TESIS DOCTORAL:

Evaluación de la activación de la Red Neuronal por Defecto en la Esquizofrenia mediante dos tareas de autorreflexión y memoria autobiográfica

AUTORA:

MARTA MARTÍN SUBERO

DIRECTORA:

Dra. Edith Pomarol-Clotet

FIDMAG Germanes Hospitalàries Research Foundation

CIBERSAM

TUTOR:

Dr. Crisanto Díez Quevedo

Departamento de Psiquiatría y Medicina Legal
Universidad Autónoma de Barcelona

Programa de Doctorado en Psiquiatría

Departamento de Psiquiatría y Medicina Legal

Facultad de Medicina

Universidad Autónoma de Barcelona

2020

La **Dra. Edith Pomarol-Clotet**,

Doctora en Psiquiatría, directora gerente de la Fundació per a la Investigació i la Docència FIDMAG Germanes Hospitalàries Research Foundation

declara y confirma que ha supervisado la Tesis Doctoral titulada:

Evaluación de la activación de la Red Neuronal por Defecto en la Esquizofrenia mediante dos tareas de autorreflexión y memoria autobiográfica

Presentada por **Marta Martín Subero** para optar al grado de

Doctor en Psiquiatría

Departamento de Psiquiatría y Medicina Legal,

Universidad Autónoma de Barcelona

Firma,

POMAROL CLOTET EDITH – 43428268J

Firmado digitalmente por POMAROL CLOTET EDITH - 43428268J
Fecha: 2020.11.13 09:34:16 +01'00'

Dra. Edith Pomarol-Clotet

Esta tesis está dedicada a la memoria de mi padre;

el cual me transmitió sus valores de esfuerzo, determinación y dedicación.

Sin él, no podría haber llegado hasta aquí.

"Sólo aquellos que se arriesgan a ir muy lejos,

pueden llegar a saber lo lejos que pueden ir"

T.S. Eliot

AGRADECIMIENTOS

Este trabajo ha sido posible gracias a la colaboración de un gran número de personas.

En primer lugar quiero agradecer su generosidad a todos los pacientes que aceptaron participar en el estudio y se esforzaron por hacerlo de la mejor manera. Esta tesis es para vosotros.

A mi directora de tesis, Edith, por darme la oportunidad de formar parte de un gran equipo de investigadores y guiarme en todo el proceso de desarrollo de esta tesis doctoral. Gracias por tu tiempo y dedicación; no hubiera logrado llegar hasta aquí sin tu ayuda y entusiasmo.

También quisiera agradecer de un modo especial la colaboración de Peter Mckenna, por la supervisión de esta tesis; y por sus consejos y recomendaciones; ya que has sido como un director más para mí.

Gracias a mi tutor, Crisanto, por facilitarme el camino siempre. Por su disponibilidad y generosidad.

Gracias también a toda la unidad de investigación de FIDMAG, por el apoyo que me han proporcionado en todo momento y por todo lo que me han enseñado en el campo de la investigación, el trabajo en equipo y la neuroimagen. Quiero mencionar especialmente a mis compañeros: Silvia Alonso, Isabel Argila, Alicia García, Sònia Calvet, Erick J. Canales, Mar Fatjó, Isabel Feria, Paola Fuentes, Miguel Lechón, Ana Moreno, Joaquim Raduà, Anna Romaguera, Pilar Salgado, Raymond Salvador, Aniol Santo, Salvador Sarró.

A Paola, por su amistad, su compañía y su inestimable ayuda durante todo el camino doctoral. Para mí, eres un modelo de mujer investigadora a seguir.

A todo el equipo de Benito Menni CASM, gracias por vuestro esfuerzo e implicación y por la ayuda en el reclutamiento de los pacientes. Me llevo el recuerdo de grandes compañeros.

Agradezco también al INAD del Parc de Salut Mar el precioso tiempo y facilidades que me ha dado para poder acabar esta tesis.

Y finalmente, gracias a Víctor y a Eva por acompañarme, entenderme y ser mi ilusión y felicidad cada día.

ÍNDICE

ABREVIATURAS

AC-PC = Anterior Comissure – Posterior Comissure

AP = Antipsicótico

AMI = Autobiographical Memory Interview

BOLD = Blood-Oxygenation-Level-Dependent

CEN = Central Executive Network

CGI = Clinical Global Impression

CI = Coeficiente Intelectual

CIE = Clasificación Internacional de las Enfermedades

DLPFC = Dorsolateral Prefrontal Cortex

DMN = Default Mode Network

DSM = Diagnostic and Statistical Manual for Mental Disorders

FEAT= FMRI Expert Analysis Tool software

FOV = Field of View

fMRI = Functional Magnetic Resonance Imaging

FSL = FMRIB Software Library

GAF = Global Assessment of Functioning scale

GLM = General Linear Model

HP = Hipocampo

IPL = Inferior Parietal Lobe

mPFC = Medial Prefrontal Cortex

MRI = Magnetic Resonance Imaging

PANSS = Positive and Negative Syndrome Scale

PCC = Posterior Cingulate Cortex

PCUN = Precuneus

ROI = Region of Interest

SANS = Scale for the Assessment of Negative Symptoms

SAPS = Scale for the Assessment of Positive Symptoms

SCID = Structured Clinical Interview for DSM-IV-TR Disorders

SN = Salience Network

SNC = Sistema Nervioso Central

TAP = Test de Acentuación de Palabras

TE = Echo Time

TOM = Theory of Mind

TPJ = Temporo-Parietal Junction

TR = Repetition Time

VBM = Voxel Based Morphometry

VMPFC = Ventromedial Prefrontal Cortex

VLPFC = Ventrolateral Prefrontal Cortex

WCST = Wisconsin Card Sorting Test

PRÓLOGO

Esta tesis, presentada para obtener el grado académico de Doctor por la Universidad Autónoma de Barcelona (U.A.B.), es el resultado del trabajo realizado durante los años 2016 - 2020 en la Unidad de investigación de la FIDMAG Germanes Hospitalàries Research Foundation.

Esta tesis se presenta por compendio de publicaciones y está formada por dos artículos publicados en revistas internacionales indexadas con alto factor de impacto, en el ámbito de las neurociencias. A continuación se nombran otros artículos que han sido publicados y que están relacionados con el tema de la presente tesis. Los resultados de estos estudios han sido también difundidos en diversos congresos nacionales e internacionales, en forma de pósteres y/o comunicaciones orales.

PUBLICACIONES DE LA TESIS

Autobiographical memory and default mode network function in schizophrenia: An fMRI study.

Martin-Subero, M., Fuentes-Claramonte, P., Salgado-Pineda, P., Salavert, J., Arevalo, A., Bosque, C., Sarri, C., Guerrero-Pedraza, A., Santo-Angles, A., Capdevila, A., Sarró, S., Salvador, R., McKenna, P. J., & Pomarol-Clotet, E. (2019). Psychol Med, 1-8. doi:10.1017/S0033291719003052.

Brain imaging correlates of self- and other-reflection in schizophrenia.

Fuentes-Claramonte, P., **Martin-Subero, M.**, Salgado-Pineda, P., Santo-Angles, A., Argila-Plaza, I., Salavert, J., Arévalo, A., Bosque, C., Sarri, C., Guerrero-Pedraza, A., Capdevila, A., Sarró, S., McKenna, P. J., Pomarol-Clotet, E., & Salvador, R. (2019). NeuroImage. Clinical, 25, 102134. doi:10.1016/j.nicl.2019.102134.

ARTÍCULOS RELACIONADOS

Shared and differential default-mode related patterns of activity in an autobiographical, a self-referential and an attentional task.

Fuentes-Claramonte P, **Martín-Subero M**, Salgado-Pineda P, Alonso-Lana S, Moreno-Alcázar A, Argila-Plaza I, Santo-Angles A, Albajes-Eizagirre A, Anguera-Camós M, Capdevila A, Sarró S, McKenna PJ, Pomarol-Clotet E, Salvador R. PLoS One. 2019 Jan 4;14(1):e0209376. doi: 10.1371/journal.pone.0209376.

P.1.i.038 Testing theories of default mode function and its dysfunction in schizophrenia

M. Martin-Subero, P. Salgado-Pineda, P. Fuentes, S. Alonso-Lana, J. Salavert, A. Arévalo, R. Salvador, E. Pomarol-Clotet, P. McKenna. European Neuropsychopharmacology, 26 (Suppl 2): S319-S320. 2016. doi: 10.1016/S0924-977X(16)31230-5

P.1.i.031 Brain correlates of impaired insight and social cognition in schizophrenia.

M. Martin-Subero, P. Salgado-Pineda, P. Fuentes, R. Salvador, E. Pomarol-Clotet, P. McKenna. European Neuropsychopharmacology, 27 (Suppl 4): S711. 2017. doi: 10.1016/S0924-977X(17)31313-5.

RESUMEN

La esquizofrenia es un trastorno mental severo relativamente frecuente y que generalmente comporta una severa discapacidad a quien lo padece. Se caracteriza por la aparición de síntomas psicóticos y deterioro cognitivo que se presentan de forma compleja y heterogénea. Parece tener su origen en el neurodesarrollo debido a la combinación de factores genéticos, neurobiológicos y ambientales.

Los estudios de neuroimagen han aportado muchos datos sobre la estructura y la función cerebral en la esquizofrenia. Entre los resultados de los estudios de neuroimagen funcional, existe una creciente evidencia de la disfunción de la llamada red neuronal por defecto (DMN, del inglés *Default Mode Network*), un conjunto de regiones que se desactivan en lugar de activarse durante la realización de tareas que requieren atención externa, en la esquizofrenia. Específicamente, los estudios han observado un fallo en la desactivación de la corteza prefontal medial en esquizofrenia durante la realización de tareas cognitivas. Se conoce también un pequeño número de tareas cognitivas que son capaces de activar la DMN. Sin embargo, se han desarrollado muy pocos estudios examinando las activaciones que producen estas tareas en la esquizofrenia.

El objetivo principal de la presente tesis es estudiar el comportamiento de la DMN en esquizofrenia mediante dos novedosas tareas de imagen por resonancia magnética funcional (fMRI, del inglés *functional Magnetic Resonance Imaging*) destinadas a activarla, la memoria autobiográfica y la autorreflexión.

El primer experimento examinó los patrones de activación y desactivación durante la realización de una tarea de memoria autobiográfica por parte de un grupo de pacientes con esquizofrenia crónica y en comparación a un grupo de sujetos sanos. Los pacientes mostraron un patrón de activación similar en las regiones de la DMN. No obstante, mostraron un fallo en desactivar regiones fuera de la DMN.

El segundo experimento examinó los patrones de activación y desactivación cerebral en relación a la realización de un paradigma de autorreflexión y reflexión sobre el otro en pacientes con esquizofrenia crónica en comparación con un grupo de sujetos sanos. Ambos grupos presentaron un patrón de activaciones similar en regiones de la DMN en las condiciones de autorreflexión y reflexión sobre el otro en comparación a la condición semántica de control. Adicionalmente, los pacientes presentaron una hiperactivación de la

corteza frontal lateral izquierda en las condiciones de autorreflexión y reflexión sobre el otro. Durante la realización de la tarea de reflexión sobre el otro, los pacientes presentaron una disminución de la activación de la unión temporoparietal (TPJ, del inglés *Temporo-Parietal Junction*) derecha respecto a los controles sanos; una región involucrada en el procesamiento de información social.

De manera conjunta, los resultados de ambas publicaciones muestran que los pacientes son capaces en general de activar las regiones de la DMN a un nivel similar al de los controles sanos durante la ejecución de las tareas. Al mismo tiempo, los dos estudios aportan evidencia de un patrón de activación anormal fuera de la DMN en la esquizofrenia. Estos hallazgos sugieren que la alteración cerebral en la esquizofrenia radicaría en un desequilibrio en las dinámicas de las redes cerebrales y en su interacción; y no tanto en una red concreta o una región específica. Por otro lado, la alteración en la TPJ derecha apoya la disfunción en la diferenciación entre el yo y el otro en esquizofrenia que podría subyacer a algunos de los síntomas característicos de la enfermedad como son sus dificultades en cognición social.

ABSTRACT

Schizophrenia is a relatively common psychiatric disorder that is often severely disabling. It is characterized by both psychotic symptoms and cognitive impairment which are heterogeneous in presentation, and is believed to involve disruption of brain development caused by genetic or environmental factors, or both.

Neuroimaging studies have provided much data on brain structure and function in schizophrenia. Among functional neuroimaging studies, there is increasing evidence that the default mode network (DMN), a series of brain regions that de-activate rather than activate during performance of attention demanding tasks, is dysfunctional in the disorder. Specifically, these studies have found failure of de-activation during cognitive task performance, especially in the medial frontal cortex. A small number of cognitive tasks are known to activate rather than de-activate the DMN. However, relatively few studies examining activations in response to these tasks have been carried out in schizophrenia.

The aim of this thesis was to examine the functionality of the default mode network in schizophrenia using two tasks that have been found to activate it, autobiographical memory and making self-judgements.

The first study examined patterns of brain activation and de-activation in schizophrenic patients and matched healthy controls during a novel autobiographical recall task. The schizophrenic patients showed a similar pattern of activations to the controls in DMN regions. However, they showed clusters of failure of de-activation in regions outside the DMN.

The second study examined patterns of brain activation and de-activation in schizophrenic patients during performance of a task requiring make judgments about one's own and others' attributes. Both the patients and healthy controls showed a similar pattern of activation in regions of the DMN during self- and other- processing compared to a baseline condition of semantic processing. Compared to the healthy subjects, the patients hyperactivated the left lateral frontal cortex during both self- and other-reflection. During other-reflection, the patients also showed reduced activation compared to the controls in the right temporo-parietal junction, a region involved in processing of social information.

Overall, the results from both studies show that patients with schizophrenia show similar activations in the DMN to healthy subjects while performing tasks which normally activate this network. At the same time, both studies found evidence for abnormal activations outside the

DMN in schizophrenia. These findings suggest that the brain dysfunction in schizophrenia may involve an imbalance between so-called task-positive and task-negative networks rather than a fixed alteration in a particular brain region. The alteration of the activity in the right TPJ supports a disturbance in self/other differentiation in schizophrenia, which could underlie some of its symptoms such as social cognition disturbances.

1. INTRODUCCIÓN

1.1. Nosología

Generalmente se acepta que el concepto de esquizofrenia como entidad propia surge a partir de la reconocida definición del psiquiatra alemán Emil Kraepelin (1856-1926) de su *dementia praecox* (Kraepelin, 1909). El autor la identificó como una de las dos formas principales de psicosis; separándola específicamente de las *psicosis maníaco-depresivas*. Kraepelin consideró que la esquizofrenia se caracterizaba por la aparición de síntomas psicóticos, como delirios, alucinaciones, incoherencia del discurso, trastornos psicomotores y síntomas catatónicos; que se asociaban a toda una serie de síntomas deficitarios –empobrecimiento afectivo, apatía, indiferencia, desorganización del pensamiento, disgregación psíquica, etc.–; y que progresaban a un estado de deterioro. Kraepelin completó esta definición diferenciando dos formas evolutivas de la demencia precoz: la progresiva, que conducía a un deterioro permanente; y la que cursaba con brotes y sin un déficit irreversible (Berrios & Fernández, 1996). Su intención era establecer el trastorno como una enfermedad degenerativa que afectaba al cerebro; pero a su vez diferenciarla de otras enfermedades mentales y estados psicopatológicos degenerativos (Jaspers, 2006; K. Schneider, 1950).

Cabe destacar que hasta la primera mitad del siglo XIX, los psiquiatras franceses habían dominado el campo de las definiciones y clasificaciones de las enfermedades mentales. De hecho, fue Benedict Augustin Morel (1809-1873) el primero en utilizar el término de *démence stupide o stupidité aboutisant à la démence* que utilizó para diagnosticar algunos casos de jóvenes que se caracterizaban por presentar actitudes, gestos y lenguaje estereotipados y un negativismo evidente; síndrome que además observó que evolucionaba rápidamente hacia una pérdida de las facultades mentales y, en definitiva, hacia la demencia (Berrios & Fernández, 1996; Shorter, 2015). Pero no fue hasta 1860 cuando Morel utilizó por primera vez el término *démence précoce* para referirse a la evolución de un joven paciente que inició con un deterioro de su actividad habitual, invadido por un estado que él denominó de "torpeza próxima al embrutecimiento (*hébétement*)" y cuya evolución describió como "una inmovilización súbita de todas las facultades, una demencia precoz, que indican que el joven sujeto ha alcanzado el término de su vida intelectual" (Bleuler, 1987; Shorter, 2015).

El término *esquizofrenia* (que significa literalmente, "mente escindida") fue introducido en 1911 por el psiquiatra suizo Eugen Bleuler (1857-1940) centrando la caracterización del cuadro

no en su evolución, sino en lo que él consideraba el rasgo psicopatológico fundamental: la escisión del yo (Berrios & Fernández, 1996; Bleuler, 1987). Bleuler disoció la esquizofrenia de su connotación inicial de demencia: argumentó que, aunque los pacientes con esquizofrenia a menudo presentaban un mal desempeño en las pruebas de la función cognitiva, esto era debido a que los síntomas de la enfermedad estaban interfiriendo con las funciones intelectuales, funciones que permanecerían esencialmente intactas.

Posteriormente, en 1913, Karl Jaspers publicó su libro "Psicopatología General". Heredero de la escuela alemana y francesa, realizó una brillante descripción de los fenómenos psicopatológicos presentes en la esquizofrenia. Mantenía los subtipos de hebefrenia, catatonía y formas paranoides. En su esquema diagnóstico, en el Grupo II (los tres círculos de las grandes psicosis) incluyó la Epilepsia, la Esquizofrenia y las Enfermedades maníaco-depresivas como tres entidades diferenciadas (Jaspers, 2006).

Más adelante, el concepto de esquizofrenia evolucionó estrechamente ligado a la jerarquización de los síntomas. Kurt Schneider, a partir de 1950, invirtió la jerarquía entre los síntomas fundamentales y accesorios de Bleuler y aisló una serie de experiencias psicóticas que denominó como "síntomas de primer rango" por ser especialmente característicos de la esquizofrenia. En su obra "Psicopatología clínica" dividió los síntomas en dos grupos:

Síntomas de primer rango: Pensamiento sonoro; voces que discuten; experiencias de pasividad somática; influencia, imposición y robo de pensamiento; transmisión de pensamiento; percepciones delirantes; cualquier experiencia que implique voluntad, afectos e impulsos dirigidos.

Síntomas de segundo rango: Otros trastornos de la percepción; ideas delirantes súbitas; cambios depresivos o eufóricos; sentimientos de empobrecimiento emocional; otros.

Y así la aportación de Schneider conformó el tercer pilar del concepto de esquizofrenia (Nancy C. Andreasen & Olsen, 1982; Crow, 1982) junto con el deterioro kraepeliniano y la desorganización bleuleriana.

En la segunda mitad del siglo XX, el concepto de esquizofrenia evolucionó de forma diferente en los distintos continentes. En Estados Unidos la categoría diagnóstica se flexibilizó y amplió; de manera que los psiquiatras americanos diagnosticaban con mayor frecuencia esquizofrenia que los psiquiatras de Reino Unido (Cooper, 1972). Estas distinciones se fueron subsanando con el desarrollo de unos criterios diagnósticos consensuados y publicados en las sucesivas

ediciones de los manuales diagnósticos de la Asociación Americana de Psiquiatría y de la Organización Mundial de la Salud.

