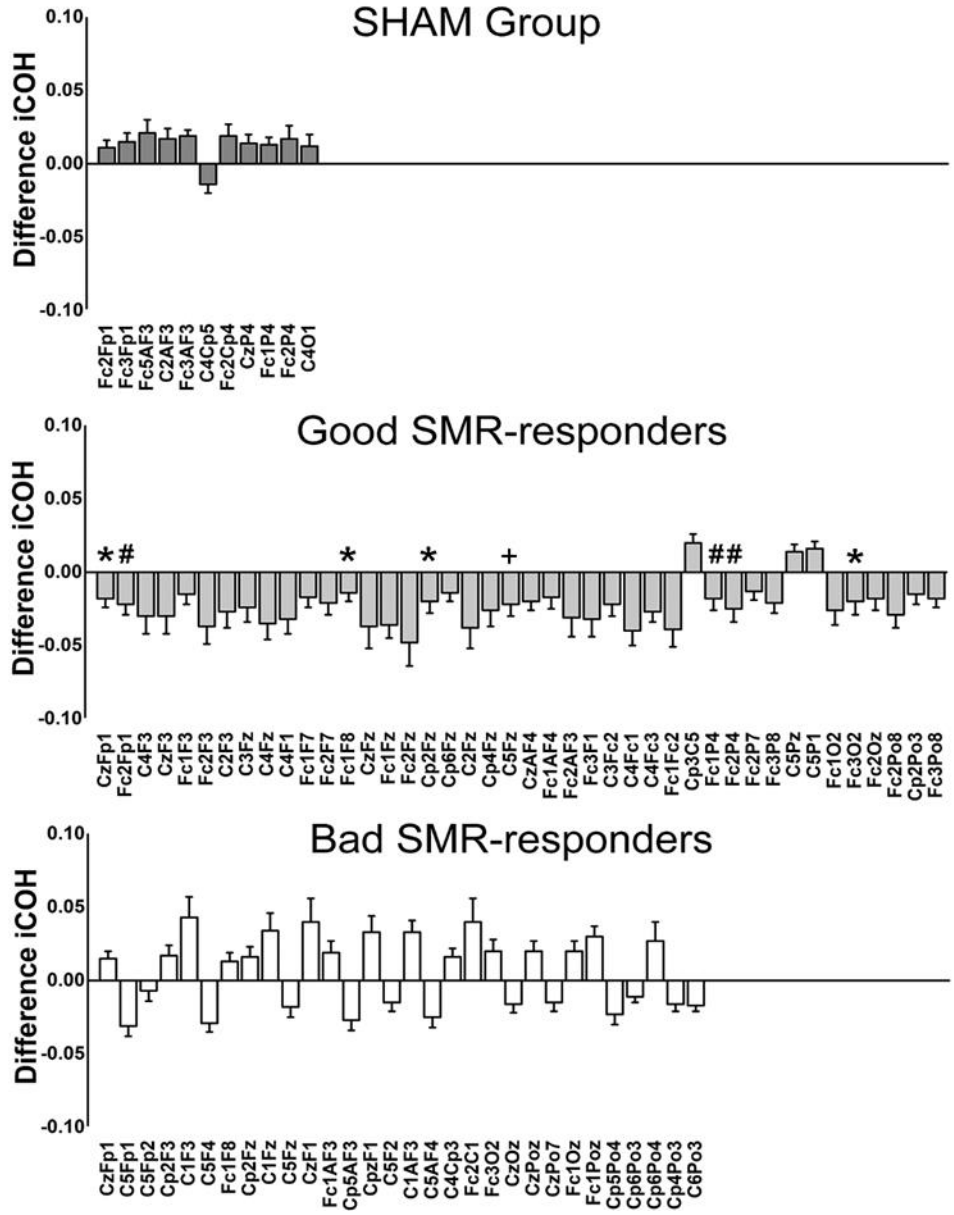

Figure 2. Means of differences and standard errors of significant differences ($p < .05$) between Post and Pre SMR resting state sessions in Central-EEG links. The symbols indicate if increases and decreases in common links between groups were equal or different (# Good ≠ SHAM; * Good ≠ Bad; + Good = Bad).

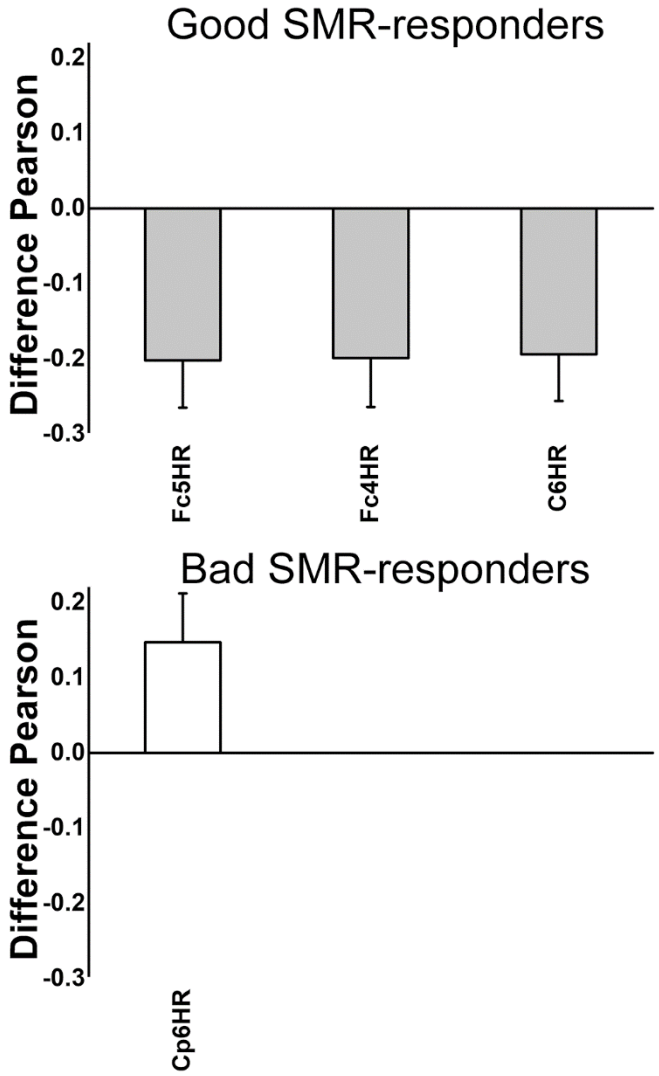

Figure 3. Means and standard errors of significant differences ($p < .05$) between Post and Pre sessions of central-heart activity links.