En 1974 apareció la división entre grupos de síntomas gracias a las aportaciones de Strauss, Carpenter y Bartko que clasificaron las manifestaciones de los trastornos esquizofrénicos en tres grandes grupos de síntomas (Strauss, Carpenter, & Bartko, 1974):

Síntomas positivos: delirios, alucinaciones, comportamientos catatónicos y algunas formas de trastornos formales del pensamiento, como la distraibilidad, con poco poder predictivo sobre evolución y antecedentes familiares.

Síntomas negativos: afecto embotado, apatía y algunas formas de trastornos formales del pensamiento, como el bloqueo, que se relacionan con la cronicidad del trastorno.

Trastornos de las relaciones personales: que se evidenciaría como una dimensión relativamente independiente de las dos anteriores.

En esta línea, Timothy Crow, en 1982, consideraba que los síntomas positivos y negativos eran las manifestaciones de dos procesos patológicos diferentes en el cerebro, uno asociado con la esquizofrenia aguda, que era potencialmente reversible y que, posiblemente, tenía una base en la anormalidad neuroquímica; y el otro que definía un grupo de enfermedades con un pronóstico grave, que Crow especulaba que podrían reflejar cambios estructurales irreversibles en el cerebro (Cuesta MJ, Peralta V, & Serrano JF, 2000).

Diversos estudios de los años 1970 y 1980 encontraron de forma consistente que los síntomas positivos y negativos no están significativamente correlacionados entre sí; lo que sugiere que podrían tener diferentes causas subyacentes (Nancy C. Andreasen & Olsen, 1982; S. R. Kay, Fiszbein, & Opler, 1987; Lewine, Fogg, & Meltzer, 1983; Rosen et al., 1984). De hecho, el grupo de Andreasen y Olsen (1982) estableció la clasificación de la esquizofrenia en tres grandes grupos: esquizofrenia positiva, negativa y mixta (Nancy C. Andreasen & Olsen, 1982). Desde esta conceptualización de la esquizofrenia se desarrollaron las escalas para la Evaluación de Síntomas Positivos (SAPS, del inglés *Scale for the Assesment of Positive Symptoms*) y la Escala de Evaluación de Síntomas Negativos de la esquizofrenia (SANSS, del inglés *Scale for the Assessment of Negative Symptoms*) (N. C. Andreasen, 1989). Y también la escala para la Evaluación de los síntomas Positivos y Negativos de la esquizofrenia (PANSS, del inglés *Positive and Negative Syndrome Scale*) cuya repercusión en la investigación de la esquizofrenia a nivel mundial ha sido incuestionable (S. R. Kay et al., 1987).

En 1987, Peter F. Liddle realizó un estudio de análisis factorial en pacientes con esquizofrenia crónica y encontró que tres factores definían la enfermedad: la distorsión de la realidad (delirios y alucinaciones), la desorganización (trastorno formal del pensamiento y afecto inapropiado) y los síntomas negativos (Liddle, 1987). Numerosos estudios posteriores han apoyado esta división de los síntomas de la esquizofrenia (Nancy C. Andreasen, Arndt, Alliger, Miller, & Flaum, 1995; Barrera, McKenna, & Berrios, 2005; Thompson & Meltzer, 1993).

Por otra parte, la esquizofrenia es extremadamente heterogénea en sus presentaciones y muchos autores consideran que no puede hablarse de un único trastorno (Murray, Lewis, & Reveley, 1985). De hecho, después de tanto tiempo, los profesionales en salud mental seguimos debatiendo qué es la esquizofrenia. Parece claro que el establecimiento de unos criterios diagnósticos consensuados ha permitido realizar estudios e investigaciones en los diferentes campos de las neurociencias en pacientes afectos de esquizofrenia; pero que nos encontramos ante una entidad extremadamente compleja. Profundizar en el conocimiento de la neurobiología de la esquizofrenia es esencial para mejorar nuestra capacidad de diagnóstico; poder identificar futuras dianas terapéuticas y, en definitiva, mejorar el pronóstico de los pacientes.

1.2. Epidemiología

Clásicamente se ha reportado que la esquizofrenia afecta a poco menos del 1% de la población en algún momento de su vida (Stilo & Murray, 2010); aunque los estudios han indicado oscilaciones de la prevalencia en la esquizofrenia, que se sitúa entre el 0,3 y el 2% a lo largo de la vida, con un promedio entre el 0,7-1% en todo el mundo (Jablensky, 2010).

Durante muchos años se ha considerado que la incidencia de la esquizofrenia era constante tanto geográfica como temporalmente. Pero una revisión sistemática mostró que la incidencia de la esquizofrenia variaba entre 7,7 a 43,0 por 100.000 personas/año (Stilo & Murray, 2010). De hecho, la incidencia media de la esquizofrenia en un reciente meta-análisis fue de 21 por 100.000 persona/año (Jongsma, Turner, Kirkbride, & Jones, 2019), siendo mayor que en la última revisión sistemática sobre este tema que era de 15 por 100.000 personas/año (McGrath, Saha, Chant, & Welham, 2008).

Algunos autores consideran que los hombres tienen más riesgo que las mujeres de padecer esquizofrenia en una proporción de 1,3-1,4:1 (Aleman, Kahn, & Selten, 2003); sin embargo,

otros autores no han encontrado diferencias de género (Charlson et al., 2018; Mueser & McGurk, 2004). Por otro lado, lo que sí parece que está bien establecido es que los varones tienen peor pronóstico que las mujeres (Malla & Payne, 2005; Mueser & McGurk, 2004).

La esquizofrenia suele debutar con un primer episodio entre los 15 y 45 años; pero aparece con más frecuencia en la adolescencia tardía o en primeros años de la edad adulta (DeLisi, 2008; Tandon, Keshavan, & Nasrallah, 2008). Los varones suelen presentar la enfermedad 5-7 años antes que las mujeres (Häfner et al., 1998). Por su parte, las mujeres suelen presentar un segundo pico de presentación más tarde, después de la menopausia (Stilo & Murray, 2010).

La evolución de la esquizofrenia puede variar desde la recuperación completa hasta la discapacidad grave permanente que requiere atención institucional. Una revisión sistemática basada en 50 estudios mostró que la proporción de pacientes con esquizofrenia que cumplían criterios de recuperación clínica y social alcanzaba tan sólo el 13,5% (Jääskeläinen et al., 2013).

Por lo tanto, se puede considerar que la esquizofrenia es habitualmente un trastorno psiquiátrico grave y debilitante. De hecho, en un reciente meta-análisis ocupó el puesto 12º entre las 310 enfermedades y lesiones más incapacitantes (Charlson et al., 2018). También se asocia con importantes costes humanos y económicos: según la Organización Mundial de la Salud, es el tercero de los principales contribuyentes a la carga mundial de todos los trastornos mentales, neurológicos y por abuso de sustancias (Correction Collins et al., 2011). Además el desempleo entre estos pacientes es asombrosamente alto, entre un 80–90% (Marwaha & Johnson, 2004; Marwaha et al., 2007). Cabe destacar también que la esperanza de vida de un paciente con esquizofrenia se reduce entre 10 y 20 años (Laursen, Nordentoft, & Mortensen, 2014; Owen, Sawa, & Mortensen, 2016).

1.3. Etiología

La esquizofrenia es un trastorno cuya causa continúa siendo desconocida (Macher, 2010). Sin embargo, actualmente se acepta la relevancia de una serie de factores genéticos, neurobiológicos y ambientales en su etiopatogenia.

1.3.1. Factores genéticos

La esquizofrenia es un trastorno altamente hereditario (Sullivan, Kendler, & Neale, 2003). Los estudios basados en gemelos son clásicamente los que se han usado para estimar la contribución relativa de los genes y el ambiente en su aparición. En un meta-análisis de 12

estudios publicados sobre gemelos, Sullivan y colaboradores observaron que la heredabilidad de la esquizofrenia se sitúa alrededor del 80% (Cardno & Gottesman, 2000; Sullivan et al., 2003). El hecho de que sea inferior al 100% implica que también existen factores ambientales en la etiología de la enfermedad.

Se han descubierto numerosas asociaciones entre la esquizofrenia y distintos genes, destacando entre ellos: el NRG1 (gen de la neurorregulina) (Schwab et al., 2003; Williams et al., 2003), el de la disbindina (Blackwood et al., 2001), el DISC-1 (implicado en el crecimiento de las neuritas y el desarrollo cortical) (Fan et al., 2005), el gen de la prolina deshidrogenasa (Mirnics & Lewis, 2001), el PIP4K2A (gen de la fosfatidilinositol-5-fosfato-4-cinasa tipo II-alfa), el RGS4 (regulador de la proteína G señalización-4), el GRM3 (relacionado con receptores glutamatérgicos), el COMT (metabolizador de la dopamina intersináptica), el DRD2 (receptor de dopamina) (Harrison & Weinberger, 2005; Tiwari, Zai, Müller, & Kennedy, 2010). Estos genes estarían implicados en funciones tales como la migración neuronal, la plasticidad sináptica, la orientación de axones, la formación de sinapsis, el desarrollo de oligodendrocitos, en los receptores de neurotransmisores, y un largo etc. que condicionarían tanto el desarrollo cerebral como su funcionamiento.

Los estudios más recientes llevan a cabo comparaciones genómicas de millones de marcadores genéticos en decenas de miles de sujetos (Genome Wide Association Studies, GWAS). Un reciente estudio del Consorcio de Genómica Psiquiátrica con 36 989 casos y 113 075 controles identificó 108 loci significativos en todo el genoma (Ripke et al., 2014). Más recientemente, un nuevo estudio de este mismo consorcio ha ampliado el número de loci de riesgo para esquizofrenia hasta 145 (Pardiñas et al., 2018). Los loci implicados incluirían genes involucrados con la síntesis de dopamina, los canales de calcio, los neurorreceptores de glutamato y la inmunidad (concretamente, con el complejo mayor de histocompatibilidad). Sin embargo, estos estudios explican sólo un pequeño porcentaje de la variabilidad en la predisposición a padecer esquizofrenia en la población general. Esto reflejaría que una parte significativa de la predisposición sería debida a interacciones de tipo gen-ambiente o a mecanismos epigenéticos (Stilo & Murray, 2019).

1.3.2. Factores neurobiológicos

La neurobiología subyacente a la esquizofrenia implica a diferentes sistemas: el sistema dopaminérgico, el glutamatérgico, el sistema inmune y, más recientemente el endocannabinoide.

La hipótesis dopaminérgica se basa en un exceso de síntesis de dopamina a nivel presináptico en el núcleo estriado de los pacientes al inicio de los síntomas positivos (O. D. Howes et al., 2009). Sin embargo, no parece que la disfunción dopaminérgica sea una anomalía primaria, sino más bien que es capaz de desencadenar anomalías en otros sistemas como el sistema glutamatérgico (O. Howes, McCutcheon, & Stone, 2015). Además parece que los factores ambientales también jugarían un papel significativo a partir del modelo de diátesis-estrés que sugiere que el eje hipotálamico-pituitario-adrenal podría desencadenar una cascada de eventos que resultarían en una disfunción de los circuitos neuronales con alteraciones en la señalización dopaminérgica (Jones & Fernyhough, 2007; Walker & Diforio, 1997).

1.3.3. Factores ambientales

Los factores ambientales incluyen las complicaciones en el embarazo y en el parto, el trauma en la infancia, migración, aislamiento social, urbanicidad y el uso de sustancias (Arseneault et al., 2002; Bourque, Van Der Ven, & Malla, 2011; Cannon, Jones, & Murray, 2002; Vassos, Pedersen, Murray, Collier, & Lewis, 2012).

Sobre la base de la evidencia anterior, actualmente se acepta que la esquizofrenia tiene una etiología multifactorial. En este sentido, la presencia de un conjunto de genes que incrementan la susceptibilidad, junto con el impacto de los factores ambientales, tales como eventos adversos pre y perinatales, podrían provocar alteraciones en el neurodesarrollo. Si a estas alteraciones se añade una maduración cerebral alterada con afectaciones de las vías dopaminérgicas y glutamatérgicas; tendríamos la cascada de factores que pueden llevar al desarrollo de la enfermedad tal y como se representa en la Figura 1.
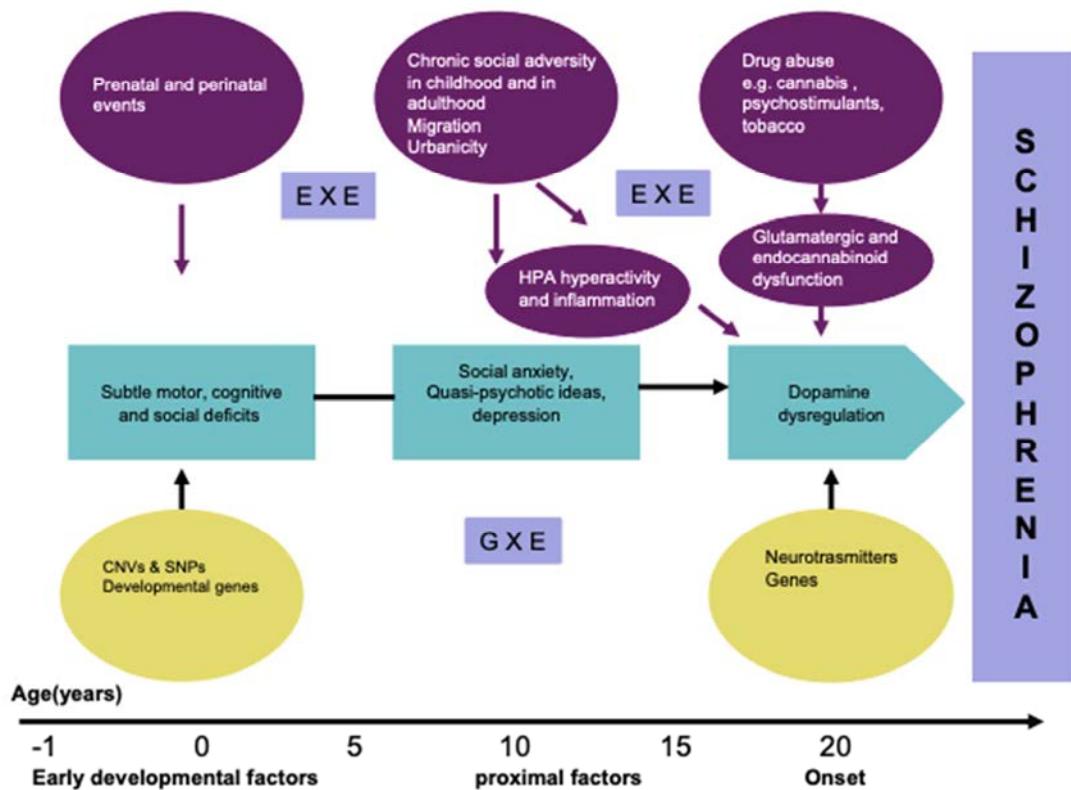
Figura 1. Cascada de factores que llevan al desarrollo de esquizofrenia. (Stilo & Murray, 2019).

1.4 Síntomas y criterios diagnósticos

El diagnóstico de la esquizofrenia es un diagnóstico clínico. Éste depende de la identificación de síntomas psicóticos característicos en ausencia de la presencia de una alteración importante depresiva o de elevación del estado de ánimo. A partir de 1980, el diagnóstico se basó en los criterios del sistema americano, *Diagnostic and Statistical Manual of Mental Disorder* (DSM), DSM-III, DSM-IV y actualmente el DSM-5. (APA, 1994, 2013) y del sistema europeo denominado *Clasificación Internacional de las Enfermedades* (CIE) (Organización Mundial de la Salud, 1995). Los criterios DSM-5 para la esquizofrenia se muestran en la Tabla 1. Los criterios CIE-10 son muy similares y se muestran en la Tabla 2.

Tabla 1. Criterios para el diagnóstico de la esquizofrenia según DSM-5

CRITERIOS DIAGNÓSTICOS DSM-5

A. Dos o más de los siguientes síntomas, cada uno de ellos presente durante una parte significativa de tiempo durante un periodo de un mes (o menos si se trató con éxito).
Al menos uno de ellos ha de ser (1), (2) o (3):
1. Delirios
2. Alucinaciones
3. Discurso desorganizado (p.ej. disgregación o incoherencia frecuente)
4. Comportamiento desorganizado o catatónico
5. Síntomas negativos (es decir, expresión emotiva disminuida o abulia)

B. Durante una parte significativa del tiempo desde el inicio del trastorno, el nivel de funcionamiento en uno o más ámbitos principales, como el trabajo, las relaciones interpersonales o el cuidado personal, está muy por debajo del nivel alcanzado antes del inicio (o cuando comienza en la infancia o adolescencia, fracasa la consecución del nivel esperado de funcionamiento interpersonal, académico o laboral).

C. Los signos continuos del trastorno persisten durante un mínimo de seis meses. Este periodo de seis meses ha de incluir al menos un mes de síntomas (o menos si se trató con éxito) que cumplan el Criterio A (es decir, síntomas de fase activa) y puede incluir períodos de síntomas prodrómicos o residuales. Durante estos periodos prodrómicos o residuales los signos del trastorno se pueden manifestar únicamente por síntomas negativos o por dos o más síntomas enumerados en el Criterio A presentes de forma atenuada (p.ej. creencias extrañas, experiencias perceptivas inhabituales).

D. Se han descartado el trastorno esquizoafectivo y el trastorno depresivo o bipolar con características psicóticas porque
1) no se han producido episodios maníacos o depresivos mayores de forma concurrente con los síntomas de fase activa, o
2) si se han producido episodios del estado de ánimo durante los síntomas de fase activa, han estado presentes solo durante una mínima parte de la duración total de los períodos activo y residual de la enfermedad.

E. El trastorno no se puede atribuir a los efectos fisiológicos de una sustancia (p.ej. una droga o medicamento) o a otra afección médica.

F. Si existen antecedentes de un trastorno del espectro autista o de un retraso de la comunicación de inicio en la infancia, el diagnóstico adicional de esquizofrenia sólo se hace si los delirios o las alucinaciones notables, además de los otros síntomas requeridos para la esquizofrenia, también están presentes durante un mínimo de un mes (o menos si se trató con éxito).

Tabla 2. Criterios generales para el diagnóstico de la esquizofrenia según CIE-10

CRITERIOS DIAGNÓSTICOS CIE-10

A) Al menos uno de los síndromes, síntomas o signos incluidos en el apartado 1, o al menos dos de los síntomas y signos incluidos en 2 deben estar presentes la mayor parte del tiempo durante un episodio de enfermedad psicótica de por lo menos 1 mes de duración (o durante algún tiempo la mayor parte de los días):

1. Por lo menos uno de los siguientes:

a) Eco, inserción, robo o difusión del pensamiento.

b) Ideas delirantes de ser controlado, de influencia, o de pasividad, referidas claramente al cuerpo, a los movimientos de los miembros o a pensamientos, acciones o sensaciones específicas y percepciones delirantes.

c) Voces alucinatorias que comentan la propia actividad o que discuten entre sí acerca del enfermo, u otro tipo de voces alucinatorias procedentes de alguna parte del cuerpo.

d) Ideas delirantes persistentes de otro tipo que no son propias de la cultura del individuo y que son completamente imposibles.