DISCUSIÓN GENERAL

El objetivo de esta tesis fue estudiar la conectividad funcional cerebral y de la actividad periférica relacionada con la modulación del dolor. Es bien conocido, que el dolor afecta tanto a la actividad central como periférica, y que afecta a áreas cerebrales relacionadas con el control de las respuestas autonómicas. Sin embargo, el abordaje integral de ambos sistemas como pertenecientes a una *network physiology,* ha sido escasamente abordado con anterioridad. Por ello, se comenzó explorando la relación entre la flexibilidad cognitiva, la actividad periférica y la conectividad funcional central en un grupo de voluntarios sanos. En primer lugar, los participantes realizaron el *Test de Cambios* (Seisdedos, 2004), que evalúa la capacidad de concentración mientras se atiende a varias condiciones cambiantes. A continuación, se registraba la actividad cardíaca y cerebral en estado de reposo. Se calculó el número de aciertos y errores de la tarea cognitiva, la HRV y la variabilidad de la conectividad funcional del EEG (en las bandas delta, theta, alfa y beta). Los análisis señalaron que el rendimiento en la tarea estaba correlacionado tanto con la HRV, como con la variabilidad de la conectividad cerebral en todas las frecuencias. Sin embargo, se observó que el principal predictor de la flexibilidad cognitiva fue la variabilidad de la conectividad del EEG. Es más, la relación entre HRV y flexibilidad cognitiva estaba mediada por la variabilidad de la conectividad funcional del EEG.

Nuestros resultados apuntan a que existe una integración central-autonómica, que actúa de manera sincronizada y que se relaciona con procesos mentales, Además, en el caso del estudio de la flexibilidad cognitiva, los resultados apuntan a que la conectividad cerebral es mejor predictora de la flexibilidad cognitiva que la HRV. Esto nos lleva a pensar que, la relación que se encuentra entre el aumento de la HRV y mayor flexibilidad cognitiva (Thayer & Lane, 2009) es indirecta y que es la variabilidad de la conectividad cerebral la que media entre la HRV y la flexibilidad cognitiva. Así, para la comprensión de los procesos psicológicos desde una perspectiva fisiológica, resulta necesario el

estudio de la actividad fisiológica central y periférica como una red integrada de sistemas que interactúan y se regulan para alcanzar un objetivo.

A partir de la metodología propuesta en el estudio primero, nos propusimos estudiar la relación entre el dolor y la respuesta afectiva. Para ello, estudiamos los cambios que produce el dolor tónico en los patrones de respuestas autonómicas y conectividad funcional del EEG ante diferentes estímulos afectivos. Un conjunto de voluntarios sanos visualizó tres bloques de imágenes afectivas dos veces (agradables, desagradables y neutras). En paralelo, se aplicó un estímulo doloroso térmico en uno de los bloques de cada categoría afectiva. Durante la tarea experimental se registró de manera continua la conductancia eléctrica de la piel, la tasa cardíaca y la conectividad funcional del EEG (bandas delta, theta, alfa y beta). Los resultados mostraron que el dolor alteró el patrón de respuesta fisiológica típico producido por las imágenes afectivas, aumentando los niveles de conductancia en imágenes neutras y acelerando la tasa cardíaca en imágenes agradables y desagradables. En cuanto a la conectividad funcional de EEG, se observa que el dolor provocó cambios en la conectividad funcional del hemisferio derecho, durante la visualización de imágenes agradables y desagradables comparadas con las neutrales. En el análisis de la conectividad por regiones y bandas de frecuencia, se encontró que el dolor aumentó principalmente la conectividad de las regiones frontal y central en las bandas delta y theta, cuando se estaban visualizando imágenes agradables y desagradables. Por otro lado, el dolor disminuyó la conectividad de la región frontal en la banda alfa, cuando se estaban visualizando imágenes agradables. Respecto a los cambios de conectividad que el dolor provocó durante la visualización de imágenes neutras, tan sólo se observa un aumento la conectividad entre la región central derecha y la región frontal derecha en las bandas theta y alfa.

Sabiendo que las imágenes agradables y desagradables empleadas fueron seleccionadas por su relevancia motivacional, se puede concluir que el dolor tónico se volvió un estímulo lo suficientemente relevante como para captar los recursos atencionales dedicados al procesamiento de las imágenes. En consonancia con otros estudios (Van Damme et al., 2010), cuando el dolor ocurre durante la consecución de un objetivo (en nuestro caso era visualizar las imágenes), es capaz de capturar la atención

impidiendo el procesamiento de la tarea principal. Así, nuestros resultados parecen indicar que los problemas emocionales y de alexitimia que se observan en pacientes con dolor crónico (Roselló, et al., 2011), son consecuencia de la intensidad y persistencia del propio dolor, que impide el procesamiento atencional de otros estímulos afectivos. Esto conlleva como consecuencia que, para modular el dolor, es necesario contar con estímulos lo suficientemente interesantes para captar los recursos atencionales e impedir el procesamiento del dolor. Así, estímulos emocionales complejos, ricos a nivel estimular y que impliquen diferentes modalidades sensoriales serían potentes moduladores del dolor.

Finalmente, en el estudio tercero, comprobamos los cambios en la conectividad central-periférica (*network physiology*) mediante un entrenamiento neurofedback y su relación con la modulación del dolor. Un grupo de pacientes con fibromialgia realizó un programa de entrenamiento de neuromodulación del ritmo sensorimotor (SMR), mientras que otro grupo de pacientes realizó un entrenamiento falso (SHAM). Antes y después del entrenamiento, se registró la tasa cardíaca y la actividad cerebral durante un período de reposo de 7 minutos. Se estudió los cambios en la tasa cardíaca y la conectividad funcional del EEG en la banda de frecuencia 12_15 Hz (componente imaginario de la coherencia espectral SMR). Tras el análisis inicial de los resultados de la ejecución en la tarea, el grupo de entrenamiento SMR fue subdividido en dos grupos: aquellas participantes cuyos números de aciertos alcanzaban niveles esperados (alrededor del 75%; buenas SMR-respondedoras), y las que no alcanzaron los niveles esperados (malas SMR-respondedoras). El análisis de las diferencias de conectividad funcional entre el Pretratamiento y el Postratamiento en cada grupo, reveló que las buenas SMR-respondedoras experimentaron una reducción de la conectividad entre la región central del EEG con el resto de regiones del cerebro y entre la región central y la tasa cardíaca tras el entrenamiento. El patrón de cambios de conectividad de las malas SMR-respondedoras no fue claro, observándose tanto reducciones como aumentos en la conectividad región central-cerebro y región central-tasa cardíaca. El grupo SHAM, sin embargo, mostró aumentos de la conectividad EEG en un reducido grupo de enlaces y no mostró ningún cambio en la conectividad EEG-tasa cardíaca.