2. Al menos 2 de los siguientes:

a) Alucinaciones persistentes de cualquier modalidad, cuando se presentan a diario durante al menos un mes, cuando se acompañan de ideas delirantes (que pueden ser fugaces o poco estructuradas) sin un contenido afectivo claro, o cuando se acompañan de ideas sobrevaloradas persistentes.

b) Neologismos, interceptación o bloqueo del curso de pensamiento, que dan lugar a un discurso incoherente o irrelevante.

c) Conducta catatónica, tal como excitación, posturas características o flexibilidad cérea, negativismo, mutismo y estupor.

d) Síntomas negativos, tales como marcada apatía, pobreza del discurso y embotamiento o incongruencia de las respuestas emocionales (debe quedar claro que estos síntomas no se deben a depresión o medicación neuroléptica).

B) Criterios de exclusión usados con más frecuencia:

1. Si el paciente cumple criterios de un episodio maníaco o de un episodio depresivo, los criterios enumerados arriba en A1.1 y A1.2 deben satisfacerse antes del desarrollo del trastorno del humor.

2. El trastorno no es atribuible a una enfermedad orgánica cerebral, o a intoxicación, dependencia o abstinencia de alcohol u otras drogas.

1.5. Tratamiento

El tratamiento actual de la esquizofrenia son los fármacos antipsicóticos (Marder & Cannon, 2019). Estos fármacos son eficaces cuando sus niveles en el sistema nervioso central (SNC) son suficientes para ocupar aproximadamente el 70% de los receptores dopaminérgicos D2 (Uchida et al., 2011). No hay evidencia de mayor eficacia terapéutica cuando se superan estos niveles de ocupación receptorial, pero sí se incrementan los efectos secundarios. En general, los pacientes con un primer episodio psicótico tienen mayor tasa de respuesta a los fármacos antipsicóticos y responden a dosis menores que los pacientes que han sufrido múltiples episodios (Kreyenbuhl, Buchanan, Dickerson, & Dixon, 2010). Aproximadamente un tercio de los pacientes con esquizofrenia muestran resistencia al tratamiento. En estos casos, se han ensayado múltiples estrategias como aumentar la dosis de antipsicótico por encima de lo recomendado; asociar fármacos antipsicóticos de distinto perfil receptorial o añadir un estabilizador del ánimo como el litio o el ácido valproico. Sin embargo, en la actualidad hay escasa evidencia científica que respalde estos enfoques. El fármaco más eficaz para pacientes con escasa respuesta a la medicación antipsicótica es la clozapina (Leucht et al., 2013; Tiihonen et al., 2017). La terapia electroconvulsiva no se ha considerado un tratamiento de primera elección en esquizofrenia; pero puede ser útil en caso de resistencia al tratamiento con clozapina, como potenciadora de otros fármacos antipsicóticos, para el manejo de la catatonía o en situaciones especiales como pacientes embarazadas. La literatura reciente sugiere que podría ser una técnica infrautilizada para el tratamiento de la esquizofrenia (Grover, Sahoo, Rabha, & Koirala, 2019). Recientemente se ha ensayado la estimulación transcraneal profunda como nueva vía terapéutica para la esquizofrenia resistente (Corripio et al., 2020). La terapia cognitivo-conductual está recomendada en pacientes que tienen síntomas psicóticos persistentes y una aceptable conciencia de enfermedad (Dixon et al., 2010). Aunque su efectividad para los síntomas de la esquizofrenia ha sido cuestionada en un reciente meta-análisis (Jauhar et al., 2014).

1.6. Neuroimagen en la esquizofrenia

A través de los años, la esquizofrenia ha sido ampliamente estudiada en búsqueda de evidencia de una patología cerebral subyacente. En este sentido, los estudios de neuroimagen han permitido estudiar el cerebro de una manera no invasiva y han mostrado evidencia clara de anormalidad. Los principales hallazgos de estos estudios se resumen a continuación.

1.6.1. Neuroimagen estructural en la esquizofrenia

1.6.1.1. Tomografía computerizada

El primer estudio de neuroimagen estructural en esquizofrenia se realizó en 1976 por Eve Johnstone y cols. Los autores observaron que una muestra de 13 pacientes con esquizofrenia paranoide presentaban un agrandamiento de los ventrículos laterales respecto al grupo de 8 controles sanos (Johnstone, Frith, Crow, Husband, & Kreel, 1976). Desde entonces, numerosos estudios han replicado este hallazgo (Nancy C. Andreasen et al., 1990; Raz & Raz, 1990; Van Horn & McManus, 1992).

1.6.1.2. Resonancia magnética

El descubrimiento de la imagen por resonancia magnética (MRI, del inglés *Magnetic Resonance Imaging)* supuso un gran avance en el estudio de la estructura cerebral. Esta técnica permite obtener imágenes tridimensionales del cerebro humano. Con ella se han realizado estudios mediante la búsqueda de regiones de interés (ROI, del inglés *Region of Interest*) y posteriormente mediante la técnica de morfometría basada en vóxel (VBM, del inglés *Voxel Based Morphometry*) que permite comparar el volumen o densidad de los tejidos entre dos grupos de sujetos.

Numerosos estudios de MRI han constatado la existencia de alteraciones volumétricas en pacientes afectos de esquizofrenia crónica. Lawrie y Abukmeil (1998) analizaron 40 estudios y hallaron diferencias con reducciones en el porcentaje medio de volumen en todo el cerebro (3 %), el lóbulo temporal (6 % el izquierdo; 9,5 % el derecho) y el complejo amígdala / hipocampo (6,5 %; 5,5 %); así como un aumentos en los ventrículos laterales (44 %; 36 %) (Lawrie & Abukmeil, 1998).

Un meta-análisis de 58 estudios estructurales de MRI que incluyeron 1.588 participantes encontró apoyo para los siguientes cambios estructurales en la esquizofrenia: una reducción del 2 % en el volumen total del cerebro y un aumento de los ventrículos laterales de alrededor del 25 %. Las reducciones de volumen regional variaban entre el 2% de los lóbulos temporales, el 4% en el tálamo, el 5% en el lóbulo frontal, el 6% en el hipocampo, y el 7% en la amígdala (Wright et al., 2000).

Un estudio reciente del grupo de trabajo en esquizofrenia ENIGMA analizó las fMRI de 2.028 pacientes con esquizofrenia y 2.540 controles sanos, evaluados con métodos estandarizados

en 15 centros de todo el mundo. Encontraron que, en comparación con controles sanos, los pacientes con esquizofrenia tenían menores volúmenes en el hipocampo, amígdala, tálamo, accumbens y menor volumen intracraneal, así como volúmenes mayores del pálido y del ventrículo lateral. La disminución de volumen en el hipocampo era más severa en las muestras con una mayor proporción de pacientes no medicados. Los aumentos de volumen del putamen y del pálido se asociaron positivamente con la duración de la enfermedad (van Erp et al., 2018).

Respecto al tratamiento antipsicótico (AP), los estudios muestran una asociación entre la duración del tratamiento AP y la dosis total acumulada y una disminución global de la sustancia gris cerebral (Fusar-Poli et al., 2013; Haijma et al., 2013). No obstante, hay que tener en cuenta que los pacientes que reciben tratamiento AP durante más tiempo y más dosis son también los más graves o más crónicos. Para resolver si esta disminución de sustancia gris es debida a la gravedad de la esquizofrenia, a su duración o a un efecto de los AP se han realizado algunos estudios con pacientes que no han estado expuestos a los AP con resultados contradictorios. Un estudio longitudinal que comparó volúmenes de materia gris en pacientes con un primer episodio antes y después del inicio del tratamiento AP, encontró que los AP minimizaron estas disminuciones, particularmente en el cuerpo estriado (Leung et al., 2011). Otro estudio de pacientes que se estabilizaron con el tratamiento AP y se asignaron al mantenimiento del tratamiento o a la retirada del mismo, encontró que transcurrido un año no había diferencias en los parámetros volumétricos entre los dos grupos (Boonstra et al., 2011).

1.6.2. Neuroimagen funcional en la esquizofrenia

1.6.2.1. Hipofrontalidad en la esquizofrenia

El primer estudio de imagen funcional en la esquizofrenia lo llevaron a cabo Ingvar y Franzen en 1974 (Ingvar & Franzén, 1974). Utilizando la técnica de inhalación de xenón marcado radioactivamente, hallaron que un grupo de 9 pacientes crónicos hospitalizados y otro de 11 pacientes crónicos más jóvenes mostraban un patrón regional de actividad diferente a los observados en los sujetos controles sanos, con un menor flujo en las regiones anteriores que los autores denominaron como "hipofrontalidad". Un número importante de estudios posteriores que se llevaron a cabo bajo condiciones de reposo tuvieron resultados contradictorios ya que algunos de éstos hallaron evidencia para la hipofrontalidad y, en cambio, otros no (Chua & McKenna, 1995).

Weinberger, Berman y Zec propusieron que la hipofrontalidad sería más marcada en la esquizofrenia cuando las demandas cognitivas implicaran al córtex prefrontal. Estudiaron la actividad cerebral en 20 pacientes con esquizofrenia y 25 sujetos sanos apareados por edad y sexo, ambos en reposo y en realización de una tarea ejecutiva, el Wisconsin Card Sorting Test (WCST). Los pacientes con esquizofrenia mostraron una tendencia no significativa hacia la hipofrontalidad en reposo, pero durante la tarea del WCST sí era significativa (Weinberger, Berman, & Zec, 1986).

Hill y colaboradores meta-analizaron estudios que se llevaron a cabo tanto durante el estado de reposo (76 estudios) como durante tareas que activaban la corteza prefrontal (28 estudios). Este meta-análisis apoyó la hipótesis de la hipofrontalidad en ambos casos (Hill et al., 2004). Posteriormente un meta-análisis de 41 estudios de fMRI utilizando el análisis basado en vóxeles de todo el cerebro también encontró resultados positivos para la hipofrontalidad durante la ejecución de una tarea (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009).

Por otro lado, un número notable de estudios de fMRI, en lugar de hipofrontalidad, hallaron evidencia para un aumento de la activación durante la ejecución de tareas de memoria de trabajo y otras tareas relacionadas con el córtex dorsolateral prefrontal (DLPFC, del inglés *Dorsolateral Prefrontal Cortex*), lo que se denominó como hiperfrontalidad (Callicott et al., 2000, 2003; Manoach et al., 1999; Tan et al., 2006). El meta-análisis de Minzenberg y colaboradores también corroboró estos resultados, hallando evidencia para una reducción de la activación en algunas áreas frontales y en cambio un aumento de la activación en otras (Minzenberg et al., 2009). Otros autores (Callicott et al., 2003; Tan et al., 2006; Weinberger et al., 2001) siguieron desarrollando esta teoría y postularon que la activación del lóbulo prefrontal no era lineal, sino que seguiría una función de U invertida; esto es, a mayor exigencia de la tarea, mayor activación hasta llegar a un umbral de exigencia a partir del cual la activación cerebral decaería. Si se considera que los pacientes tienen menor capacidad de memoria de trabajo, mostrarían mayores niveles de activación que los controles en tareas fáciles consiguiendo mantener el rendimiento, aunque con menor eficiencia (necesidad de mayor activación). Las tareas difíciles resultarían inasumibles para los pacientes y la actividad cerebral decaería junto con el rendimiento (hipoactividad). El resultado sería que en los pacientes con esquizofrenia la curva U invertida estaría desplazada hacía la izquierda, encontrándose entonces tanto hiper como hipoactividad en relación con los controles dependiendo del nivel de dificultad de la tarea realizada.
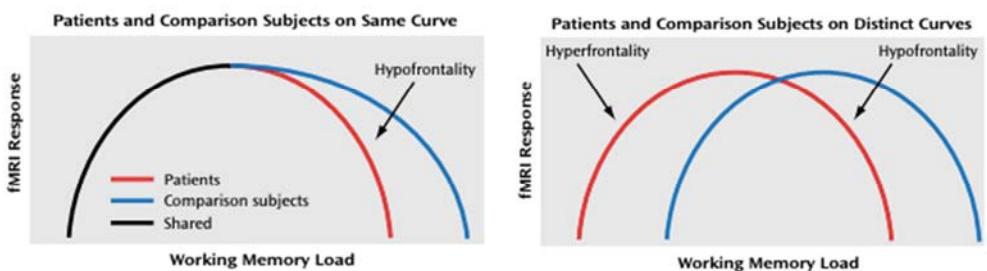
Figura 2. Curva invertida que representa de manera teórica la respuesta del DLPFC frente al aumento de dificultad de una tarea de memoria del trabajo en pacientes con esquizofrenia y sujetos sanos (Callicott et al., 2003).

1.6.2.2. Fallo de desactivación en la esquizofrenia

Una nueva teoría surgió para explicar el patrón de activaciones prefrontales descrito hasta la fecha. Gusnard, Raichle y colaboradores relacionaron los hallazgos de las hiperactivaciones descritas en estudios previos con la descripción de una red que en individuos sanos se desactivaba cuando se realizaba una tarea cognitiva (Broyd et al., 2009; Gusnard & Raichle, 2001). Para ello, estos autores argumentaron que durante el desempeño de una tarea, la aparición de una activación se podría interpretar de dos maneras distintas (Figura 3).
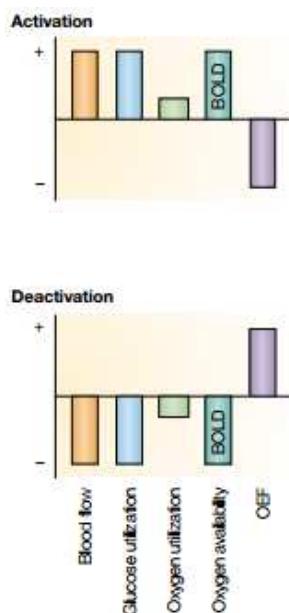
Figura 3. La sustracción en ambos casos se detectaría como activación aparente. En el primer caso, denominado como "Activation" en la figura, al realizar la tarea de interés se observaría un aumento de activación por encima de línea de base. La explicación sería que la tarea de interés produce más activación que la tarea de control. En el segundo caso, denominado como "Desactivation", la tarea de interés presentaría una menor disminución de activación respecto a la línea de base y respecto a la tarea de control (que desactiva más con puntuaciones más negativas). Sin embargo, la sustracción en ambos casos se interpretaría como un aumento en la actividad entre la tarea de control y la tarea de interés (Gusnard & Raichle, 2001).

Siguiendo esta teoría, el grupo de Pomarol-Clotet y McKenna (2008) fue el primero en describir un fallo en la desactivación de la DMN en pacientes con esquizofrenia. Los autores estudiaron a 32 pacientes esquizofrénicos crónicos y a 32 pacientes controles durante la realización de una tarea de memoria de trabajo, la tarea n-back. Como en otros estudios, encontraron una reducción de la actividad en el DLPFC derecho así como en otras áreas frontales y no frontales. Sin embargo, también observaron un fallo en la desactivación en una amplia área del córtex frontal medial. Consideraron que este fallo en la desactivación reflejaba una disfunción del núcleo anterior de la DMN (Pomarol-Clotet, E., Salvador, R., Sarro, S., Gomar, J., Vila, F., Martinez, A., Guerrero, A., Ortiz-Gil, J., Sans-Sansa, B., Capdevila, A. et al., 2008).

1.6.2.3. La Red Neuronal por Defecto

El término "Default Mode Network" (DMN) o Red Neuronal por Defecto en castellano fue utilizado por primera vez en 2001 por el científico Marcus Raichle a partir de la observación de que ciertas áreas corticales se activaban de manera bilateral y simétrica durante el estado de reposo. Éstas áreas se encontraban a nivel de la corteza prefrontal medial y el cingulado posterior y precuneus (Marcus E. Raichle et al., 2001). La corteza parietal medial, la corteza temporal lateral y el hipocampo también pertenecen a esta red (Buckner, Andrews-Hanna, & Schacter, 2008). El estado de reposo hace referencia al hecho de estar despierto y alerta, pero sin realizar ninguna tarea que requiera fijar la atención. Además, se observó que estas áreas disminuían su activación durante la realización de tareas cognitivas (M. L. Hu et al., 2017). Un pequeño número de estudios han aportado indicios de las funciones que puede desarrollar la DMN a partir de tareas que han conseguido activarla. Estas tareas comparten el hecho de implicar el pensamiento introspectivo (Gusnard, 2005).

a)   Anatomía

Las áreas cerebrales que actualmente se acepta que forman parte de la DMN son la corteza medial prefrontal (mPFC) que incluye a la corteza prefrontal ventromedial (VMPFC, del inglés *Ventromedial Prefrontal Cortex*) y a la corteza prefrontal dorsomedial (DMPFC, del inglés *Dorsomedial Prefrontal Cortex*), la corteza cingulada posterior (PCC, del inglés *Posterior Cingulate Cortex*) y precuneus (PCUN), el lóbulo parietal inferior (IPL, del inglés *Inferior Parietal Lobe*) y el hipocampo (HP) (Buckner et al., 2008; Marcus E. Raichle et al., 2001).