En líneas generales, el estudio demuestra que el entrenamiento SMR provoca cambios a largo plazo en la conectividad EEG y, de manera novedosa, encuentra que también cambia la conectividad entre el EEG y la actividad cardíaca. Conviene señalar, que estos resultados son modestos y hay que tomarlos con precaución, porque se observan algunas diferencias entre los grupos en el Pretratamiento y el tamaño de la muestra fue pequeño. Pese a ello, los cambios de la conectividad del EEG en la banda SMR van en la línea de lo esperado en el grupo de buenas SMR-respondedoras (Kober et al., 2015; Reicherts et al., 2016), observando reducciones en los autoinformes de dolor (Terrasa et al., 2020). Nuestros resultados aunque modestos, vuelven a sostener la necesidad del estudio integral desde un punto de vista fisiológico. Más aún, demuestran las relaciones existentes entre los diferentes sistemas fisiológicos y cómo es posible modificar la relación entre ellos mediante el aprendizaje de la autorregulación cerebral.

CONCLUSIONES

a) La actividad cardíaca y cerebral se relacionan entre sí en estado de reposo.

b) La sincronización entre la actividad cardíaca y la actividad cerebral influye sobre el rendimiento cognitivo y la modulación del dolor.

c) La relación entre variabilidad de la tasa cardíaca y rendimiento cognitivo está mediada por la variabilidad de la conectividad funcional del EEG.

d) El dolor afecta a los patrones de activación autonómica típicos provocados por los estímulos afectivos.

e) El dolor afecta a la conectividad funcional del EEG asociada con la atención hacia los estímulos afectivos.

f) El dolor produce cambios fisiológicos asociados con una captura de la atención por parte del estímulo doloroso y con una reducción de la atención hacia estímulos afectivos.

g) La relación entre dolor y emoción es a través de los mecanismos atencionales.

h) El neurofeedback es capaz de alterar la conectividad de la *network physiology*.

i) La reducción de la conectividad SMR de los electrodos centrales con otros sistemas de la *network physiology* ayuda a reducir el dolor de pacientes con dolor crónico.

j) El estudio de la *network physiology* es importante para tener una mejor compresión y menos sesgos en el estudio del dolor.

MENCIÓN INTERNACIONAL/INTERNATIONAL PhD

AFFECTIVE MODULATION OF BRAIN ACTIVITY TO RELIEVE PAIN: EEG FUNCTIONAL CONNECTIVITY STUDY

Abstract

In Spain the prevalence of chronic pain is 16.6% (Dueñas et al., 2015). Approximately 50% of patients report limitations in their daily life, 30% feelings of sadness and / or anxiety, and 47.2% pain affects their family life. Pathologies related to chronic pain represent one of the highest economic costs for health systems in developed world. The Pain Treatment Unit issued a report in 2011 through the Ministry of Health, Social Policy and Equality of Spain where pain is considered a multidimensional problem and it is specified that the treatment of pain must be multidisciplinary. Moreover, it is proposed that intervention programs should be comprehensive and treat the different dimensions of pain.

Physiological studies have been important in understanding pain and in developing more effective treatments. Painful stimuli cause changes in the synchronization between brain regions and an increase in sympathetic activity. Patients with chronic pain show in resting state: abnormal sympathetic activity, altered functional brain connectivity (between sensory, attentional and affective areas), and sensitization of the central nervous system towards nociceptive stimuli. These changes are related to difficulties in the processing of affective stimuli and the existence of comorbid disorders with chronic pain, such as depression and anxiety. Furthermore, studies that attempt to study the influence of pain on affective processing show that pain inhibits it. Thus, patients with chronic pain present alterations in the processing of affective stimuli, which could be related to an attentional bias towards pain and a reduction in attention to affective stimuli. The model of motivational account of attention to pain (Van Damme et al., 2010), proposes that pain is a powerful motivator that captures cognitive resources competing with other relevant stimuli for attention. Thus, it is observed that, in cognitive tasks,

patients with chronic pain show worse performance than healthy volunteers. However, there is no research that studies how these attentional deficits can affect to the attentional resources to process affective stimuli.

As a result of findings about the physiology of pain, biofeedback treatments have been developed, whose objective is that patients learn to modulate their physiological activity and reduce their pain. The neurofeedback for the treatment of chronic pain shows potential benefits in reducing pain and improving mood. Among the different features of the electroencephalography (EEG) signal that can be trained, the modulation of the spectral density of the sensorimotor rhythm (SMR) is one of those that are being largest used in the treatment of chronic pain syndromes. Recently, some studies found that SMR training produces changes in functional brain connectivity and these are related with a reduction of pain in chronic patients (Caro & Winter, 2011; Kayiran et al., 2010). However, it is unknown whether neurofeedback training can reverse the autonomic alterations that chronic pain patients also present.

The main objective of this thesis is to study brain functional connectivity and peripheral activity related to pain modulation. Functional connectivity is a type of measure that reflects the statistical dependence that exists between two sources of physiological activity without there is physical connection necessarily. The connectivity between two brain regions reflects the integration of the information of each region for the processing of a cognitive task or an emotional state. In addition, these measures offer the possibility of studying the synchronization between brain regions, peripheral responses and psychological variables. The research of the relationship between central and peripheral variables has given rise to new research topics, such the Neurovisceral Integration Model and the *network physiology* (Thayer & Lane, 2009; Ivanov & Bartsch, 2013), which focus on the study of the interaction between the central nervous system and the autonomic nervous system. Despite the growing interest in the holistic study of physiology, there are scarce studies that explore the relationship between functional connectivity, peripheral physiology, and affective modulation in patients with chronic pain.

The current document is divided into three studies presented in article format. In the first paper, the objective was to test the analysis methods of EEG functional connectivity and the relationship between EEG connectivity, peripheral activity and psychological variables. Specifically, it was studied the relationship between heart rate variability (HRV), functional connectivity variability, and cognitive flexibility. Previous literature seems to indicate that there is a positive relationship between HRV in resting state and cognitive flexibility (Gillie & Thayer, 2014). However, the relationship of these two variables with the variability of brain functional connectivity in resting state is unknown (Liu et al., 2018). The experimental task was based on performing the "*Test de Cambios*" (Seisdedos, 2004) and then recording the heart rate and brain activity in resting state. HRV and the variability of EEG functional connectivity were related to cognitive flexibility and to each other. Multiple linear regression analyzes revealed that the main predictor of cognitive flexibility was the variability of EEG connectivity and not HRV, as proposed by the Neurovisceral Integration Model (Thayer & Lane, 2009). Furthermore, the partial correlation analysis revealed that the relationship between HRV and cognitive flexibility was mediated by the variability of the EEG functional connectivity. In conclusion, the study of mental processes based only on central or peripheral physiological activity can lead to a partial and biased view of the phenomenon to be studied.

In the second study, the effect of tonic pain on the processing of affective stimuli was investigated, through the analysis of peripheral responses and functional brain connectivity. The experimental task was based on the viewing of affective images (pleasant, neutral and unpleasant) with and without pain while the skin conductance response (SCR), heart rate and brain electrical activity was recording. The results indicated that the pattern of response to affective images in the non-pain condition was as expected, an increase in conductance and cardiac deceleration in pleasant and unpleasant images, compared with neutral images. However, when these images were presented join with pain, the physiological pattern changed, with no difference being found between the three types of images. On the other hand, the pattern of brain functional connectivity changed between pain and non-pain conditions, an increase in connectivity between brain regions related to attentional processing was found. These

results seem to indicate that pain reduces attention to other stimuli, pointing to an attentional bias towards pain that could explain the difficulties in processing affective stimuli present in patients with chronic pain.

The objective of the third study was to verify the efficacy of neurofeedback training to modulate EEG functional connectivity and EEG-Heart Rate connectivity in patients with chronic pain. A group of fibromyalgia patients underwent a neurofeedback training for learn to modulate the sensorimotor rhythm (SMR) of the brain in central and left central-parietal regions. Another group of patients received fake training. After the analysis of neurofeedback performance, the group of patients was divided into two groups: those who had learned to modulate their brain activity and those who had a bad performance. Analysis of pain ratings during training revealed that those patients who were successful in their training reduced their pain. Likewise, the group that was successful in their training reduced the functional connectivity of the central electrodes with the rest of EEG and with Heart Rate. Despite the limitations of the study, the findings seem to indicate that neurofeedback, in addition to affecting brain networks, also affects the brain's networks with the rest of the body.

Conclusions

a) Cardiac and brain activity are synchronized in resting state.

b) Synchronization between heart and brain activities are related with pain modulation and cognitive performance.

c) The relationship between HRV and cognitive performance is mediated by the variability of EEG functional connectivity.

d) Pain affects typical autonomic patterns elicited by affective stimuli.

e) Pain affects EEG functional connectivity associated with attention to affective stimuli.

f) Pain produces physiological changes associated with a catch of attention by the painful stimulus and with a decrease of attention to affective stimuli.

g) The relationship between pain and emotion is through attentional mechanisms.

h) Neurofeedback training can change *network physiology* connectivity.

i) Reducing the SMR connectivity of the central electrodes with other *network physiology* systems reduce pain in chronic pain patients.

j) The study of *network physiology* is important to improve the understanding of pain and reduce bias in the study of pain.

REFERENCIAS

Aldhafeeri, F. M., Mackenzie, I., Kay, T., Alghamdi, J., & Sluming, V. (2012). Regional brain responses to pleasant and unpleasant IAPS pictures: Different networks. *Neuroscience Letters*, *512*(2), 94–98. https://doi.org/10.1016/j.neulet.2012.01.064

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*(4), 463. https://doi.org/10.1016/j.ejpain.2004.11.001

Apkarian, A. V., Hashmi, J. A., & Baliki, M. N. (2011). Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. *Pain*, *152*(3 Suppl), S49. https://doi.org/10.1016/j.pain.2010.11.010

Aziz, Q., Barke, A., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Rief, W., Scholz, J., Schug, S., Smith, B. H., Svensson, P., … Wand, S.-J. (2015). A classification of chronic pain for ICD-11. *Pain*, *156*(6), 1003–1007.

Bashan, A., Bartsch, R. P., Kantelhardt, J. W., Havlin, S., & Ivanov, P. C. (2012). Network physiology reveals relations between network topology and physiological function. Nature communications, 3(1), 1-9. doi: https://doi.org/10.1038/ncomms1705

Bartsch RP, Liu KKL, Bashan A, Ivanov PC. (2015). Network Physiology: How Organ Systems Dynamically Interact. Perc M, ed. PLoS One. 10(11): e0142143. https://doi.org/10.1371/journal.pone.0142143

Bingel, U., Rose, M., Gläscher, J., & Büchel, C. (2007). fMRI reveals how pain modulates visual object processing in the ventral visual stream. Neuron, 55(1), 157-167. doi: https://doi.org/10.1016/j.neuron.2007.05.032

Benarroch, E. E. (2006). Pain-autonomic interactions. *Neurological Sciences*, *27*(S2), s130–s133. https://doi.org/10.1007/s10072-006-0587-x

Bradley, M. M. (2009). Natural selective attention: Orienting and emotion. *Psychophysiology*, *46*(1), 1–11. https://doi.org/10.1111/j.1469-8986.2008.00702.x

Campos da Paz, V. K., Garcia, A., Campos da Paz Neto, A., & Tomaz, C. (2018). SMR Neurofeedback Training Facilitates Working Memory Performance in Healthy Older Adults: A Behavioral and EEG Study. *Frontiers in Behavioral Neuroscience*, *12*(December), 1–11. https://doi.org/10.3389/fnbeh.2018.00321

Caro, X. J., & Winter, E. F. (2011). EEG Biofeedback Treatment Improves Certain Attention and Somatic Symptoms in Fibromyalgia: A Pilot Study. *Applied Psychophysiology and Biofeedback*, *36*(3), 193–200. https://doi.org/10.1007/s10484-011-9159-9

Chand, T., Li, M., Jamalabadi, H., Wagner, G., Lord, A., Alizadeh, S., Danyeli, L. V., Herrmann, L., Walter, M., & Sen, Z. D. (2020). Heart Rate Variability as an Index of Differential Brain Dynamics at Rest and After Acute Stress Induction. *Frontiers in Neuroscience*, *14*(July). https://doi.org/10.3389/fnins.2020.00645

Chang, C., Metzger, C. D., Glover, G. H., Duyn, J. H., Heinze, H. J., & Walter, M. (2013). Association between heart rate variability and fluctuations in resting-state functional connectivity. *NeuroImage*, *68*, 93–104. https://doi.org/10.1016/j.neuroimage.2012.11.038

Choe, M. K., Lim, M., Kim, J. S., Lee, D. S., & Chung, C. K. (2018). Disrupted Resting State Network of Fibromyalgia in Theta frequency. *Scientific Reports*, *8*(1), 1–9. https://doi.org/10.1038/s41598-017-18999-z

Coulombe, M. A., Lawrence, K. S., Moulin, D. E., Morley-Forster, P., Shokouhi, M., Nielson, W. R., & Davis, K. D. (2017). Lower functional connectivity of the periaqueductal gray is related to negative affect and clinical manifestations of fibromyalgia. *Frontiers in Neuroanatomy*, *11*(June), 1–12.

https://doi.org/10.3389/fnana.2017.00047

D'Agostino, G. (2014). Preface. *Understanding Complex Systems*, 203–222. https://doi.org/10.1007/978-3-319-03518-5

Davelaar, E. J., & Jilek, J. (2020). Sensorimotor Rhythm is Associated with Reinforcement Learning and Cognitive Impulsivity: A Neurofeedback Study. *Curr Neurobiol*, *11*(2), 27–36.

de la Cruz, F., Schumann, A., Köhler, S., Reichenbach, J. R., Wagner, G., & Bär, K.-J. (2019). The relationship between heart rate and functional connectivity of brain regions involved in autonomic control. *NeuroImage*, *196*(April), 318–328. https://doi.org/10.1016/j.neuroimage.2019.04.014