Tabla 3. Principales regiones asociadas a la red neuronal por defecto

REGIÓN	ABREVIATURAS
Corteza prefrontal medial	mPFC
Corteza prefrontal ventromedial	VMPFC
Corteza prefrontal dorsomedial	DMPFC
Corteza cingulada posterior / Precuneus	PCC/PCUN
Lóbulo parietal inferior	LPI
Hipocampo	HP

Figura 4. Componentes de la DMN. 1, corteza orbito-frontal; 2/3, corteza prefrontal medial; 4, corteza temporal lateral; 5, lóbulo parietal inferior; 6, corteza cingulada posterior/precuneus; 7, hipocampo (N = 39, thresholded at z >2.1, corrected p < 0.05). (M E Raichle, 2015).
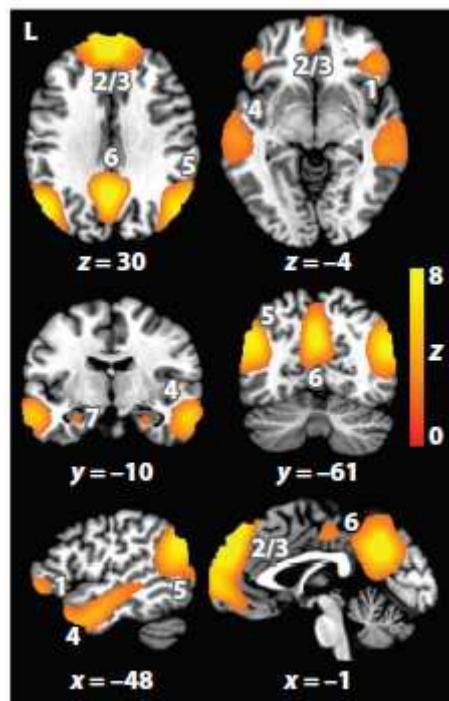
b)   Activaciones y desactivaciones de la DMN

Estudios recientes de neuroimagen han fijado su foco de interés en la conexión entre distintas redes cerebrales. En los últimos años se ha postulado que las funciones cognitivas complejas se llevan a cabo mediante la coordinación de tres grandes redes cerebrales en lo que se conoce como el modelo de la triple red. La red ejecutiva central (CEN, del inglés *Central Executive Network*) que se encargaría de mantener la atención hacia estímulos externos durante la ejecución de tareas cognitivamente demandantes y estaría formada por la DLPFC y la corteza

parietal posterior (PPC, del inglés *Posterior Parietal Cortex*) (Nekovarova, Fajnerova, Horacek, & Spaniel, 2014; Wu & Jiang, 2020). En contraposición a esta red, tenemos a la DMN que se desactiva típicamente ante tareas cognitivas (Fransson, 2006). Se observó, además, que a mayor demanda de la tarea mayor era el grado de desactivación en estas regiones cerebrales que formaban la DMN (McKiernan, D'Angelo, Kaufman, & Binder, 2006). Diversos autores han sugerido que esta asociación de anticorrelación entre las dos redes formaría parte de los mecanismos dinámicos de organización cerebral. Y que sería la interacción entre los dos sistemas, más que la actividad de la DMN per se, lo que garantizaría el correcto funcionamiento cerebral (Fox et al., 2005). En este sentido, la red de prominencia (SN, del inglés Salience Network) actuaría como bisagra entre la CEN y la DMN (Nekovarova et al., 2014; Wu & Jiang, 2020). De hecho, se cree que la SN tendría la capacidad de cambiar entre la activación de una u otra red a través de una respuesta a los estímulos prominentes internos o externos que estaría mediada por la liberación de dopamina (Menon & Uddin, 2010).

c)   Funciones de la DMN

En relación a la función o funciones que ejerce la DMN, se han desarrollado dos hipótesis principales. Por un lado, se ha postulado que la DMN podría tener una función "centinela" y monitorizar el ambiente externo. En este sentido, la DMN permitiría focalizar la atención del individuo en el mundo exterior en espera de sucesos inesperados pero con un bajo coste energético (C. D. Gilbert & Sigman, 2007). La segunda hipótesis se basa en que son los procesos introspectivos espontáneos los que provocan la actividad de la DMN (Buckner et al., 2008). Andrews-Hanna en 2010 realizó experimentos que relacionaron la actividad en la DMN con   tareas que requieren del procesamiento de información relevante al yo, como la autorreflexión, la emisión de juicios morales, la planificación de planes futuro y la realización de operaciones que involucran a la teoría de la mente (TOM) (Addis, Wong, & Schacter, 2007; Andrews-Hanna, Reidler, Huang, & Buckner, 2010; Spreng & Grady, 2010; Whitfield-Gabrieli & Ford, 2012). Las áreas de la DMN que se han visto asociadas a los procesos de autorreflexión y reflexión sobre el otro son el mPFC, el PCC y la unión temporoparietal (TPJ, del inglés *temporo-parietal junction*) (Denny, Kober, Wager, & Ochsner, 2012). Otros estudios han observado que la DMN también está implicada en el recuerdo autobiográfico. Un meta-análisis de estudios de tomografía por emisión de positrones y fMRI sobre memoria autobiográfica mostró activaciones en regiones de la DMN como la mPFC, la PCC y el PCUN, así como la corteza parietal inferior y el HP. Otra función que se ha atribuido a la DMN ha sido la de la toma de decisiones a través de la integración de información procedente de procesos emocionales y cognitivos (S. J. Gilbert, Dumontheil, Simons, Frith, & Burgess, 2007). Además,

recientemente se ha postulado que la DMN podría estar dividida en subsistemas que son identificables mediante análisis de conectividad funcional (Braga & Buckner, 2017) y que tendrían un papel diferenciado en respuesta a las distintas tareas a realizar. De esta manera, el subsistema del lóbulo temporal medial estaría asociado a la memoria autobiográfica, la prospección y la realización de planes de futuro (Andrews-Hanna, 2012). Por otro lado, el subsistema dorsal se relacionaría con los procesos de mentalización, TOM y la reflexión sobre los estados mentales actuales del sujeto (Andrews-Hanna, 2012; Andrews-Hanna, Saxe, & Yarkoni, 2014; Braga & Buckner, 2017). Ambos subsistemas estarían altamente correlacionados con los dos nodos centrales: la corteza prefrontal medial y la corteza cingulada posterior (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010).

1.6.2.4 La Red Neuronal por Defecto en esquizofrenia

a)   Activaciones y desactivaciones de la DMN en esquizofrenia

Como hemos visto anteriormente, el grupo de Pomarol-Clotet y McKenna fue el primero en describir un fallo en la desactivación de la DMN en pacientes con esquizofrenia (Pomarol-Clotet, E., Salvador, R., Sarro, S., Gomar, J., Vila, F., Martinez, A., Guerrero, A., Ortiz-Gil, J., Sans-Sansa, B., Capdevila, A. et al., 2008). Observaron un fallo en la desactivación en una amplia área del córtex frontal medial durante la realización de una tarea de memoria del trabajo. Este hallazgo ha sido replicado posteriormente por diversos autores (Dreher et al., 2012; Milanovic et al., 2011; Salgado-Pineda et al., 2011; F. C. Schneider et al., 2011; Whitfield-Gabrieli et al., 2009). Además, este fallo en la desactivación de la mPFC se ha observado también en pacientes con primeros episodios psicóticos (Guerrero-Pedraza et al., 2012), en familiares de primer grado de pacientes con esquizofrenia (Landin-Romero et al., 2015), en pacientes afectos de trastorno afectivo bipolar (Fernández-Corcuera et al., 2013), en pacientes con trastorno esquizoafectivo (Madre et al., 2013), en pacientes con depresión mayor (Rodríguez-Cano et al., 2014), en el trastorno por déficit de atención e hiperactividad (Salavert et al., 2018) y en el trastorno límite de personalidad (Aguilar-Ortiz et al., 2020).

En un reciente meta-análisis de 52 estudios, se analizaron los patrones de activación y desactivación que presentaban los pacientes con esquizofrenia cuando realizaban una tarea de memoria del trabajo respecto a un grupo de controles sanos (Wu & Jiang, 2020). Los resultados evidenciaron que en 34 estudios se encontraban hipoactivaciones en esquizofrenia en la DLPFC bilateral, la ínsula, el claustrum y algunas regiones inferiores del lóbulo prefrontal. En 31 estudios se describían hiperactivaciones en el IPL izquierdo, el área suplementaria

motora y el núcleo accumbens dorsal. Y finalmente encontraron 12 estudios en los que aparecía un fallo en la desactivación en el VMPFC y la PCC, áreas que se consideran como parte de la DMN. Los autores postularon que las alteraciones en activación y desactivación propias de la esquizofrenia aparecían en tres redes específicas: la CEN, la DMN y la SN. De hecho, algunos de los síntomas principales de la esquizofrenia podrían estar relacionados con una alteración de la anti-correlación entre la DMN y la CEN; posiblemente asociada a un malfuncionamiento de la SN (Nekovarova et al., 2014).

b)   Conectividad funcional de la DMN en esquizofrenia

Otra forma de estudiar la DMN en esquizofrenia ha sido mediante los análisis de conectividad funcional, los cuales han demostrado alteraciones tanto en reposo (Liu et al., 2012; Salvador, Anguera, Gomar, Bullmore, & Pomarol-Clotet, 2010; Zhou et al., 2007) como durante la realización de una tarea (Garrity et al., 2007; Whitfield-Gabrieli et al., 2009).

Bluhm y colaboradores fueron los primeros en reportar alteraciones de conectividad asociadas a la DMN en esquizofrenia. Específicamente hallaron una disminución en la conectividad funcional entre la PCC y regiones prefrontales mediales, parietales laterales y cerebelosas en comparación a los controles sanos (Bluhm et al., 2007).

Sin embargo, el hallazgo más consistentemente replicado ha sido la hiperconectividad funcional entre las regiones de la DMN; asociada a la hiperactivación de dichas regiones (M. L. Hu et al., 2017; Whitfield-Gabrieli & Ford, 2012). Esto se ha visto tanto en pacientes con esquizofrenia crónica, como en primeros episodios psicóticos, en individuos con estados mentales de alto riesgo para el desarrollo de psicosis y en los familiares de primer grado de pacientes con esquizofrenia (M. L. Hu et al., 2017).

2.   OBJETIVOS E HIPÓTESIS DE LA TESIS DOCTORAL

La presente tesis doctoral pretende profundizar en el conocimiento de las alteraciones neurobiológicas subyacentes a la esquizofrenia, específicamente las relacionadas con la disfunción de la DMN que presentan estos pacientes. Este conocimiento es esencial de cara a comprender la patogénesis del trastorno y podrá ser utilizado para mejorar su conceptualización, diagnóstico y tratamiento.

2.1. Objetivos

El objetivo general de la presente tesis es estudiar el comportamiento de la DMN en esquizofrenia mediante tareas que normalmente activan dicha red. En concreto, se examinarán los patrones de activación y desactivación cerebral en pacientes con esquizofrenia y controles sanos durante la realización de una tarea de memoria autobiográfica y una tarea de autorreflexión.

Los objetivos específicos de los dos estudios que componen la tesis doctoral son los siguientes:

Estudio 1:

1)   Evaluar cómo se comporta la DMN en esquizofrenia durante la realización de una tarea de memoria autobiográfica, en la que se compara la activación durante el recuerdo autobiográfico con una condición de control y con el estado de reposo, que constituye una línea base.

2)   Determinar si existen diferencias entre pacientes afectos de esquizofrenia y controles sanos en cuanto a las activaciones / desactivaciones durante la realización de las tareas.

Estudio 2:

1)   Evaluar cómo se comporta la DMN en esquizofrenia durante la realización de una tarea de autorreflexión y reflexión sobre el otro; al comparar estas condiciones en las que se presupone que la DMN se activará, con una condición semántica de control y con el estado de reposo, que constituye una línea base.

2)   Determinar si existen diferencias entre pacientes afectos de esquizofrenia y controles sanos en cuanto a las activaciones / desactivaciones durante la realización de las tareas.

3)   Evaluar si existen alteraciones entre el procesamiento de la información referente al yo y al otro en los pacientes afectos de esquizofrenia.

2.2. Hipótesis

Estudio 1:

1)   Los controles sanos mostrarán activación de las regiones de la DMN (corteza prefrontal medial, cortezas cingulada anterior y posterior, precuneus, corteza parietal inferior e hipocampo) durante la realización de la tarea de memoria autobiográfica.

2)   Los pacientes con esquizofrenia mostrarán un patrón diferente de activación y/o desactivación en las regiones de la DMN en relación a los controles sanos. No se puede establecer la direccionalidad de estas diferencias debido a la ausencia de hallazgos previos en la literatura.

Estudio 2:

1)   Los controles sanos mostrarán activación de las regiones de la DMN (corteza prefrontal medial, corteza cingulada posterior y precuneus) durante la realización de la tarea de autorreflexión y reflexión sobre el otro.

2)   Los pacientes con esquizofrenia mostrarán un patrón diferente de activación y/o desactivación en las regiones de la DMN en relación a los controles sanos. No se puede establecer la direccionalidad de estas diferencias debido a la ausencia de hallazgos previos en la literatura.

3)   Los pacientes con esquizofrenia presentarán un déficit en la activación de las regiones de la DMN especialmente implicadas en la diferenciación entre el yo y el otro (corteza prefrontal medial, precuneus y la unión temporoparietal) en relación a los controles sanos.

3.   MÉTODOS

3.1. Participantes

La muestra de pacientes con esquizofrenia se reclutó en tres hospitales de Barcelona: Hospital Sant Rafael, Hospital Benito Menni de Sant Boi de Llobregat y Hospital Sagrat Cor de Martorell. El diagnóstico se estableció siguiendo los criterios para esquizofrenia paranoide del DSM-IV-TR (APA, 2002).

Criterios de inclusión:

1. Edad 18-65 años.

2. Cumplir criterios DSM-IV-TR para esquizofrenia.

3. Coeficiente intelectual (CI) premórbido dentro del rango de normalidad ($\geq$ 70), estimado usando el   Test de Acentuación de Palabras (TAP) (Del Ser, González-Montalvo, Martínez-Espinosa, Delgado-Villapalos, & Bermejo, 1997).
4. Dominancia manual derecha.

Criterios de exclusión:

1. Antecedentes de traumatismo craneoencefálico o enfermedad neurológica.

2. Antecedentes de cualquier trastorno por dependencia de sustancias durante los 12 meses previos a la participación en el estudio.

3. Antecedentes de enfermedad somática que afecte a la cognición.

4. Criterios de exclusión para realizar pruebas de MRI: Portador de prótesis metálicas, portador de válvulas cardíacas, claustrofobia evidente, embarazo.

La muestra de control consistió en individuos sanos seleccionados para ser similares en edad, sexo y CI premórbido estimado a los pacientes. Fueron reclutados a través de un anuncio publicitario en el hospital y en la comunidad local, además de referencias de boca en boca. Los controles cumplieron los mismos criterios de exclusión que los pacientes. También fueron interrogados y excluidos si presentaban antecedentes de enfermedad mental y/o tratamiento con medicación psicotrópica.

La investigación se llevó a cabo siguiendo los principios de la Declaración de Helsinki y el protocolo fue aprobado por el comité ético del hospital "Comité Ético de Investigación Clínica de las Hermanas Hospitalarias". Todos los participantes dieron su consentimiento informado por escrito.

3.2. Diseño del estudio

Figura 5. Diagrama de flujo CONSORT del estudio.
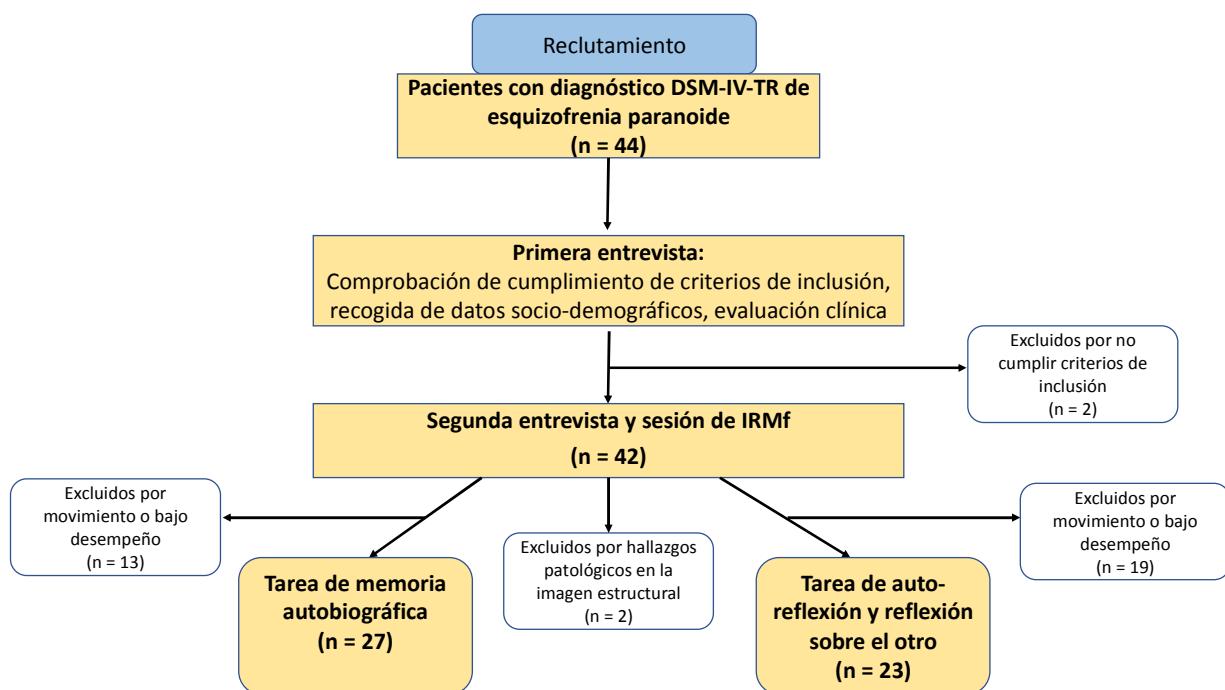
3.3. Reclutamiento

Se reclutaron un total de 44 pacientes diagnosticados de esquizofrenia a los que se les realizó la entrevista inicial. De los cuales, 2 fueron excluidos por no cumplir todos los criterios de inclusión y 2 más fueron excluidos por hallazgos patológicos en la imagen estructural valorada por un radiólogo clínico. En cuanto a la ejecución de las tareas, 13 pacientes fueron excluidos por movimiento excesivo en el escáner de resonancia magnética o mala ejecución durante la tarea de memoria autobiográfica y 19, durante la tarea de autorreflexión.

Se reclutaron un total de 40 controles sanos, de los cuales 3 se tuvieron que descartar por no cumplir todos los criterios de inclusión y 2 más por hallazgos patológicos en la imagen

estructural. 4 controles más se descartaron por movimiento excesivo en el escáner de resonancia magnética o mala ejecución de las tareas. Finalmente, para cada tarea se seleccionó, del total de controles sanos, una muestra que fuera similar en cuanto edad, género y CI estimado (CI premórbido para los pacientes) a la muestra de pacientes con esquizofrenia.

3.4. Evaluaciones clínicas

Un psiquiatra con experiencia clínica realizó la primera evaluación de los pacientes y constató que cumplían los criterios DSM-IV-TR para esquizofrenia. Se recogieron datos socio-demográficos así como otros antecedentes médicos y psiquiátricos. También se realizó una evaluación exhaustiva de los posibles consumos de sustancias (First, 2002). Los síntomas psicóticos fueron evaluados con la PANSS (Stanley R. Kay, Fiszbein, Vital-Herne, & Fuentes, 1990) y la SANS (N. C. Andreasen, 1989). Para evaluar el funcionamiento psicosocial, se administró la escala de evaluación global de funcionamiento (GAF, del inglés *Global Assessment of Functioning*) (APA, 2002). La gravedad global de la enfermedad se evaluó mediante la escala de Impresión Clínica Global (CGI, del inglés *Clinical Global Impression*) (Guy, 1976).

Todos los pacientes estaban tomando tratamiento con antipsicóticos durante la realización del estudio. Se recogieron las dosis de medicación antipsicótica (medida en equivalentes de clorpromazina), estabilizadores del estado de ánimo y otros psicofármacos que estaban tomando los pacientes en ese momento.

Los controles sanos fueron evaluados también para descartar la presencia de trastornos mentales actuales o pasados mediante la entrevista clínica estructurada para los trastornos mentales del DSM-IV-TR (SCID, del inglés *Structured Clinical Interview for DSM-IV-TR Disorders*) (First, 2002). También se recogió información relativa al consumo de sustancias en el último año de manera específica y por el uso de medicación psicótropa para evaluar si cumplían los criterios de inclusión.

Todos los participantes en el estudio fueron evaluados mediante el TAP (Del Ser et al., 1997), para realizar la estimación del CI (estimación del CI premórbido para los pacientes). Esta prueba requiere de la pronunciación de palabras de baja frecuencia cuyos acentos han sido eliminados. El TAP ha sido estandarizado en comparación con la Escala de Inteligencia de Wechsler para Adultos, 3ª edición, y las puntuaciones pueden ser convertidas en estimaciones de CI de escala completa (Gomar et al., 2011).