De Vico Fallani, F., Richiardi, J., Chavez, M., & Achard, S. (2014). Graph analysis of functional brain networks: practical issues in translational neuroscience. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *369*(1653), 20130521. https://doi.org/10.1098/rstb.2013.0521

Dépelteau, A., Racine-Hemmings, F., Lagueux, É., & Hudon, C. (2019). Chronic pain and frequent use of emergency department: A systematic review. *American Journal of Emergency Medicine*, *38*(2), 358–363. https://doi.org/10.1016/j.ajem.2019.158492

Ding, K., Tarumi, T., Wang, C., Vernino, S., Zhang, R., & Zhu, D. C. (2020). Central autonomic network functional connectivity: correlation with baroreflex function and cardiovascular variability in older adults. *Brain Structure and Function*, *225*(5), 1575–1585. https://doi.org/10.1007/s00429-020-02075-w

Dueñas, M., Salazar, A., Ojeda, B., Fernández-Palacín, F., Micó, J. A., Torres, L. M., & Failde, I. (2015). A Nationwide Study of Chronic Pain Prevalence in the General Spanish Population: Identifying Clinical Subgroups Through Cluster Analysis. *Pain Medicine (United States)*, *16*(4), 811–822. https://doi.org/10.1111/pme.12640

Enriquez-Geppert, S., Huster, R. J., & Herrmann, C. S. (2017). EEG-Neurofeedback as

a Tool to Modulate Cognition and Behavior: A Review Tutorial. *Frontiers in Human Neuroscience*, *11*(February), 1–19. https://doi.org/10.3389/fnhum.2017.00051

Giel, K. E., Paganini, S., Schank, I., Enck, P., Zipfel, S., & Junne, F. (2018). Processing of Emotional Faces in Patients with Chronic Pain Disorder: An Eye-Tracking Study. *Frontiers in Psychiatry*, *9*(MAR). https://doi.org/10.3389/fpsyt.2018.00063

Gillie, B. L., & Thayer, J. F. (2014). Individual differences in resting heart rate variability and cognitive control in posttraumatic stress disorder. *Frontiers in Psychology*, *5*(JUL), 1–7. https://doi.org/10.3389/fpsyg.2014.00758

González-Roldán, A. M., Cifre, I., Sitges, C., & Montoya, P. (2016). Altered Dynamic of EEG Oscillations in Fibromyalgia Patients at Rest. *Pain Medicine*, *17*(6), pnw023. https://doi.org/10.1093/pm/pnw023

Gould van Praag, C. D., Garfinkel, S. N., Sparasci, O., Mees, A., Philippides, A. O., Ware, M., Ottaviani, C., & Critchley, H. D. (2017). Mind-wandering and alterations to default mode network connectivity when listening to naturalistic versus artificial sounds. *Scientific Reports*, *7*(1), 45273. https://doi.org/10.1038/srep45273

Gruzelier, J. H. (2014a). EEG-neurofeedback for optimising performance. I: A review of cognitive and affective outcome in healthy participants. *Neuroscience and Biobehavioral Reviews*, *44*, 124–141. https://doi.org/10.1016/j.neubiorev.2013.09.015

Gruzelier, J. H. (2014b). EEG-neurofeedback for optimising performance. II: Creativity, the performing arts and ecological validity. *Neuroscience and Biobehavioral Reviews*, *44*, 142–158. https://doi.org/10.1016/j.neubiorev.2013.11.004

Hajcak, G., & Foti, D. (2020). Significance?... Significance! Empirical, methodological, and theoretical connections between the late positive potential and P300 as neural responses to stimulus significance: An integrative review. *Psychophysiology*, *57*(7), 1–15. https://doi.org/10.1111/psyp.13570

Hargrove, J. B., Bennett, R. M., Simons, D. G., Smith, S. J., Nagpal, S., & Deering, D. E. (2010). Quantitative Electroencephalographic Abnormalities in Fibromyalgia Patients. *Clinical EEG and Neuroscience*, *41*(3), 132–139. https://doi.org/10.1177/155005941004100305

Hohenschurz-Schmidt, D. J., Calcagnini, G., Dipasquale, O., Jackson, J. B., Medina, S., O'Daly, O., O'Muircheartaigh, J., de Lara Rubio, A., Williams, S. C. R., McMahon, S. B., Makovac, E., & Howard, M. A. (2020). Linking Pain Sensation to the Autonomic Nervous System: The Role of the Anterior Cingulate and Periaqueductal Gray Resting-State Networks. *Frontiers in Neuroscience*, *14*(February). https://doi.org/10.3389/fnins.2020.00147

Huishi Zhang, C., Sohrabpour, A., Lu, Y., & He, B. (2016). Spectral and spatial changes of brain rhythmic activity in response to the sustained thermal pain stimulation. *Human Brain Mapping*, *37*(8), 2976–2991. https://doi.org/10.1002/hbm.23220

Ivanov PCH, Liu KKL, Bartsch RP. (2016). Focus on the emerging new fields of network physiology and network medicine. *New Journal of Physics,* 18(10):100201. https://doi.org/10.1088/1367-2630/18/10/100201

Ivanov, P. C., & Bartsch, R. P. (2014). Network physiology: mapping interactions between networks of physiologic networks. In *Networks of Networks: the last Frontier of Complexity* (pp. 203–222). Springer.

Jennings, J. R., Sheu, L. K., Kuan, D. C. H., Manuck, S. B., & Gianaros, P. J. (2016). Resting state connectivity of the medial prefrontal cortex covaries with individual differences in high-frequency heart rate variability. *Psychophysiology*, *53*(4), 444–454. https://doi.org/10.1111/psyp.12586

Jensen, M. P., Day, M. A., & Miró, J. (2014). Neuromodulatory treatments for chronic pain: efficacy and mechanisms. *Nature Reviews Neurology*, *10*(3), 167–178. https://doi.org/10.1038/nrneurol.2014.12

Jensen, M. P., Gertz, K. J., Kupper, A. E., Braden, A. L., Howe, J. D., Hakimian, S., &

Sherlin, L. H. (2013). Steps Toward Developing an EEG Biofeedback Treatment for Chronic Pain. *Applied Psychophysiology and Biofeedback*, *38*(2), 101–108. https://doi.org/10.1007/s10484-013-9214-9

Jensen, M. P., Hakimian, S., Sherlin, L. H., & Fregni, F. (2008). New Insights Into Neuromodulatory Approaches for the Treatment of Pain. *The Journal of Pain*, *9*(3), 193–199. https://doi.org/10.1016/j.jpain.2007.11.003

Karafin, M. S., Chen, G., Wandersee, N. J., Brandow, A. M., Hurley, R. W., Simpson, P., Ward, D., Li, S.-J., & Field, J. J. (2019). Chronic pain in adults with sickle cell disease is associated with alterations in functional connectivity of the brain. *PLOS ONE*, *14*(5), e0216994. https://doi.org/10.1371/journal.pone.0216994

Kayıran, S., Dursun, E., Dursun, N., Ermutlu, N., & Karamürsel, S. (2010). Neurofeedback Intervention in Fibromyalgia Syndrome; a Randomized, Controlled, Rater Blind Clinical Trial. *Applied Psychophysiology and Biofeedback*, *35*(4), 293–302. https://doi.org/10.1007/s10484-010-9135-9

Keil, A., Debener, S., Gratton, G., Junghöfer, M., Kappenman, E. S., Luck, S. J., Luu, P., Miller, G. A., & Yee, C. M. (2014). Committee report: Publication guidelines and recommendations for studies using electroencephalography and magnetoencephalography. *Psychophysiology*, *51*(1), 1–21. https://doi.org/10.1111/psyp.12147

Khalsa, S., Mayhew, S. D., Chechlacz, M., Bagary, M., & Bagshaw, A. P. (2014). The structural and functional connectivity of the posterior cingulate cortex: Comparison between deterministic and probabilistic tractography for the investigation of structure–function relationships. *NeuroImage*, *102*(P1), 118–127. https://doi.org/10.1016/j.neuroimage.2013.12.022

Khan, H. S., & Stroman, P. W. (2015). Inter-individual differences in pain processing investigated by functional magnetic resonance imaging of the brainstem and spinal cord. *Neuroscience*, *307*, 231–241. https://doi.org/10.1016/j.neuroscience.2015.08.059

Kim, J., Loggia, M. L., Cahalan, C. M., Harris, R. E., Beissner, F., Garcia, R. G., Kim, H., Barbieri, R., Wasan, A. D., Edwards, R. R., & Napadow, V. (2015). The Somatosensory Link in Fibromyalgia: Functional Connectivity of the Primary Somatosensory Cortex Is Altered by Sustained Pain and Is Associated With Clinical/Autonomic Dysfunction. *Arthritis & Rheumatology*, *67*(5), 1395–1405. https://doi.org/10.1002/art.39043

Kober, S. E., Witte, M., Stangl, M., Väljamäe, A., Neuper, C., & Wood, G. (2015). Shutting down sensorimotor interference unblocks the networks for stimulus processing: An SMR neurofeedback training study. *Clinical Neurophysiology*, *126*(1), 82–95. https://doi.org/10.1016/j.clinph.2014.03.031

Kobuch, S., Fazalbhoy, A., Brown, R., Macefield, V. G., & Henderson, L. A. (2018). Muscle sympathetic nerve activity-coupled changes in brain activity during sustained muscle pain. *Brain and Behavior*, *8*(3), e00888. https://doi.org/10.1002/brb3.888

Kumral, D., Schaare, H. L., Beyer, F., Reinelt, J., Uhlig, M., Liem, F., Lampe, L., Babayan, A., Reiter, A., Erbey, M., Roebbig, J., Loeffler, M., Schroeter, M. L., Husser, D., Witte, A. V., Villringer, A., & Gaebler, M. (2019). The age-dependent relationship between resting heart rate variability and functional brain connectivity. *NeuroImage*, *185*(October 2018), 521–533. https://doi.org/10.1016/j.neuroimage.2018.10.027

Lane, R. D., McRae, K., Reiman, E. M., Chen, K., Ahern, G. L., & Thayer, J. F. (2009). Neural correlates of heart rate variability during emotion. *Neuroimage,* 44(1), 213-222. https://doi.org/10.1016/j.neuroimage.2008.07.056

Lee, Y.-Y., & Hsieh, S. (2014). Classifying Different Emotional States by Means of EEG-Based Functional Connectivity Patterns. *PLoS ONE*, *9*(4), e95415. https://doi.org/10.1371/journal.pone.0095415

Legrain, V., Damme, S. Van, Eccleston, C., Davis, K. D., Seminowicz, D. A., & Crombez, G. (2009). A neurocognitive model of attention to pain: Behavioral and neuroimaging evidence. *Pain*, *144*(3), 230–232. https://doi.org/10.1016/j.pain.2009.03.020

Levitt, J., Choo, H. J., Smith, K. A., LeBlanc, B. W., & Saab, C. Y. (2017). Electroencephalographic frontal synchrony and caudal asynchrony during painful hand immersion in cold water. *Brain Research Bulletin*, *130*, 75–80. https://doi.org/10.1016/j.brainresbull.2016.12.011

Li, W., Liu, P., Hu, Y., & Meng, J. (2020). Pain Modulates Responses to Emotional Stimuli. *Frontiers in Psychology*, *11*. https://doi.org/10.3389/fpsyg.2020.595987

Liu, Y., Subramaniam, S. C. H., Sourina, O., Shah, E., Chua, J., & Ivanov, K. (2018). NeuroFeedback training for enhancement of the focused attention related to athletic performance in elite rifle shooters. In *Transactions on Computational Science XXXII* (pp. 106–119). Springer.

Makovac, E., Meeten, F., Watson, D. R., Herman, A., Garfinkel, S. N., D. Critchley, H., & Ottaviani, C. (2016). Alterations in Amygdala-Prefrontal Functional Connectivity Account for Excessive Worry and Autonomic Dysregulation in Generalized Anxiety Disorder. *Biological Psychiatry*, *80*(10), 786–795. https://doi.org/10.1016/j.biopsych.2015.10.013

McCarberg, B., & Peppin, J. (2019). Pain Pathways and Nervous System Plasticity: Learning and Memory in Pain. *Pain Medicine*, *20*(12), 2421–2437. https://doi.org/10.1093/pm/pnz017

Meeus, M., Goubert, D., De Backer, F., Struyf, F., Hermans, L., Coppieters, I., De Wandele, I., Da Silva, H., & Calders, P. (2013). Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: A systematic review. *Seminars in Arthritis and Rheumatism*, *43*(2), 279–287. https://doi.org/10.1016/j.semarthrit.2013.03.004

Merskey, H., & Bogduk, N. (1994). Classification of chronic pain, IASP Task Force on Taxonomy. *Seattle, WA: International Association for the Study of Pain Press (Also Available Online at Www. Iasp-Painorg)*.