3.5. Procedimiento de resonancia magnética funcional

3.5.1 Tarea de memoria autobiográfica

La tarea utilizada en esta tesis es innovadora y está basada en la tarea desarrollada por Oertel-Knöchel y colaboradores, la cual utilizaba claves personalizadas que habían demostrado ser evocadoras de recuerdos autobiográficos para la persona. Estos autores utilizaron como condición control la búsqueda de una palabra semánticamente apropiada para completar una frase dada (Oertel-Knöchel et al., 2012). En nuestro estudio desarrollamos la tarea modificando la condición control por la visualización de claves que no eran capaces de evocar ningún recuerdo autobiográfico en los sujetos (Fuentes-Claramonte et al., 2019) (Annexo 1).

Antes de cada sesión de fMRI, se realizaba una entrevista con cada participante en la cual se le interrogaba por recuerdos autobiográficos de diferentes momentos de su vida. Para generar los recuerdos autobiográficos se utilizaban dos herramientas, la Entrevista de Memoria Autobiográfica (AMI, del inglés *Autobiogrpahical Memory Interview*) (Kopelman, Wilson, & Baddeley, 1989) y la lista de palabras del test de Crovitz (Crovitz & Schiffman, 1974). Mediante la AMI, le pedimos al participante que nos contara sucesos de su vida. Los recuerdos debían ser concretos y situados en el tiempo para ser válidos. Se recogían un total de 20 recuerdos repartidos entre cuatro periodos (infancia, adolescencia, vida adulta y recuerdos recientes, que se referían al último año).

Los estímulos escogidos para la tarea de fMRI consistían en grupos de tres palabras y estaban personalizados para cada sujeto. La primera palabra del grupo hacía referencia a unos de los cuatro periodos temporales, y las otras dos se escogían entre las palabras que habían evocado recuerdos autobiográficos al sujeto (p.ej. "infancia abuela pastel", "recientemente graduación enfermería"). Todos los recuerdos debían tener la puntuación máxima de 3 de la AMI, indicando que estaban bien especificados en tiempo y lugar y que eran ricos a nivel descriptivo.

Para generar la condición control, se necesitaban otros 20 estímulos con la misma estructura pero que no evocasen recuerdos autobiográficos al sujeto. Para ello, se seleccionaban grupos de tres palabras encabezados por una de las palabras de referencia temporal (infancia, adolescencia, vida adulta y recientemente) y seguidos por dos palabras procedentes de la lista de palabras y que no habían generado recuerdos autobiográficos al sujeto.

Antes de iniciar la tarea en el escáner, se le daban al sujeto las siguientes instrucciones: "Ahora irá viendo los grupos de palabras de los que hemos hablado antes. Algunas palabras estarán relacionadas con los recuerdos que me ha contado, cuando las vea debe recordar los sucesos que se asocien con esas palabras. Otras palabras no se asociarán con recuerdos, en ese caso, cuando las vea no tiene que hacer nada. Las palabras estarán poco tiempo en la pantalla, por lo que debe permanecer atento ya que irán cambiando y deberá ir rememorando cada recuerdo."
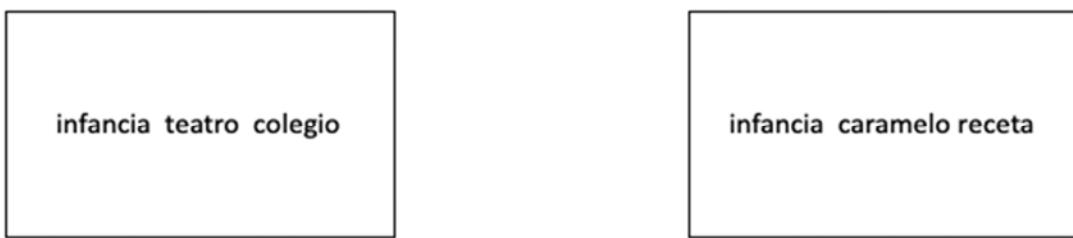
Figura 6. Tarea de memoria auto-biográfica. A la izquierda, un ejemplo de pantalla con tres palabras evocadoras de recuerdo autobiográfico. A la derecha, un ejemplo de pantalla con tres palabras neutras.

Se alternaban diez bloques de estímulos evocadores de memoria autobiográfica con diez bloques de estímulos no evocadores y todos los bloques duraban 20 segundos. La tarea tenía también períodos de línea base en los que se presentaba una cruz como punto de fijación durante 16 segundos. La duración total de la tarea era de 12 minutos y 20 segundos.

Al finalizar la sesión de fMRI, se les preguntaba a todos los participantes si se habían mantenido despiertos y atentos durante toda la sesión y si habían sido capaces de recordar y evocar los episodios autobiográficos durante la condición evocadora de recuerdos autobiográficos. Si alguno de los participantes respondía negativamente a cualquiera de estas preguntas, se descartaba del estudio.

3.5.2. Tarea de autorreflexión y reflexión sobre el otro

La tarea utilizada en esta tesis es novedosa y se basa en una adaptación de la tarea descrita por Modinos y colaboradores (Modinos, Ormel, & Aleman, 2009). La nueva tarea ha sido utilizada en una muestra de controles sanos en un estudio ya publicado por nuestro grupo (Fuentes-Claramonte et al., 2019) (Annexo 1). Dicha tarea pretende investigar el procesamiento de información relacionada con uno mismo y con una tercera persona conocida y compararlo con el procesamiento de información de conocimiento semántico general. Para aislar los componentes de interés del estudio, esta tarea utiliza:

(1)   Una condición semántica de control. Ésta era equiparable en cuanto a requerimientos perceptuales y motores así como en complejidad semántica a las condiciones de interés.

(2)   Una condición de 'auto-reflexión' con afirmaciones sobre uno mismo.

(3)   Una condición 'sobre el otro' destinada a poder comparar el proceso de reflexión sobre uno mismo al proceso de reflexión sobre una tercera persona del entorno del participante.

Para ello, previo a la sesión de fMRI se les explicaba detalladamente a todos los participantes cómo se desarrollaría la tarea y se les pedía que seleccionaran una persona a la que conocieran personalmente, pero con la que no tuvieran una relación excesivamente íntima (por ejemplo, no podía ser la pareja, padres o hermanos, o amigos muy cercanos). La persona escogida se consensuaba con el investigador para comprobar que el grado de intimidad con el 'otro' era similar para todos los participantes.

Durante la tarea, los participantes visualizaban una serie de afirmaciones sobre el mundo, sobre uno mismo o sobre otra persona, las cuales eran similares en cuanto a longitud y complejidad. Los participantes tenían que responder si creían que las afirmaciones eran verdaderas o falsas apretando un pulsador.

En la condición de autorreflexión se presentaban frases en relación a características, atributos y actitudes personales (p. ej. "En general, me gusta el orden"). De igual manera, en la condición de reflexión sobre el otro, las frases hacían referencia a rasgos de personalidad o comportamientos de la persona escogida (p.ej. "El Otro siempre toma decisiones sin pensar" o "El Otro normalmente tiene buenas ideas"). En la condición semántica, las frases hacían referencia a hechos de conocimiento general, como por ejemplo, "Una década es un periodo de diez años". En las condiciones de auto-reflexión y reflexión sobre el otro, la mitad de las frases eran positivas y la mitad negativas. En la condición semántica, la mitad de las frases eran verdaderas y la otra mitad, falsas.

La tarea consistía en 54 frases (18 por condición) divididas en un diseño de bloques. Cada bloque venía precedido por una pantalla indicando la condición que correspondía al bloque ("Frases sobre mí", "Frases sobre el otro", "Frases sobre hechos") que duraba 3 segundos. Después de 1 segundo, se presentaban tres pantallas con una frase cada una y las opciones "SÍ" y "NO" en los cuadrantes inferior derecho e inferior izquierdo respectivamente y una duración de 9 segundos por pantalla. El sujeto tenía un mando en cada mano y debía presionar con el índice de la mano derecha en caso afirmativo y con el índice de la mano izquierda en caso negativo. Las frases iban separadas por una pantalla en blanco de 1 segundo de duración.

Cada condición constaba de 6 bloques y cada 3 bloques había un periodo de descanso en el que se presentaba una cruz como punto de fijación. El orden de los bloques estaba pseudoaleatorizado. La duración total de la tarea era de 12 minutos y 12 segundos. Como se muestra en el artículo de Fuentes-Claramonte y colaboradores, esta versión de la tarea era capaz de provocar la activación de las regiones de la DMN relacionadas con la auto-reflexión y la reflexión sobre el otro (Fuentes-Claramonte et al., 2019) (Annexo 1).

Figura 7. Tarea de auto-reflexión y reflexión sobre el otro. Ejemplo de tres pantallas en las que se debe responder SÍ o NO a afirmaciones sobre tópicos generales ("Hechos"), uno mismo ("Yo") u otra persona elegida previamente por el paciente y que éste conozca ("Otro").

Al finalizar la sesión de fMRI, se les preguntaba a todos los participantes si se habían mantenido despiertos y atentos durante toda la sesión y si habían sido capaces de responder a todas las afirmaciones. Si alguno de los participantes respondía negativamente a cualquiera de estas preguntas, se descartaba del estudio.

3.5.3. Adquisición de los datos de resonancia magnética funcional

Las imágenes se adquirieron mediante un escáner de 3 Teslas Philips Achieva (Philips Medical Systems, Best, The Netherlands). Para las dos tareas, los datos funcionales se adquirieron utilizando una secuencia de imágenes ecoplanar de gradiente eco (EPI) potenciada en T2 que representa el contraste dependiente del nivel de oxigenación (BOLD, del inglés *Blood Oxigenation Level-Dependent*) con los siguientes parámetros: tiempo de repetición (TR) = 2000 ms, tiempo de eco (TE) = 30 ms, ángulo de inclinación = 78 grados, grosor de la sección = 3 mm, salto de la sección = 1 mm, resolución del plano = 3x3 mm, FOV (del inglés, *Field of Vision*) = 240 mm. Se adquirieron 32 cortes por volumen en orden intercalado paralelos al plano AC-PC (del inglés, *Anterior Comissure-Posterior Comissure*). La tarea de memoria autobiográfica consistió en 360 volúmenes y la tarea de auto-reflexión y reflexión sobre el otro consistió en 364 volúmenes.

Previo a las secuencias funcionales, se adquirió un volumen anatómico 3D en alta resolución utilizando una secuencia Turbo Field Echo para inspección y referencia anatómica (TR = 8.15 ms; TE = 3.73 ms; ángulo de inclinación = 8°; tamaño del voxel = 0.9375 ×0.9375 mm; del corte = 1 mm; de cortes = 160; FOV = 240 mm).

3.5.4. Pre-procesado de los datos

El pre-procesado de las imágenes fMRI se realizaron con el módulo FEAT (*FMRI Expert Analysis Tool*) incluido en el software FSL (*FMRIB Software Library*), versión 5.0 (Smith et al., 2004). Los primeros 20 segundos (10 volúmenes) de cada secuencia se descartaron para evitar los efectos de saturación de T1. En un primer nivel, se aplicó una corrección por movimiento (utilizando el algoritmo MCFLIRT) y, finalmente, las imágenes se registraron conjuntamente y se normalizaron en un espacio estereotáxico común (plantilla del Instituto de Neurología de Montreal). Previo al análisis grupal, a las imágenes se les aplicó un filtro espacial Gaussiano (FWHM = 5mm). Para minimizar los efectos no deseados relacionados con el movimiento, se excluyeron del estudio los individuos con un movimiento absoluto máximo estimado > 3.0 mm o un movimiento absoluto promedio > 0.3 mm.

3.6. Análisis estadístico

3.6.1. Análisis de los datos clínicos

Los datos socio-demográficos y clínicos fueron analizados y comparados con el software Excel de Windows y mediante las pruebas apropiadas (estadísticos descriptivos, prueba T para comparaciones de variables continuas y prueba de Chi-cuadrado para variables categóricas).

3.6.2. Análisis de los datos de neuroimagen

El análisis estadístico de las dos tareas se llevó a cabo en base a un modelo lineal general (GLM, del inglés *General Linear Model*).

En la tarea de memoria autobiográfica, los GLM se ajustaron para generar mapas de activación individuales para los contrastes de bloques de memoria y bloques no evocadores de memoria respecto a la línea base (punto de fijación). Las comparaciones entre pacientes y controles se realizaron dentro del módulo FEAT, con un GLM de efectos mixtos (Beckmann et al., 2006).
Todas las pruebas estadísticas se llevaron a cabo a nivel de clúster con un valor de p corregido por comparaciones múltiples de 0.05 utilizando métodos de campos aleatorios gaussianos.

Para definir el conjunto inicial de clústeres, se utilizó como umbral el valor z = 3.1 (equivalente a *p* < 0.001, sin corregir).

En la tarea de auto-reflexión y reflexión sobre el otro, los GLM se ajustaron para generar mapas de activación individuales para los contrastes de línea de base versus los bloques de las tres condiciones de interés (Yo, Otro, Hechos) y para las comparaciones entre condiciones (Yo versus Hechos, Otro versus Hechos y Otro versus Yo). Las comparaciones entre pacientes y controles se realizaron dentro del módulo FEAT, con un GLM de efectos mixtos (Beckmann et al., 2006).

Todas las pruebas estadísticas se llevaron a cabo a nivel de clúster con un valor de p corregido por comparaciones múltiples de 0.05 utilizando métodos de campos aleatorios gaussianos. Para definir el conjunto inicial de clústeres, se utilizó como umbral el valor predeterminado de z = 2.3 (equivalente a *p* < 0.01, sin corregir).

4.   RESULTADOS

4.1. Estudio 1

Autobiographical memory and default mode network function in schizophrenia: an fMRI study

PSYCHOLOGICAL MEDICINE

IMPACT FACTOR 2019: 5.813   QUARTIL 2019: Q1

Referencia:

Martin-Subero, M., Fuentes-Claramonte, P., Salgado-Pineda, P., Salavert, J., Arevalo, A., Bosque, C., … Pomarol-Clotet, E. (2019). Autobiographical memory and default mode network function in schizophrenia: an fMRI study. *Psychological Medicine*, 1–8.

Acceso Pubmed: https://doi.org/10.1017/S0033291719003052

Autobiographical memory and default mode network function in schizophrenia: an fMRI study

Marta Martin-Subero[a,b,c*], Paola Fuentes-Claramonte[a,b*], Pilar Salgado-Pineda[a,b], Josep Salavert [a,c,d], Antoni Arevalo [a,,e], Clara Bosque[a,f], Carmen Sarri[a,f], Amalia Guerrero-Pedraza[a,f], Aniol Santo-Angles[a], Antoni Capdevila[g,h], Salvador Sarró[a,b], Raymond Salvador[a,b], Peter J. McKenna[a,b**], Edith Pomarol-Clotet[a,b]

a. FIDMAG Germanes Hospitalàries Research Foundation, Barcelona, Spain
b. CIBERSAM (Centro de Investigación Biomédica en Red de Salud Mental), Spain
c. Universitat Autònoma de Barcelona, Barcelona, Spain
d. Psychiatry Department, Hospital Sant Rafael, Barcelona, Spain
e. Psychiatry Department, Hospital Sagrat Cor Martorell Barcelona, Spain
f. Benito Menni Centre Assistencial en Salut Mental, Sant Boi de
Llobregat, Barcelona, Spain.
g. Radiology Unit, Hospital de la Santa Creu i Sant Pau (HSCSP), Barcelona, Spain
h. CIBER-BBN (Centro de Investigación Biomédica en Red en Bioingeniería,
Biomateriales y Nanomedicina), Spain

*These authors contributed equally to the study

**Correspondence to:
Peter J. McKenna
FIDMAG Germanes Hospitalàries Research Foundation, Carrer Dr. Antoni
Pujadas, 38, 08830 Sant Boi de Llobregat, Barcelona (Spain)
+34 963 52 99 99 ext. 1487
Email: mckennapeter1@gmail.com

Conflict of interest statement

All authors declare that they have no conflicts of interest.

Abstract

Background: The brain functional correlates of autobiographical recall are well established, but have been little studied in schizophrenia. Additionally, autobiographical memory is one of a small number of cognitive tasks that activates rather than de-activates the default mode network, which has been found to be dysfunctional in this disorder.

Methods: Twenty-seven schizophrenic patients and 30 healthy controls underwent fMRI while viewing cue words that evoked autobiographical memories. Control conditions included both non-memory-evoking cues and a low level baseline (cross fixation).

Results: Compared to both non-memory evoking cues and low level baseline, autobiographical recall was associated with activation in default mode network regions in the controls including the medial frontal cortex, the posterior cingulate cortex and the hippocampus, as well as other areas. Clusters of de-activation were seen outside the default mode network. There were no activation differences between the schizophrenic patients and the controls, but the patients showed clusters of failure of de-activation in non-default mode network regions.

Conclusions: According to this study, patients with schizophrenia show intact activation of the default mode network and other regions associated with recall of autobiographical memories. The finding of failure of de-activation outside the network suggests that schizophrenia may be associated with a general difficulty in de-activation rather than dysfunction of the default mode network *per se*.

Key words: schizophrenia, default mode network, autobiographical memory, fMRI

Autobiographical recall refers to the conscious re-imagining of events from one's past, with the memories typically being accompanied by some of their original sensory and emotional qualities (Rubin, 1996, Svoboda *et al.*, 2006). Autobiographical memory forms part of the broader construct of episodic memory, but differently from standard episodic memory tasks, which employ experimenter-generated stimuli such as lists of words, it is tested by asking subjects to recall memorable events in their lives. These may be elicited in response to cue words like 'river' or 'puppy' (the Crovitz task; Crovitz and Schiffman, 1974), or by means of prompts about events such as starting a new job or attending a wedding (the Autobiographical Memory Test, AMI; Kopelman *et al.*, 1989). Autobiographical memory has been linked conceptually to the ability to imagine future events, and together they form the concept of 'mental time travel' (Schacter *et al.*, 2007). Autobiographical memory has also been argued to play a key role in the construction of one's sense of self (Conway and Pleydell-Pearce, 2000).

As expected, given the evidence for episodic memory impairment in the disorder (eg (Palmer *et al.*, 2009), autobiographical memory has been found to be impaired in schizophrenia. A meta-analysis of 20 studies (Berna *et al.*, 2016) found significantly poorer performance compared to healthy controls in all aspects of autobiographical recall examined; effect sizes were large for richness of detail and specificity of memories, and moderate for conscious recollection, i.e. the degree of personal awareness of participating in the re-experienced events. To date, however, there has been only one study of the brain functional correlates of autobiographical recall in schizophrenia: Cuervo-Lombard *et al.* (2012) compared 13 schizophrenic patients and 14 healthy controls using a task where they saw cue words and pressed a button when

they recalled a personal event associated with them. The control task consisted of a button press in response to instructions to use either the middle or index finger to do this. Whole-brain fMRI with correction for multiple comparisons revealed no major clusters of significant difference between the groups in the cortex, but there were small clusters of reduced activation in the patients in the lateral ventral tegmental area, the right cerebellum and both caudate nuclei. Uncorrected comparisons within a mask comprising the areas activated by the patients and/or the controls, however, revealed additional areas of reduced activation in the patients in the medial frontal cortex, the precuneus, the left lateral prefrontal cortex, the left medial temporal lobe and the occipital cortex.