Mills, E. P., Di Pietro, F., Alshelh, Z., Peck, C. C., Murray, G. M., Vickers, E. R., &

Henderson, L. A. (2018). Brainstem Pain-Control Circuitry Connectivity in Chronic Neuropathic Pain. *The Journal of Neuroscience*, *38*(2), 465–473. https://doi.org/10.1523/JNEUROSCI.1647-17.2017

Mischkowski, D., Palacios-Barrios, E. E., Banker, L., Dildine, T. C., & Atlas, L. Y. (2019). Pain or nociception? Subjective experience mediates the effects of acute noxious heat on autonomic responses-corrected and republished. *Pain*, *160*(6), 1469. https://doi.org/10.1097/j.pain.0000000000001573

Moore, D. J., Eccleston, C., & Keogh, E. (2017). Cognitive load selectively influences the interruptive effect of pain on attention. *PAIN*, *158*(10), 2035–2041. https://doi.org/10.1097/j.pain.0000000000001011

Moore, D. J., Keogh, E., & Eccleston, C. (2012). The Interruptive Effect of Pain on Attention. *Quarterly Journal of Experimental Psychology*, *65*(3), 565–586. https://doi.org/10.1080/17470218.2011.626865

Nickel, M. M., Ta Dinh, S., May, E. S., Tiemann, L., Hohn, V. D., Gross, J., & Ploner, M. (2020). Neural oscillations and connectivity characterizing the state of tonic experimental pain in humans. *Human Brain Mapping*, *41*(1), 17–29. https://doi.org/10.1002/hbm.24784

Nolte, G., Bai, O., Wheaton, L., Mari, Z., Vorbach, S., & Hallett, M. (2004). Identifying true brain interaction from EEG data using the imaginary part of coherency. *Clinical Neurophysiology*, *115*(10), 2292–2307. https://doi.org/10.1016/j.clinph.2004.04.029

Palva, J. M., Zhigalov, A., Hirvonen, J., Korhonen, O., Linkenkaer-Hansen, K., & Palva, S. (2013). Neuronal long-range temporal correlations and avalanche dynamics are correlated with behavioral scaling laws. *Proceedings of the National Academy of Sciences*, *110*(9), 3585–3590. https://doi.org/10.1073/pnas.1216855110

Peláez, I., Ferrera, D., Barjola, P., Fernandes, R., & Mercado, F. (2019). Subliminal emotional pictures are capable of modulating early cerebral responses to pain in fibromyalgia. *PLOS ONE*, *14*(6), e0217909.

https://doi.org/10.1371/journal.pone.0217909

Pfurtscheller, G., & Aranibar, A. (1979). Evaluation of event-related desynchronization (ERD) preceding and following voluntary self-paced movement. *Electroencephalography and Clinical Neurophysiology*, *46*(2), 138–146. https://doi.org/10.1016/0013-4694(79)90063-4

Pfurtscheller, Gert, & Neuper, C. (1997). Motor imagery activates primary sensorimotor area in humans. *Neuroscience Letters*, *239*(2–3), 65–68. https://doi.org/10.1016/S0304-3940(97)00889-6

Reichert, J. L., Kober, S. E., Schweiger, D., Grieshofer, P., Neuper, C., & Wood, G. (2016). Shutting Down Sensorimotor Interferences after Stroke: A Proof-of-Principle SMR Neurofeedback Study. *Frontiers in Human Neuroscience*, *10*(July), 1–14. https://doi.org/10.3389/fnhum.2016.00348

Reyes del Paso, G. A., 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*(5), 462–470. https://doi.org/10.1097/PSY.0b013e3181da91f1

Rhudy, J. L., Williams, A. E., McCabe, K. M., Rambo, P. L., & Russell, J. L. (2006). Emotional modulation of spinal nociception and pain: The impact of predictable noxious stimulation. *Pain*, *126*(1), 221–233. https://doi.org/10.1016/j.pain.2006.06.027

Rhudy, J. L., Williams, A. E., McCabe, K. M., Russell, J. L., & Maynard, L. J. (2008). Emotional control of nociceptive reactions (ECON): Do affective valence and arousal play a role? *Pain*, *136*(3), 250–261. https://doi.org/10.1016/j.pain.2007.06.031

Rosário, R. S., Cardoso, P. T., Muñoz, M. A., Montoya, P., & Miranda, J. G. V. (2015). Motif-Synchronization: A new method for analysis of dynamic brain networks with EEG. *Physica A: Statistical Mechanics and Its Applications*, *439*, 7–19. https://doi.org/10.1016/j.physa.2015.07.018

Rosselló, F., Muñoz, M. A., Duschek, S., & Montoya, P. (2015). Affective Modulation of Brain and Autonomic Responses in Patients With Fibromyalgia. *Psychosomatic Medicine*, *77*(7), 721–732. https://doi.org/10.1097/PSY.0000000000000217

Roy, M., Piché, M., Chen, J., Peretz, I., & Rainville, P. (2009). *Cerebral and spinal modulation of pain by emotions*. *106*(49). https://doi.org/10.1073/pnas.0904706106

Sakaki, M., Yoo, H. J., Nga, L., Lee, T. H., Thayer, J. F., & Mather, M. (2016). Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. *NeuroImage*, *139*, 44–52. https://doi.org/10.1016/j.neuroimage.2016.05.076

Sclocco, R., Beissner, F., Desbordes, G., Polimeni, J. R., Wald, L. L., Kettner, N. W., Kim, J., Garcia, R. G., Renvall, V., Bianchi, A. M., Cerutti, S., Napadow, V., & Barbieri, R. (2016). Neuroimaging brainstem circuitry supporting cardiovagal response to pain: a combined heart rate variability/ultrahigh-field (7 T) functional magnetic resonance imaging study. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, *374*(2067), 20150189. https://doi.org/10.1098/rsta.2015.0189

Seisdedos, N. (2004). Cambios: Test de flexibilidad cognitiva. *Madrid: TEA Ediciones*, *11*. http://doi.org/10.1002/ana.20394(

Shulman, G. L., Pope, D. L. W., Astafiev, S. V., McAvoy, M. P., Snyder, A. Z., & Corbetta, M. (2010). Right Hemisphere Dominance during Spatial Selective Attention and Target Detection Occurs Outside the Dorsal Frontoparietal Network. *Journal of Neuroscience*, *30*(10), 3640–3651. https://doi.org/10.1523/JNEUROSCI.4085-09.2010

Smith, R., Thayer, J. F., Khalsa, S. S., and Lane, R. D. (2017). The hierarchical basis of neurovisceral integration. *Neurosci. Biobehav. Rev.* 75, 274–296. https://doi.org/10.1016/j.neubiorev.2017.02.003

Sporns, O., Chialvo, D., Kaiser, M., & Hilgetag, C. (2004). Organization, development and

function of complex brain networks. *Trends in Cognitive Sciences*, *8*(9), 418–425. https://doi.org/10.1016/j.tics.2004.07.008

Sprenger, C., Finsterbusch, J., & Buchel, C. (2015). Spinal Cord-Midbrain Functional Connectivity Is Related to Perceived Pain Intensity: A Combined Spino-Cortical fMRI Study. *Journal of Neuroscience*, *35*(10), 4248–4257. https://doi.org/10.1523/JNEUROSCI.4897-14.2015

Stahlschmidt, L., Rosenkranz, F., Dobe, M., & Wager, J. (2020). Posttraumatic stress disorder in children and adolescents with chronic pain. *Health Psychology*, *39*(5), 463. https://doi.org/0.1037/hea0000859

Straathof, M., Sinke, M. R. T., Dijkhuizen, R. M., & Otte, W. M. (2019). A systematic review on the quantitative relationship between structural and functional network connectivity strength in mammalian brains. *Journal of Cerebral Blood Flow & Metabolism*, *39*(2), 189–209. https://doi.org/10.1177/0271678X18809547

Terrasa, J. L., Barros-Loscertales, A., Montoya, P., & Muñoz, M. A. (2020). Self-Regulation of SMR Power Led to an Enhancement of Functional Connectivity of Somatomotor Cortices in Fibromyalgia Patients. *Frontiers in Neuroscience*, *14*(March), 1–14. https://doi.org/10.3389/fnins.2020.00236

Thayer JF, Åhs F, Fredrikson M, Sollers JJ, Wager TD. (2012). A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev.* 36(2):747-756. https://doi.org/10.1016/j.neubiorev.2011.11.009

Thayer, J. F., & Lane, R. D. (2009). Claude Bernard and the heart–brain connection: Further elaboration of a model of neurovisceral integration. *Neuroscience & Biobehavioral Reviews*, *33*(2), 81–88. https://doi.org/10.1016/j.neubiorev.2008.08.004

Thome, J., Densmore, M., Frewen, P. A., McKinnon, M. C., Théberge, J., Nicholson, A. A., Koenig, J., Thayer, J. F., & Lanius, R. A. (2017). Desynchronization of autonomic

response and central autonomic network connectivity in posttraumatic stress disorder. *Human Brain Mapping*, *38*(1), 27–40. https://doi.org/10.1002/hbm.23340

Torta, D. M., Legrain, V., Mouraux, A., & Valentini, E. (2017). Attention to pain! A neurocognitive perspective on attentional modulation of pain in neuroimaging studies. *Cortex*, *89*, 120–134. https://doi.org/10.1016/j.cortex.2017.01.010

Tousignant-Laflamme, Y., Rainville, P., & Marchand, S. (2005). Establishing a link between heart rate and pain in healthy subjects: a gender effect. *The Journal of Pain*, *6*(6), 341–347. https://doi.org/10.1016/j.jpain.2005.01.351

Tracey, I., & Mantyh, P. W. (2007). The Cerebral Signature for Pain Perception and Its Modulation. *Neuron*, *55*(3), 377–391. https://doi.org/10.1016/j.neuron.2007.07.012

Tracy, L. M., Ioannou, L., Baker, K. S., Gibson, S. J., Georgiou-Karistianis, N., & Giummarra, M. J. (2016). Meta-analytic evidence for decreased heart rate variability in chronic pain implicating parasympathetic nervous system dysregulation. *PAIN*, *157*(1), 7–29. https://doi.org/10.1097/j.pain.0000000000000360

Treede, R.-D., Kenshalo, D. R., Gracely, R. H., & Jones, A. K. P. (1999). The cortical representation of pain. *Pain*, *79*(2–3), 105–111. https://doi.org/10.1016/S0304-3959(98)00184-5

Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B. H., … Wang, S.-J. (2015). A classification of chronic pain for ICD-11. *Pain*, *156*(6), 1003. https://doi.org/10.1097/j.pain.0000000000000160

Treister, R., Kliger, M., Zuckerman, G., Aryeh, I. G., & Eisenberg, E. (2012). Differentiating between heat pain intensities: The combined effect of multiple autonomic parameters. *Pain*, *153*(9), 1807–1814. https://doi.org/10.1016/j.pain.2012.04.008

Valenza, G., Toschi, N., & Barbieri, R. (2016). Uncovering brain–heart information

through advanced signal and image processing. *Phil. Trans. R. Soc. A.37420160020* https://doi.org/10.1098/rsta.2016.0020

Valenza, G., Sclocco, R., Duggento, A., Passamonti, L., Napadow, V., Barbieri, R., & Toschi, N. (2019). The central autonomic network at rest: Uncovering functional MRI correlates of time-varying autonomic outflow. *NeuroImage*, *197*(May), 383–390. https://doi.org/10.1016/j.neuroimage.2019.04.075

Van Damme, S., Legrain, V., Vogt, J., & Crombez, G. (2010). Keeping pain in mind: A motivational account of attention to pain. *Neuroscience & Biobehavioral Reviews*, *34*(2), 204–213. https://doi.org/10.1016/j.neubiorev.2009.01.005

Vanneste, S., Ost, J., Van Havenbergh, T., & De Ridder, D. (2017). Resting state electrical brain activity and connectivity in fibromyalgia. *PLOS ONE*, *12*(6), e0178516. https://doi.org/10.1371/journal.pone.0178516

Vierck, C. J., Whitsel, B. L., Favorov, O. V, Brown, A. W., & Tommerdahl, M. (2013). Role of primary somatosensory cortex in the coding of pain. *Pain*, *154*(3), 334–344. https://doi.org/10.1016/j.pain.2012.10.021

Weber, C. S., Thayer, J. F., Rudat, M., Wirtz, P. H., Zimmermann-Viehoff, F., Thomas, A., ... & Deter, H. C. (2010). Low vagal tone is associated with impaired post stress recovery of cardiovascular, endocrine, and immune markers. *European journal of applied physiology, 109(2)*, 201-211. https://doi.org/10.1007/s00421-009-1341-x

Wieser, M. J., Gerdes, A. B., Greiner, R., Reicherts, P., & Pauli, P. (2012). Tonic pain grabs attention, but leaves the processing of facial expressions intact—evidence from event-related brain potentials. Biological Psychology, 90(3), 242-248. https://doi.org/10.1016/j.biopsycho.2012.03.019

Wieser, M. J., Gerdes, A. B. M., Reicherts, P., & Pauli, P. (2014). Mutual influences of pain and emotional face processing. *Frontiers in Psychology*, *5*(October), 1–6. https://doi.org/10.3389/fpsyg.2014.01160

Williams, A. E., & Rhudy, J. L. (2009). Emotional modulation of autonomic responses to painful trigeminal stimulation ☆. *International Journal of Psychophysiology*, *71*(3), 242–247. https://doi.org/10.1016/j.ijpsycho.2008.10.004

Xu, Y., Wang, Y., Chen, J., He, Y., Zeng, Q., Huang, Y., Xu, X., Lu, J., Wang, Z., Sun, X., Chen, J., Yan, F., Li, T., Guo, W., Xu, G., Tian, H., Xu, X., Ma, Y., Wang, L., … Li, G. (2020). The comorbidity of mental and physical disorders with self-reported chronic back or neck pain: Results from the China Mental Health Survey. *Journal of Affective Disorders*, *260*(June 2019), 334–341. https://doi.org/10.1016/j.jad.2019.08.089

Yang, S., & Chang, M. C. (2019). Chronic Pain: Structural and Functional Changes in Brain Structures and Associated Negative Affective States. *International Journal of Molecular Sciences*, *20*(13), 3130. https://doi.org/10.3390/ijms20133130