Autobiographical recall is also of interest from the functional imaging point of view because it is has been found to activate the so-called default mode network (Buckner *et al.*, 2008, Raichle, 2015). This network consists of a set of brain regions that are normally active at rest but which de-activate during performance of a wide range of attention-demanding tasks. It includes prominently two midline areas, the medial prefrontal cortex and the posterior cingulate cortex/precuneus, as well as parts of the parietal and temporal lobe cortex and the hippocampus (Buckner *et al.*, 2008, Gusnard and Raichle, 2001, Raichle *et al.*, 2001). The small number of tasks that have been found to activate rather than de-activate the default mode network regions include imagining the future (Schacter *et al.*, 2007), making judgements about oneself and others (Murray *et al.*, 2012, van der Meer *et al.*, 2010), making moral judgments (Boccia *et al.*, 2017), engaging in theory of mind-type reasoning (Schurz *et al.*, 2014) and autobiographical memory. With respect to this last paradigm, Svoboda *et al.* (2006) meta-analyzed 24 PET and fMRI studies using autobiographical memory tasks and

found pooled evidence of activations in the medial frontal cortex and the retrosplenial/posterior cingulate cortex, ie the two midline cortical 'nodes' of the default mode network, as well as other regions including the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex, other lateral prefrontal regions, the medial and lateral temporal cortex, the temporoparietal junction and the cerebellum.

Default mode network dysfunction during performance of various cognitive tasks has been reported in schizophrenia since 2007. Two initial studies (Garrity *et al.*, 2007, Harrison *et al.*, 2007) found increased de-activation or a mixed pattern of increased activation and failure of de-activation, respectively. Since then, however, the almost invariable finding has been failure of de-activation, which is typically seen in the medial frontal cortex (Dreher *et al.*, 2012, Haatveit *et al.*, 2016, Mannell *et al.*, 2010, Pomarol-Clotet *et al.*, 2008, Salgado-Pineda *et al.*, 2011, Schneider *et al.*, 2011, Whitfield-Gabrieli *et al.*, 2009), although the posterior cingulate gyrus/precuneus has also sometimes been found to be affected (Salgado-Pineda *et al.*, 2011, Schneider *et al.*, 2011). There appear to be only two exceptions: using a visual working memory task with various levels of difficulty, Hahn *et al.* (2017) found that 21 schizophrenic patients and 16 controls showed no differences in de-activation across 13 regions of interest (ROIs) placed in the default mode network, and at the two hardest levels de-activation was significantly greater in the patients. In another study using a task requiring direction of attention to visual stimuli that either predicted or did not predict the location of a subsequent target, the same group (Hahn *et al.*, 2016) again found no differences in default mode network de-activation in 20 schizophrenic patients compared to 20 healthy controls (when the cue was predictive) or greater de-activation (when the cue was non-predictive).

Given the evidence for failure of default mode de-activation (and perhaps increased de-activation in some circumstances) in schizophrenia, how the network behaves during a task like autobiographical memory, which normally activates it, is clearly of some interest. In the present study we examined both activations and de-activations associated with autobiographical recall in schizophrenia, using a larger sample of patients and controls than in Cuervo-Lombard et al.'s (2012) study and employing whole-brain analysis with correction for multiple comparisons.

Methods

Subjects

The patient sample consisted of 27 right-handed patients meeting DSM-IV criteria for schizophrenia, recruited from three psychiatric hospitals in Barcelona (Benito Menni CASM, Hospital Sagrat Cor of Martorell and Sant Rafael Hospital). The diagnosis was established using the Structured Clinical Interview for DSM Disorders (SCID) (First *et al.*, 2002). Patients were excluded if they (a) were younger than 18 or older than 65, (b) had a history of brain trauma or neurological disease, or (c) had shown alcohol/substance abuse/dependence within 12 months prior to participation. With respect to the last criterion, all participants were questioned about alcohol and drug use during the previous year, and we also excluded those who reported habitual use of cannabis. Social use of alcohol was permitted, as was non-habitual use of cannabis. All the patients were taking antipsychotic treatment (23 on atypical neuroleptics, 1 on typical neuroleptics and 3 on both).

The control sample consisted of 30 right-handed healthy individuals recruited from non-clinical staff working in the hospitals, their relatives and acquaintances, plus independent sources in the community. They met the same exclusion criteria as the patients and they were also interviewed using the SCID to exclude current and past psychiatric disorders. They were questioned and also excluded if they reported a history of treatment with psychotropic medication beyond non habitual use of night sedation.

The two groups were selected to be matched for age, sex and estimated IQ (premorbid IQ in the patients). This latter was measured using the Word Accentuation Test (Test de Acentuación de Palabras, TAP; (Del Ser *et al.*, 1997, Gomar *et al.*, 2011). All patients were scanned when in a relatively stable condition.

All participants gave written informed consent. All the study procedures were approved by the local research ethics committee.

Autobiographical memory task

The task used was based on the one developed by Oertel-Knöchel et al (2012), which employed personalized cues that had previously been found to evoke autobiographical memories in the subjects. While they employed a control which involved completing a sentence with a semantically appropriate word, we changed this to one involving viewing of cues that had previously been found not to evoke autobiographical memories.

Before the fMRI session, each participant was administered the cue words from the Crovitz test (Crovitz and Schiffman, 1974) and the autobiographical prompt phrases

from the AMI (Kopelman *et al.*, 1989), in order to generate between four and six autobiographical memories for time periods covering childhood, adolescence, adulthood and the preceding year. The stimuli chosen for the fMRI paradigm consisted of groups of three words personalized for each participant. The first word in the group referred to one of the above four time periods, and the other two words were chosen on the basis that they had previously evoked autobiographical memories (e.g. *childhood-grandmother-cake*; *adult-car-robbery*). All memories were required to have been given the maximum score of 3 in the AMI, indicating that they were clearly specified in time and place and descriptively rich. For the control condition, we randomly selected groups of three words from the words that did not evoke autobiographical memories.

Ten blocks of non-memory-evoking stimuli were alternated with ten blocks of memory-evoking stimuli; all blocks lasted 20 seconds. Each block contained two cue sentences of the appropriate type. Subjects were instructed to recollect the memory previously evoked by the three word phrase, or in the case of the non-memory-evoking phrase, to read the phrase with no further requirements. A low level baseline condition was also employed, cross fixation. This was presented between blocks for 16 seconds.

At the end of the scanning session all participants were asked what they had been thinking about during each condition. Specifically, we asked if they could recollect the memories that they reported in the previous interview during the memory-evoking condition, and whether they were wide awake and focused during the session. Participants who responded negatively to either of these questions were excluded.

Image acquisition

Images were acquired with a 3T Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands). Functional data were acquired using a T2*-weighted echo-planar imaging (EPI) sequence with the following acquisition parameters: TR = 2000ms, TE = 30ms, Flip angle = 78°, in-plane resolution= 3×3mm, FOV = 240mm, slice thickness = 3mm, inter-slice gap = 1mm. The autobiographical memory task consisted of 360 volumes. Slices (32 per volume) were acquired with an interleaved order parallel to the AC-PC plane. Before the functional sequences, a high-resolution anatomical 3D volume was acquired using a TFE (Turbo Field Echo) sequence for anatomical reference and inspection (TR = 8.15ms; TE = 3.73ms; Flip angle = 8°; voxel size = 0.9375×0.9375mm; slice thickness = 1mm; slice number = 160; FOV = 240mm).

Any subjects with excessive head movement during the fMRI sequence, defined as an estimated maximum absolute movement >3.0 mm or an average absolute movement >0.3 mm, were excluded.

Image preprocessing and analysis

Preprocessing and analysis was carried out with the FEAT module included in the FSL (FMRIB Software Library) software (Smith *et al.*, 2004). The first 20 seconds, corresponding to signal stabilization, were discarded. Preprocessing included motion correction (using the MCFLIRT algorithm) and co-registration and normalization to a common stereotactic space (MNI template). Before group analyses, normalized images were spatially filtered with a Gaussian filter (FWHM = 5mm).

Statistical analysis was performed by means of a General Linear Model (GLM). Two regressors of interest were defined at the single-subject level analysis (memory-evoking blocks and non-memory-evoking blocks) and the GLM was fitted to generate activation maps of each condition compared to baseline and the comparison between conditions. Group comparisons between patients and controls were performed within the FEAT module, with mixed-effects GLMs (Beckmann *et al.*, 2006).

Statistical tests were carried out at the cluster level with a corrected *p* value of 0.05 using Gaussian random field methods. A threshold of $z = 3.1$ was used to define the initial set of clusters.

Contrasts used in the analysis

In order to examine autobiographical memory associated activations, the main contrast employed was that between cues that evoked and did not evoke autobiographical memories, something that should eliminate 'noise' due to aspects of performance common to both tasks.

For de-activations, we focused on the contrast between memory-evoking cues and the low level baseline. This was to avoid a methodological problem identified by Gusnard and Raichle (2001), that examination of relative changes between two active tasks will not necessarily reveal the true picture of activations and de-activations. Specifically, because fMRI analysis is subtractive, task-associated decreases in activation will be obtained not only when there is greater *de-activation* from baseline levels in the task of interest (in this case memory evoking cues) than in the control task (in this case non-memory-evoking cues), but also if there is greater *activation* from baseline levels in the

control task than in the task of interest. It follows that de-activations can only be confidently identified with respect to a low level baseline.

Results

Demographic data

Age, sex and TAP-estimated IQ data for the patients and controls are shown in Table 1. As can be seen, the two groups were matched on all three variables. None of the patients and two of the controls reported sporadic use of cannabis.

[Table 1 about here]

fMRI findings: memory-evoking vs non-memory evoking cues

In this contrast the healthy controls showed a large cluster of greater activation to the memory-evoking cues than the non-memory-evoking cues in the medial frontal cortex extending to the orbitofrontal cortex and temporal poles bilaterally, as well as to the thalamus, the basal ganglia, the hippocampus and the parahippocampal cortex. This cluster also extended posteriorly to include a portion of the posterior cingulate cortex/precuneus and the calcarine cortex. Other clusters of activation included the left temporo-parietal junction (comprising the posterior portion of middle temporal cortex, the angular gyrus and the middle occipital cortex), the left middle temporal cortex, and the right angular gyrus (see Figure 1, top panel, and Supplementary Table S1).

[Figure 1 about here]

The healthy controls also showed three clusters of increased activation to non-memory-evoking than to memory-evoking cues. These were in the occipital cortex bilaterally, the

lateral parietal cortex bilaterally, more in the right hemisphere, the superior temporal cortex bilaterally and the right frontal polar cortex.

The schizophrenic patients (Figure 1, middle panel) showed a broadly similar pattern of activation, although this appeared visually less extensive in the medial frontal cortex and subcortical regions. Unlike the controls, they showed no regions where there was relatively greater activation in response to non-memory-evoking cues.

Significant group differences (Figure 1, bottom panel) were observed in four relatively small clusters: the right lingual gyrus [294 voxels, peak activation at BA 19, MNI (26, -54, -4), z score=4.52, p=0.003], the right cuneus [279 voxels, peak activation at BA 18, MNI (6, -90, 26), z score=3.86, p=0.004], the left middle temporal cortex [263 voxels, peak activation at BA 21, MNI (-68, -10, -2), z score=4.48, p=0.006] and the right angular gyrus [199 voxels, peak activation at BA 40, MNI (54, -52, 38), z score=4.03, p=0.02]. As can be seen from Figure 1, these clusters of significant difference were all in regions where the healthy controls showed greater activation to non-memory-evoking cues than to memory-evoking cues. Box plots of mean activations within these four clusters are shown in Supplementary Figure S1. This confirmed that they all represented regions of relatively greater activation in the patients.

To investigate the possible influence of antipsychotic treatment on the above findings, the within-group analysis for the schizophrenic patients was repeated adding medication dose (in chlorpromazine equivalents) as a covariate. The findings in this group remained closely similar (see Supplementary Material, Figure S2A).

fMRI findings: memory-evoking cues vs low level baseline

Compared to cross fixation, the healthy controls showed a similar but more extensive pattern of activation than in the autobiographical memory-evoking vs non-evoking cue contrast. A large cluster encompassed the posterior cingulate cortex and precuneus, the left angular gyrus, the middle temporal cortex bilaterally, parts of the lateral prefrontal cortex and anterior insula bilaterally and the medial prefrontal cortex, and also extended to the occipital cortex, the hippocampus and parahippocampus, the thalamus, the basal ganglia and the cerebellum. A second cluster covered the posterior portion of the right middle temporal cortex and right angular gyrus. The third cluster of activation was located in the precuneus. The findings are shown in Figure 2, top panel; further details are given in Supplementary Table S2.

[Figure 2 about here]

As can also be seen in Figure 2, the healthy controls also showed clusters of de-activation compared to cross fixation. There were bilateral clusters in the superior temporal gyrus extending to the postcentral gyrus; the cluster on the right also extended to the superior parietal cortex and parts of the posterior cingulate and precuneus. Two more bilateral clusters were seen in the inferior temporal cortex extending to the lateral occipital cortex. A fifth cluster was in the left superior parietal cortex.

The patients showed a broadly similar pattern of activation to the healthy controls, with large clusters in the medial prefrontal cortex and the posterior cingulate cortex/precuneus, hippocampus and parahippocampus, as well as in the lateral prefrontal cortex bilaterally, the left temporal and parietal cortex and parts of the

occipital cortex bilaterally. However, they showed no clusters of de-activation (see

Figure 2, middle panel, and Supplementary Table S2). As in the contrast between

memory-evoking and non-evoking cues, repeating the within-group analysis for the

schizophrenic patients adding medication dose (in chlorpromazine equivalents) as a

covariate made little difference to the findings (see Supplementary Material, Figure

S2B).

There were no regions where the patients showed less activation compared to cross

fixation than the controls (Figure 2, bottom panel). However, the patients showed

greater activation than the controls in seven clusters: the largest was in the right parietal

cortex [1336 voxels, peak activation at BA 40, MNI (38, -44, 50), z score=4.86,

$p<0.001$]; a roughly symmetrical but smaller cluster was in the left parietal cortex [563

voxels, peak activation at BA 40, MNI (-42, -46, 52), z score=4.39, $p<0.001$]; other

clusters were in the postcentral gyrus [324 voxels, peak activation at BA 48, MNI (-64,

-18, 22), z score=4.08, $p<0.001$]; the left middle temporal cortex [255 voxels, peak

activation at BA 22, MNI (-62, -12, -2), z score=5.01, $p=0.00329$]; the left inferior

temporal cortex [191 voxels, peak activation at BA 37, MNI (-48, -56, -8), z

score=4.58, $p=0.0145$]; the left superior occipital cortex [163 voxels, peak activation at

BA 19, MNI (-20, -74, 40), z score=4.22, $p=0.029$]; and the insula [148 voxels, peak

activation at BA 48, MNI (-36, -20, 12), z score=4.56, $p=0.0426$].

Box plots of the mean activations within these seven clusters confirmed that in six cases

they represented failure of de-activation in the schizophrenic patients (see

Supplementary Figure S3). The seventh cluster (in the superior occipital cortex) was in

a region where the controls showed no significant activation or de-activation.

Discussion

This study examined the brain functional correlates of autobiographical recall in schizophrenia, comparing it to two control tasks, viewing of non-memory evoking cues and cross fixation. In both conditions the healthy controls showed activation within the territory of the default mode network, particularly in its two midline cortical regions. The patients did not differ significantly from the healthy controls in the degree of activation in these regions. However, they did show evidence of changes, which took the form mainly of failure of de-activation, in regions outside the default mode network.

The healthy controls in our study showed a pattern of autobiographical memory associated activations that was reasonably consistent with that found by Svoboda *et al*. (2006) in their meta-analysis of 24 studies. The most important difference was that, whereas Svoboda *et al*. (2006) found evidence of lateral frontal activation during task performance, in our study this was only seen in the memory cue evoking condition vs low level baseline (cross fixation), and not in the memory cue evoking vs non-evoking contrast. One possible explanation for this difference might be that the participants actively engaged in search (i.e. executive) strategies during both the active conditions, before either locating or failing to locate a relevant autobiographical memory. Some support for this explanation comes from a study of healthy subjects by Cabeza *et al.* (2004) which, as in our study, contrasted cues designed to both elicit and not elicit autobiographical memories (in this case, photographs of a university campus taken by the subject him-or herself or by others). Both conditions were found to activate the dorsolateral and ventrolateral prefrontal cortex compared to cross fixation, with no differences being found between the two active conditions.

Our findings in schizophrenic patients differ markedly from those of the only other study to date, that of Cuervo-Lombard *et al*. (2012). These authors found reduced activation in the patients in the medial frontal cortex and the precuneus, and also in the left lateral prefrontal cortex, the left medial temporal lobe and other areas, whereas we found no evidence of reduced activation in any region. However, there is an obvious potential explanation for this discrepancy: as noted in the introduction, Cuervo-Lombard *et al's*. (2012) findings of reduced cortical activation in the schizophrenic patients were only obtained when a masked analysis using an uncorrected threshold was employed; whole brain corrected analysis revealed differences between the patients and the controls only in small clusters located in non-cortical regions.

Nevertheless, the schizophrenic patients in our study did show evidence of brain functional abnormality at the whole-brain corrected level. Clusters of significant difference were seen in both the memory-evoking vs non-memory evoking cues and in the memory-evoking cues vs low level contrasts, which took the form of relatively greater activation in both cases. As pointed out by Gusnard and Raichle (2001, see Methods), the interpretation of relative changes between two active tasks can be difficult, but the findings in the contrast between autobiographical memory-evoking cues and low-level baseline were clear: they represented failure of de-activation in the patients in six of the seven clusters of significant difference that emerged (the pattern in the seventh cluster, in the superior occipital cortex, was one of activation in a region where the controls showed neither activation nor de-activation). All these seven clusters were outside the regions usually considered to form part of the default mode network as

identified by de-activations in studies using attention-demanding tasks (Buckner *et al.*, 2008) or based on resting state connectivity (Yeo *et al.*, 2011).

The obvious interpretation of this finding is that schizophrenic patients show failure of de-activation outside the default mode network during performance of a task that normally activates it. Clearly, however, such an interpretation depends on how robustly autobiographical recall can be considered to be normally associated with a pattern of non-default mode network de-activation. Unfortunately, this question is difficult to answer, as most studies of autobiographical recall in healthy subjects have not reported de-activations. Four early studies of autobiographical recall using PET noted both task related activations (ie recall>rest) and de-activations (ie rest>recall) (Andreasen *et al.*, 1995, Andreasen *et al.*, 1999, Fink *et al.*, 1996, Gemar *et al.*, 1996), but the sample sizes were mostly small (7-19 subjects) in these studies and the areas of de-activation varied widely. Only two fMRI studies appear to have reported de-activations. Ino et al (2011) examined 21 healthy subjects and found greater activation in a 'no thinking' condition than during autobiographical recall in the temporal poles, orbitofrontal cortex, posterior insula, and different portions of the bilateral middle/superior temporal, inferior parietal, and occipital cortex. De-activation was also observed in the mid-cingulate cortex and precuneus, extending into the superior parietal cortex. Bado et al (2014) examined 18 healthy subjects and found greater activation during a 'relax and stay awake' condition than during recall of both emotional and neutral autobiographical memories in the subgenual anterior cingulate cortex, the ventral striatum and the hypothalamus/septal area, and in the inferior parietal lobe bilaterally during recall of emotional memories. Collectively, these findings support the idea that autobiographical

recall is associated with de-activations, and there are hints of an overlap with the findings from our own group of healthy controls.

The only other relevant data come from a study by DuPre et al (2016) in which 31 healthy adults viewed emotional pictures and engaged in autobiographical recall, prospection or theory of mind reasoning based on their content. Data from this study are publicly available at NeuroVault (https://neurovault.org/collections/1866/). Contrasting self-generated thought (ie combining all three task conditions) to a baseline consisting of viewing a scrambled image followed by a button press, clusters of de-activation were seen in the parietal and temporal regions not dissimilar to those we observed in our study, as well as in the occipital cortex.

If replicated, the present study's finding of intact default mode activation but failure of de-activation outside the default mode network in schizophrenia would appear to have two main implications for the pathophysiology of the disorder. The first is that, rather than there being dysfunction of the default mode network specifically in schizophrenia, it may be that there is a more general problem with de-activation, which manifests itself in different regions (ie within or outside the default mode network) depending on the task used. Just such a proposal has recently been made by Allen *et al.* (2019), who argue that instead of schizophrenia being associated with 'static' dysfunctions in the prefrontal cortex and the default mode network, in reality the underlying brain dysfunction involves the dynamic balance between the 'task positive' networks (one of which is the fronto-parietal, executive or cognitive control network) and the 'task negative' or default mode network with which they are normally 'anticorrelated' (Fox *et al.*, 2005). Allen *et al.* (2019) go on to relate such a dysfunction to a change in the balance between

the main excitatory and inhibitory transmitters in the brain, glutamate and GABA, although the evidence for dysfunction in these transmitter systems in schizophrenia is currently slender.

Secondly, the present study's findings bear on of the issue of how far default mode network dysfunction might underlie the cognitive impairment seen in schizophrenia. Anticevic *et al.* (2012) reviewed the evidence on the relationship between default mode network activity and cognitive function in healthy subjects, noting that lower default mode network activity has been found to be associated with better performance across a number of cognitive tasks, and that higher levels of activity in the network are correlated with lapses of attention. Based on this they suggested that the relevance of default mode network de-activation to cognition in schizophrenia warrants further investigation. So far, however, this investigation has been extremely limited. In what appears to be the only study to directly address this question, Ortiz-Gil et al (2011) examined 18 cognitively impaired and 19 (relatively) cognitively preserved schizophrenic patients during performance of the n-back working memory task. They found that while the cognitively impaired patients showed hypoactivation compared to the cognitively preserved patients in the DLPFC and other regions, no differences in de-activation between the two groups were seen, even though the group of patients as a whole showed the expected failure of de-activation in the medial frontal cortex. The present study's finding of intact activation during autobiographical recall, performance of which affects the default mode network in a different way, in schizophrenia adds a further, if currently not entirely clear, dimension to this debate.

In conclusion, the present study finds no evidence of altered default mode network function in schizophrenia during performance of a task which normally activates it, autobiographical recall. This finding needs to be viewed in the context of a) conflicting findings in the only other study to use such a task in schizophrenia; and b) the current lack of robust evidence that autobiographical recall is associated with de-activation outside the default mode network in healthy subjects. Further studies using not only autobiographical memory but perhaps also other tasks that activate the default mode network and, crucially, employing a low-level baseline in order to examine de-activations, would therefore be desirable. Some limitations need to be acknowledged. The sample sizes we employed were relatively small, and it is possible that activation differences between schizophrenic patients and controls may have emerged if these were larger. The schizophrenic patients were taking antipsychotic medication, and this potential confounding factor is not easy to fully address in a study making comparisons with healthy subjects. We did not measure autobiographical memory performance in the patients and so there is an unanswered question about whether and to what extent task related activations (and de-activations) were influenced by poor task performance.

Funding

Table 1. Demographic data for the patients and controls.

	Healthy controls (N=30)	Schizophrenia patients (N=27)	Differences
Sex (M/F)	19/11	17/10	$p = 0.98$
Age	40.40 (11.23)	40.15 (8.75)	$p = 0.93$
Premorbid IQ	103.70 (6.38)	100.23 (10.90)	$p = 0.16$
No. reporting social alcohol use	14	7	
No. reporting non-habitual cannabis use	2	0	
Antipsychotic dose (chlorpromazine equivalents)	-	495.41 (459.01)	

Values for age and premorbid IQ are means (SDs)

References

Allen P, Sommer IE, Jardri R, Eysenck MW & Hugdahl K (2019). Extrinsic and default mode networks in psychiatric conditions: Relationship to excitatory-inhibitory transmitter balance and early trauma. *Neuroscience and Biobehavioral Reviews* **99**, 90-100.

Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Watkins GL, Ponto LL & Hichwa RD (1995). Remembering the past: Two facets of episodic memory explored with positron emission tomography. *American Journal of Psychiatry* **152**, 1576-1585.

Andreasen NC, O'Leary DS, Paradiso S, Cizadlo T, Arndt S, Watkins GL, Ponto LL & Hichwa RD (1999). The cerebellum plays a role in conscious episodic memory retrieval. *Human Brain Mapping* **8**, 226-234.

Anticevic A, Cole MW, Murray JD, Corlett PR, Wang XJ & Krystal JH (2012). The role of default network deactivation in cognition and disease. *Trends in Cognitive Science* **16**, 584-592.

Bado P, Engel A, de Oliveira-Souza R, Bramati IE, Paiva FF, Basilio R, Sato JR, Tovar-Moll F & Moll J (2014). Functional dissociation of ventral frontal and dorsomedial default mode network components during resting state and emotional autobiographical recall. *Human Brain Mapping* **35**, 3302-3313.

Beckmann CF, Jenkinson M, Woolrich MW, Behrens TE, Flitney DE, Devlin JT & Smith SM (2006). Applying fsl to the fiac data: Model-based and model-free analysis of voice and sentence repetition priming. *Human Brain Mapping* **27**, 380-391.

Berna F, Potheegadoo J, Aouadi I, Ricarte JJ, Alle MC, Coutelle R, Boyer L, Cuervo-Lombard CV & Danion JM (2016). A meta-analysis of autobiographical memory studies in schizophrenia spectrum disorder. *Schizophrenia Bulletin* **42**, 56-66.

Boccia M, Dacquino C, Piccardi L, Cordellieri P, Guariglia C, Ferlazzo F, Ferracuti S & Giannini AM (2017). Neural foundation of human moral reasoning: An ale meta-analysis about the role of personal perspective. *Brain Imaging and Behavior* **11**, 278-292.

Buckner RL, Andrews-Hanna JR & Schacter DL (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences* **1124**, 1-38.

Cabeza R, Prince SE, Daselaar SM, Greenberg DL, Budde M, Dolcos F, LaBar KS & Rubin DC (2004). Brain activity during episodic retrieval of autobiographical and laboratory events: An fmri study using a novel photo paradigm. *Journal of Cognitive Neuroscience* **16**, 1583-1594.

Conway MA & Pleydell-Pearce CW (2000). The construction of autobiographical memories in the self-memory system. *Psychological Review* **107**, 261-288.

Crovitz HF & Schiffman H (1974). Frequency of episodic memories as a function of their age. *Bulletin of the Psychonomic Society* **4**, 517-518.

Cuervo-Lombard C, Lemogne C, Gierski F, Bera-Potelle C, Tran E, Portefaix C, Kaladjian A, Pierot L & Limosin F (2012). Neural basis of autobiographical memory retrieval in schizophrenia. *British Journal of Psychiatry* **201**, 473-480.

Del Ser T, Gonzalez-Montalvo JI, Martinez-Espinosa S, Delgado-Villapalos C & Bermejo F (1997). Estimation of premorbid intelligence in spanish people with the word accentuation test and its application to the diagnosis of dementia. *Brain and Cognition* **33**, 343-356.

Dreher JC, Koch P, Kohn P, Apud J, Weinberger DR & Berman KF (2012). Common and differential pathophysiological features accompany comparable cognitive impairments in medication-free patients with schizophrenia and in healthy aging subjects. *Biological Psychiatry* **71**, 890-897.

DuPre E, Luh WM & Spreng RN (2016). Multi-echo fmri replication sample of autobiographical memory, prospection and theory of mind reasoning tasks. *Scientific Data* **3**, 160116.

Fink GR, Markowitsch HJ, Reinkemeier M, Bruckbauer T, Kessler J & Heiss WD (1996). Cerebral representation of one's own past: Neural networks involved in autobiographical memory. *Journal of Neuroscience* **16**, 4275-4282.

First MB, Spitzer R, Miriam M & Williams JBW (2002). Structured clinical interview for DSM-IV-tr axis i disorders, research version, patient edition. (SCID-I/P). Biometrics Research, New York State Psychiatric Institute: New York.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC & Raichle ME (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences U S A* **102**, 9673-9678.

Garrity AG, Pearlson GD, McKiernan K, Lloyd D, Kiehl KA & Calhoun VD (2007). Aberrant "default mode" functional connectivity in schizophrenia. *American Journal of Psychiatry* **164**, 450-457.

Gemar MC, Kapur S, Segal ZV, Brown GM & Houle S (1996). Effects of self-generated sad mood on regional cerebral activity: A pet study in normal subjects. *Depression* **4**, 81-88.

Gomar JJ, Ortiz-Gil J, McKenna PJ, Salvador R, Sans-Sansa B, Sarro S, Guerrero A & Pomarol-Clotet E (2011). Validation of the word accentuation test (tap) as a means of estimating premorbid iq in spanish speakers. *Schizophrenia Research* **128**, 175-176.

Gusnard DA & Raichle ME (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews Neuroscience* **2**, 685-694.

Haatveit B, Jensen J, Alnaes D, Kaufmann T, Brandt CL, Thoresen C, Andreassen OA, Melle I, Ueland T & Westlye LT (2016). Reduced load-dependent default mode network deactivation across executive tasks in schizophrenia spectrum disorders. *Neuroimage Clinical* **12**, 389-396.

Hahn B, Harvey AN, Gold JM, Fischer BA, Keller WR, Ross TJ & Stein EA (2016). Hyperdeactivation of the default mode network in people with schizophrenia when focusing attention in space. *Schizophrenia Bulletin* **42**, 1158-1166.

Hahn B, Harvey AN, Gold JM, Ross TJ & Stein EA (2017). Load-dependent hyperdeactivation of the default mode network in people with schizophrenia. *Schizophrenia Research* **185**, 190-196.

Harrison BJ, Yucel M, Pujol J & Pantelis C (2007). Task-induced deactivation of midline cortical regions in schizophrenia assessed with fmri. *Schizophrenia Research* **91**, 82-86.

Ino T, Nakai R, Azuma T, Kimura T & Fukuyama H (2011). Brain activation during autobiographical memory retrieval with special reference to default mode network. *Open Neuroimaging Journal* **5**, 14-23.

Kopelman MD, Wilson BA & Baddeley AD (1989). The autobiographical memory interview: A new assessment of autobiographical and personal semantic memory in amnesic patients. *Journal of Clinical and Experimental Neuropsychology* **11**, 724-744.

Mannell MV, Franco AR, Calhoun VD, Canive JM, Thoma RJ & Mayer AR (2010). Resting state and task-induced deactivation: A methodological comparison in patients with schizophrenia and healthy controls. *Human Brain Mapping* **31**, 424-437.

Murray RJ, Schaer M & Debbane M (2012). Degrees of separation: A quantitative neuroimaging meta-analysis investigating self-specificity and shared neural activation between self- and other-reflection. *Neuroscience and Biobehavioral Reviews* **36**, 1043-1059.

Oertel-Knochel V, Reinke B, Hornung A, Knochel C, Matura S, Knopf M, Prvulovic D, O'Dwyer L, Lindner M, Rau A, Hampel H, Haenschel C & Linden DE (2012). Patterns of autobiographical memory in bipolar disorder examined by psychometric and functional neuroimaging methods. *Journal of Nervous and Mental Disease* **200**, 296-304.

Ortiz-Gil J, Pomarol-Clotet E, Salvador R, Canales-Rodriguez EJ, Sarro S, Gomar JJ, Guerrero A, Sans-Sansa B, Capdevila A, Junque C & McKenna PJ (2011). Neural correlates of cognitive impairment in schizophrenia. *British Journal of Psychiatry* **199**, 202-210.

Palmer BW, Dawes SE & Heaton RK (2009). What do we know about neuropsychological aspects of schizophrenia? *Neuropsychological Review* **19**, 365-384.

Pomarol-Clotet E, Salvador R, Sarro S, Gomar J, Vila F, Martinez A, Guerrero A, Ortiz-Gil J, Sans-Sansa B, Capdevila A, Cebamanos JM & McKenna PJ (2008). Failure to deactivate in the prefrontal cortex in schizophrenia: Dysfunction of the default mode network? *Psychological Medicine* **38**, 1185-1193.

Raichle ME (2015). The brain's default mode network. *Annual Review of Neuroscience* **38**, 433-447.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA & Shulman GL (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences U S A* **98**, 676-682.

Rubin C ed. (1996). *Remembering our past: Studies in autobiographical memory* Cambridge University Press: Cambridge.

Salgado-Pineda P, Fakra E, Delaveau P, McKenna PJ, Pomarol-Clotet E & Blin O (2011). Correlated structural and functional brain abnormalities in the default mode network in schizophrenia patients. *Schizophrenia Research* **125**, 101-109.

Schacter DL, Addis DR & Buckner RL (2007). Remembering the past to imagine the future: The prospective brain. *Nature Reviews Neuroscience* **8**, 657-661.

Schneider FC, Royer A, Grosselin A, Pellet J, Barral FG, Laurent B, Brouillet D & Lang F (2011). Modulation of the default mode network is task-dependant in chronic schizophrenia patients. *Schizophrenia Research* **125**, 110-117.

Schurz M, Radua J, Aichhorn M, Richlan F & Perner J (2014). Fractionating theory of mind: A meta-analysis of functional brain imaging studies. *Neuroscience and Biobehaval Reviews* **42**, 9-34.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM & Matthews PM (2004). Advances in functional and structural mr image analysis and implementation as fsl. *Neuroimage* **23 Suppl 1**, S208-219.

Svoboda E, McKinnon MC & Levine B (2006). The functional neuroanatomy of autobiographical memory: A meta-analysis. *Neuropsychologia* **44**, 2189-2208.

van der Meer L, Costafreda S, Aleman A & David AS (2010). Self-reflection and the brain: A theoretical review and meta-analysis of neuroimaging studies with implications for schizophrenia. *Neuroscience and Biobehavioral Reviews* **34**, 935-946.

Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW, Shenton ME, Green AI, Nieto-Castanon A, LaViolette P, Wojcik J, Gabrieli JD & Seidman LJ (2009). Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proceedings of the National Academy of Sciences U S A* **106**, 1279-1284.

Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zollei L, Polimeni JR, Fischl B, Liu H & Buckner RL (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology* **106**, 1125-1165.

Figure 1. Areas of significant differences between the autobiographical memory evoking and non-evoking cue conditions for the healthy subjects (A) and the schizophrenic patients (B). Warm colours represent autobiographical recall > non memory-evoking cues, cold colours represent non-memory-evoking cues > autobiographical recall. Bottom row (C) shows areas of significant differences between the patients and controls in this contrast. Colour bars depict Z values. Images are displayed in neurological convention (right is right).
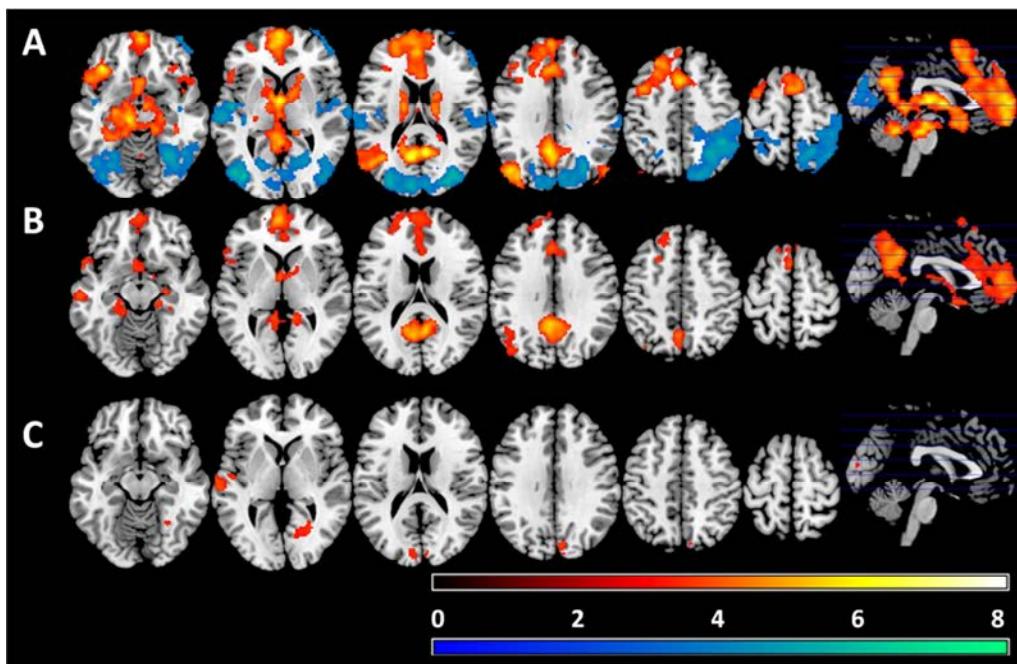
Figure 2. Activation map for the autobiographical memory-evoking cues vs fixation condition in the healthy subjects (A) and the schizophrenic patients (B). Warm colours represent autobiographical cues > baseline. Cold colours represent baseline > autobiographical cues. The third panel (C) shows areas of significant differences between the patients and the controls in this contrast. Colour bars depict Z values. Images are displayed in neurological convention (right is right).
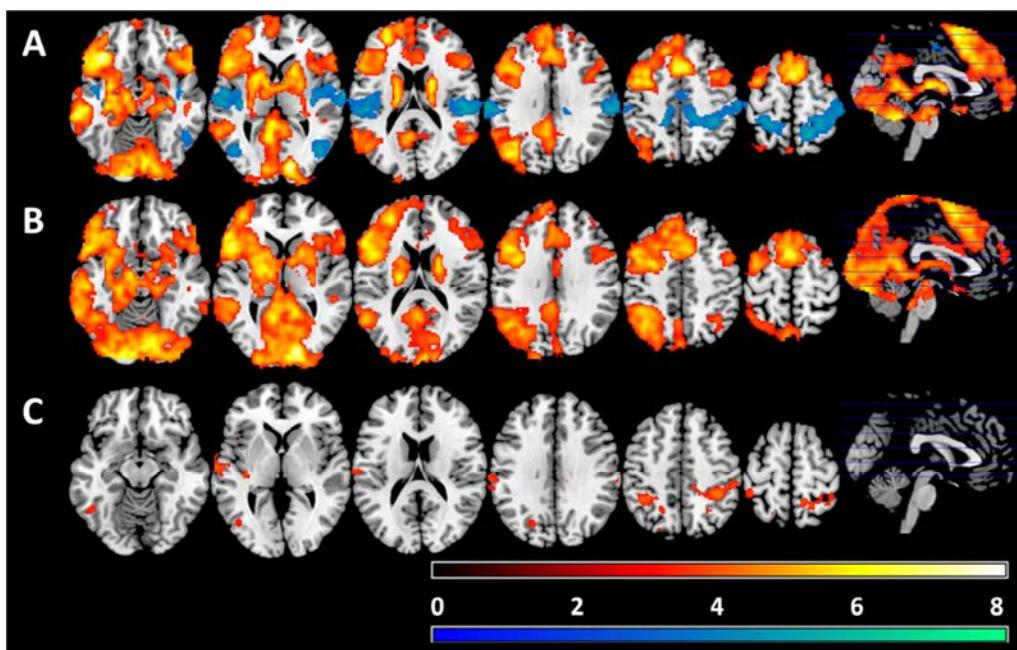
Supplementary Material

Table S1. Regions of activation and de-activation in the autobiographical recall vs non-memory-evoking conditionn.

Region/Contrast	MNI coordinates			Z-value	k	p
	x	y	z			
Controls						
recall > non-recall						
Thalamus	-2	-4	4	7.09	17834	$p < 0.001$
Precuneus	8	-56	22	6.96		
Cerebellum	36	-62	-28	6.69		
Calcarine cortex	4	-56	-16	6.59		
Medial prefrontal cortex	-2	62	6	6.32	10515	$p < 0.001$
Supplementary motor area	-2	18	48	5.67		
Anterior cingulate cortex	-4	46	16	5.55		
Middle occipital cortex	-46	-74	34	6.25	1671	$p < 0.001$
Middle temporal cortex	-50	-70	20	5.54		
Middle temporal cortex	-62	-8	-18	4.47	444	$p < 0.001$
Angular gyrus	50	-74	32	4.51	201	$p = 0.020$
Controls						
Non-recall > recall						
Middle occipital cortex	-42	-82	8	6.27	19270	$p < 0.001$
Superior occipital cortex	28	-74	38	6.24		
Superior parietal cortex	20	-56	60	6.03		
Superior temporal cortex	-50	-10	0	6.06	1929	$p < 0.001$
Middle temporal cortex	-60	-20	2	5.19		
Frontal pole	30	68	10	5.66	692	$p < 0.001$
Patients						
recall > non-recall						
Medial prefrontal cortex	-4	56	2	5.39	3372	$p < 0.001$
Anterior cingulate cortex	-4	28	32	4.16		
Posterior cingulate cortex	-4	-48	34	5.72	3248	$p < 0.001$
Precuneus	-6	-54	24	5.66		
Parahippocampal gyrus	-12	-2	-20	4.40	1032	$p < 0.001$
	24	-20	-20	5.18	878	$p < 0.001$
Superior frontal cortex	-16	36	54	4.87	803	$p < 0.001$
Angular gyrus	-42	-62	28	3.97	489	$p < 0.001$
Middle temporal cortex	-62	-22	-16	4.46	435	$p < 0.001$
	62	-6	-22	4.88	226	$p = 0.012$
Temporal pole	-58	10	-12	3.90	251	$p = 0.007$

Table S2. Regions of activation and de-activation in the autobiographical recall condition compared to fixation.

Region/Contrast	MNI coordinates			Z-value	k	p
	x	y	z			
Controls: activation						
Calcarine cortex	16	-86	2	8.14	58713	*p* < 0.001
Cerebellum	36	-62	-28	8.09		
Inferior frontal cortex	-38	30	-10	7.87		
Middle temporal cortex	-64	-34	-10	7.14		
Middle temporal cortex	58	-58	16	5.03	598	*p* < 0.001
Precuneus	-6	-74	56	3.97	144	*p* = 0.047
Controls: de-activation						
Postcentral gyrus	22	-42	76	6.17	7728	*p* < 0.001
Superior temporal gyrus	52	-30	14	5.96		
Mid-cingulate cortex	12	-30	42	5.95		
Superior parietal cortex	20	-50	64	5.78		
Heschl gyrus	-38	-20	12	6.95	3285	*p* < 0.001
Superior temporal gyrus	-54	-8	0	6.05		
Supramarginal gyrus	-64	-26	30	5.49		
Rolandic operculum	-50	-26	16	5.33		
Superior parietal cortex	-22	-44	66	5.30	1079	*p* < 0.001
Inferior temporal cortex	50	-68	-4	5.48	859	*p* < 0.001
Middle occipital cortex	-46	-72	4	4.66	242	*p* = 0.004
Patients: activation						
Calcarine cortex	14	-90	2	8.16	69677	*p* < 0.001
Cerebellum	10	-82	-16	7.46		
Lingual gyrus	-18	-94	-12	7.05		
Inferior frontal cortex	-54	16	0	7.01		
Angular gyrus	36	-58	50	4.22	240	*p* = 0.005
Middle temporal cortex	52	-34	-4	4.39	142	*p* = 0.049
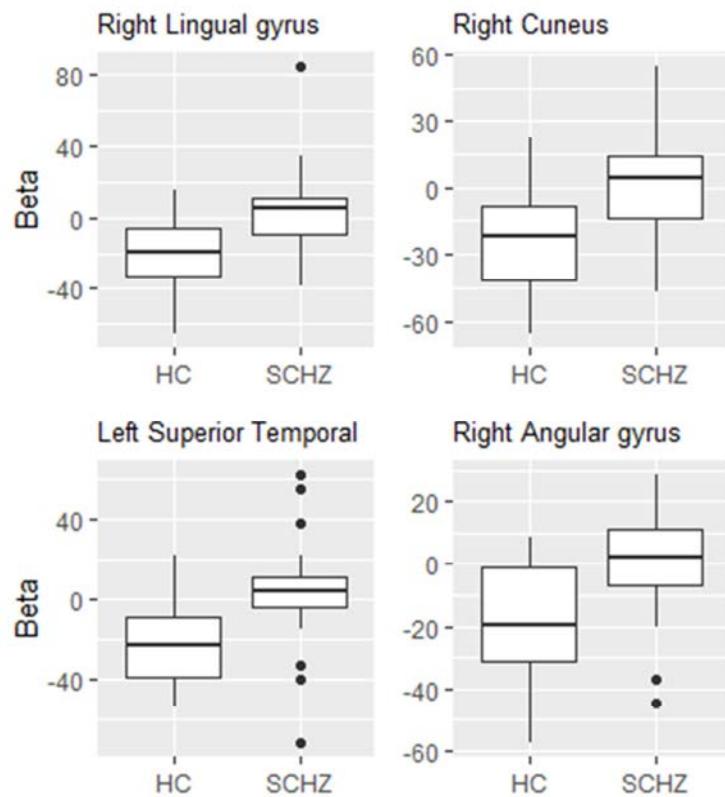
Figure S1. Boxplots showing activation levels in patients and controls for the four clusters of differences between groups in the autobiographical memory evoking vs non-evoking cues contrast. Y-axis depicts parameter estimates (beta values).
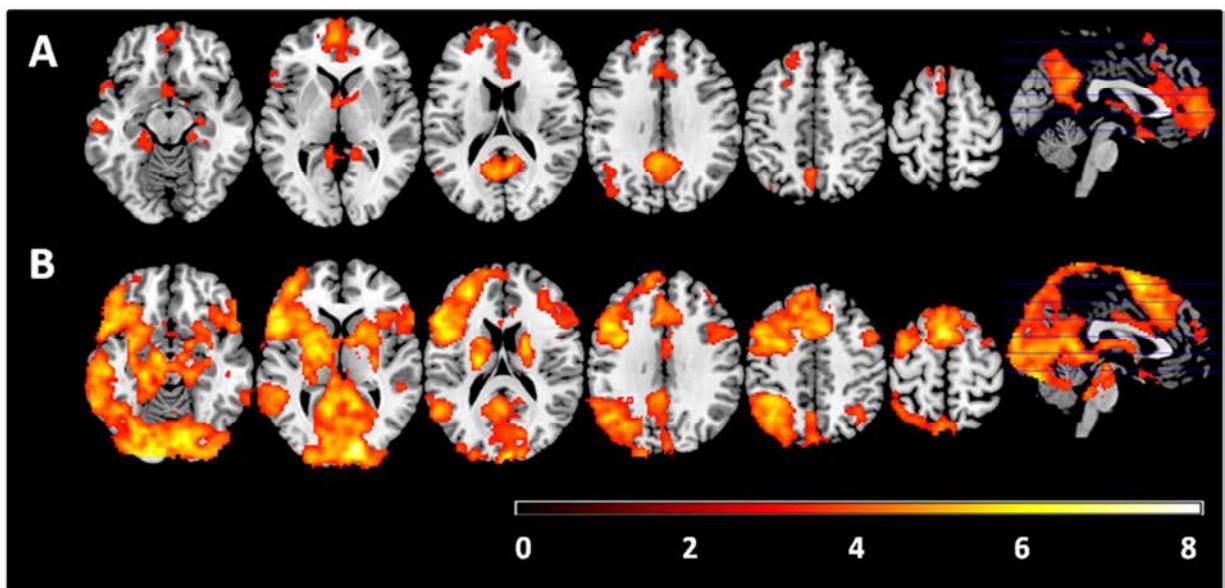
Figure S2. Mean activation maps for the patient group, controlling for antipsychotic dose (in chlorpromazine equivalents): (A) Areas of significant differences between the autobiographical memory-evoking and non-evoking cue conditions. (B) Areas of significant differences between the autobiographical memory-evoking cues and fixation conditions. Colour bars depict Z values. Images are displayed in neurological convention (right is right).
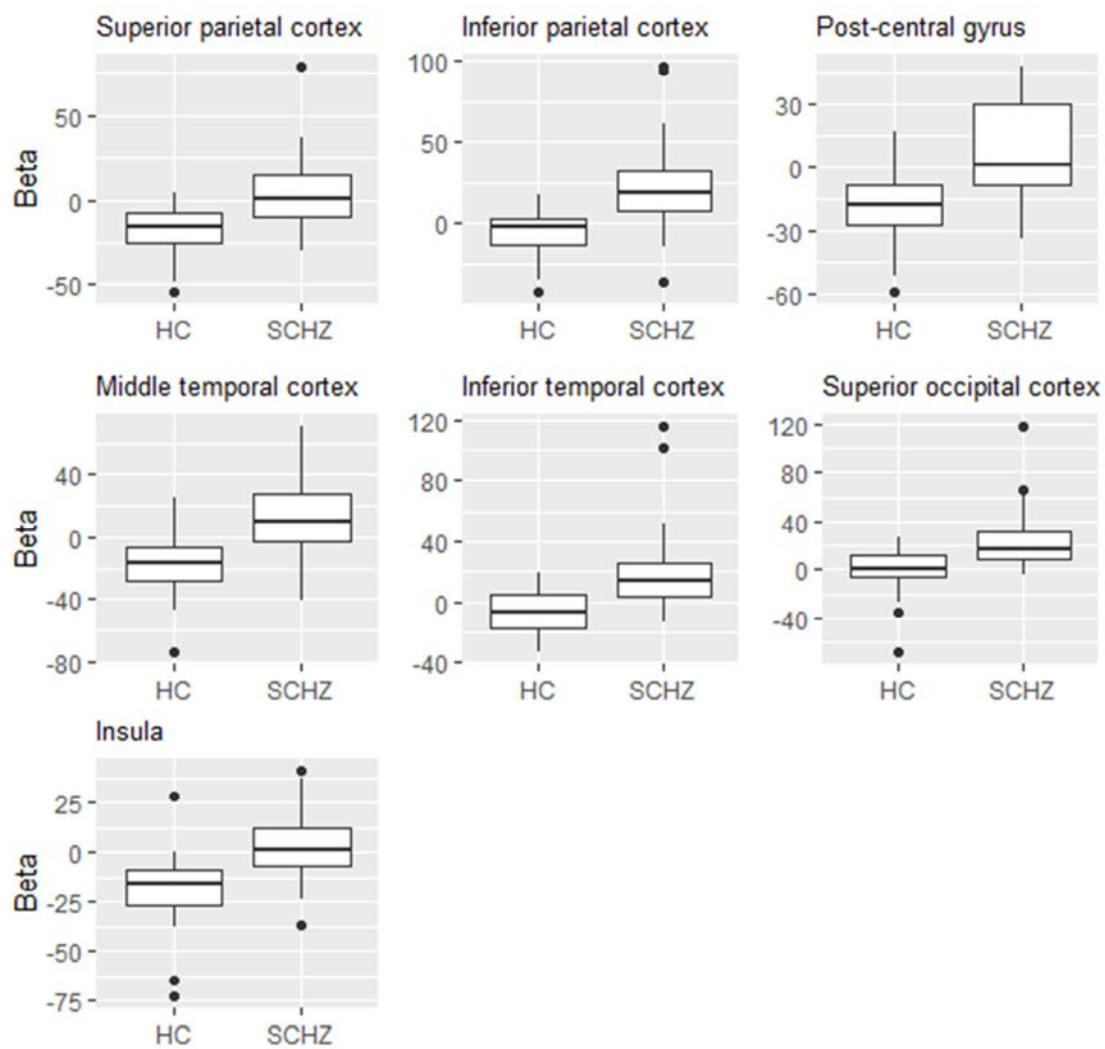
**Figure S3.** Boxplots showing activation levels in patients and controls for the seven clusters of differences between groups in the autobiographical memory evoking vs fixation contrast. Y-axis depicts parameter estimates (beta values).

4.2. Estudio 2

Brain imaging correlates of self- and other-reflection in schizophrenia

NEUROIMAGE CLINICAL

IMPACT FACTOR 2019: 4.350   QUARTIL 2019: Q1

Brain imaging correlates of self- and other-reflection in schizophrenia

Paola Fuentes-Claramonte[a,b,1], Marta Martin-Subero[a,b,c,1], Pilar Salgado-Pineda[a,b], Aniol Santo-Angles[a,b], Isabel Argila-Plaza[a], Josep Salavert[c,d], Antoni Arévalo[e], Clara Bosque[f], Carmen Sarri[f], Amalia Guerrero-Pedraza[f], Antoni Capdevila[g,h], Salvador Sarró[a,b], Peter J. McKenna[a,b], Edith Pomarol-Clotet[a,b,*], Raymond Salvador[a,b]

[a] FIDMAG Germanes Hospitalàries Research Foundation, Carrer Dr. Antoni Pujadas, 38, 08830 Sant Boi de Llobregat, Barcelona Spain
[b] CIBERSAM (Centro de Investigación Biomédica en Red de Salud Mental), Spain
[c] Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
[d] Psychiatry Department, Hospital Sant Rafael, Barcelona, Spain
[e] Psychiatry Department, Hospital Sagrat Cor Martorell Barcelona, Spain
[f] Benito Menni Centre Assistencial en Salut Mental, Sant Boi de Llobregat, Barcelona, Spain.
[g] Radiology Unit, Hospital de la Santa Creu i Sant Pau (HSCSP), Barcelona, Spain
[h] CIBER-BBN (Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina), Spain

ARTICLE INFO

ABSTRACT

Background: An alteration in self/other differentiation has been proposed as a basis for several symptoms in schizophrenia, including delusions of reference and social functioning deficits. Dysfunction of the right temporo-parietal junction (TPJ), a region linked with social cognition, has been proposed as the basis of this alteration. However, imaging studies of self- and other-processing in schizophrenia have shown, so far, inconsistent results.
Methods: Patients with schizophrenia and healthy controls underwent fMRI scanning while performing a task with three conditions: self-reflection, other-reflection and semantic processing.
Results: Both groups activated similar brain regions for self- and other-reflection compared to semantic processing, including the medial prefrontal cortex, the precuneus and the TPJ. Compared to healthy subjects, patients hyperactivated the left lateral frontal cortex during self- and other-reflection. In other-reflection, compared to self-reflection, patients failed to increase right TPJ activity.
Conclusions: Altered activity in the right TPJ supports a disturbance in self/other differentiation in schizophrenia, which could be linked with psychotic symptoms and affect social functioning in patients. Hyperactivity of the lateral frontal cortex for self- and other-reflection suggests the presence of greater cognitive demand to perform the task in the patient group.

1. Introduction

A disturbance in the process of distinguishing the self from others is proposed as a relevant factor contributing to the symptom profile in schizophrenia: poor self/other distinction may lead to incorrect attribution of one's own thoughts or intentions to others, resulting in paranoia and ideas of reference, or to a disruption of the sense of agency of behavior leading to delusions of control (Eddy, 2018). Self/other differentiation has been proposed to involve both motor processes underpinning imitation and cognitive processes linked to mentalizing and reasoning about the other's beliefs and emotions (Eddy, 2018), and its failure (self/other blending) might impair perspective taking, among

other processes (Eddy, 2016). As a result, it can also affect social interaction in terms of increasing social anhedonia and social withdrawal (Eddy, 2016; van der Meer et al., 2010; van der Weiden et al., 2015). Social functioning deficits are common in schizophrenia and can result in the misinterpretation of others' intentions and difficulties in daily social interactions (Green et al., 2015). These deficits are closely linked to worse functional outcomes (Fett et al., 2011). Therefore, a better understanding of the alterations in processing self- and other-related information will be an important contribution to the improvement of therapeutic interventions and patients' quality of life.

Brain activity related to self-reflection is typically assessed with tasks that require the participant to decide whether a particular trait

adjective or descriptive statement applies to themselves. For other-reflection, the same kind of decision is applied to another personally or publicly known person. Both conditions are associated with activation in a network of regions which include the medial prefrontal cortex (mPFC), the temporo-parietal junction (TPJ), and the posterior cingulate cortex (PCC) (Denny et al., 2012), very similar to the regions associated with social cognition, theory of mind, autobiographical memory or future planning, which are often referred to as the default-mode network (DMN, Buckner et al., 2008). The involvement of DMN regions in such a broad range of cognitive functions has led to the hypothesis that one of the core functions of the network is to process self-relevant or social information (Andrews-Hanna et al., 2014; Molnar-Szakacs and Uddin, 2013). Patients with schizophrenia have shown altered brain activity in DMN regions during self-reflection, including the PCC (Holt et al., 2011; van der Meer et al., 2013), the mPFC (Tan et al., 2015), and the temporal cortex (Pauly et al., 2014). Other-reflection has been associated with altered activation of the PCC (van der Meer et al., 2013), the temporal cortex (Murphy et al., 2010), and the mPFC and cuneus (Pauly et al., 2014), but also in regions not traditionally linked to other-reflection like the insula (Pauly et al., 2014) and the fusiform and lingual gyri (Tan et al., 2015). These findings suggest that there is altered DMN function during self- and other-reflection in schizophrenia, although the lack of consistency among the results makes it difficult to characterize the nature of the alteration precisely.

Although self- and other-reflection tend to activate a similar set of brain regions, studies have also shown differences between the two conditions in the mPFC (with ventral mPFC more linked to self-reflection and dorsal mPFC to other-reflection) and the TPJ, among other areas (Denny et al., 2012). The TPJ (especially in the right hemisphere) has been proposed as a key brain structure for self/other differentiation, with its disruption generating deficits in self and other representations in several psychiatric disorders (Eddy, 2016). Literature on the function of the right TPJ has highlighted its involvement in tasks that require processing information about others' intentions and mental states, like theory of mind or moral judgments tasks (Saxe, 2010), which is consistent with such a role. Alteration of TPJ function by means of non-invasive brain stimulation affects third-person perspective taking (Elk et al., 2016), which has signaled this region also as a potential target for intervention (Donaldson et al., 2015). It is important to note, though, that the TPJ is a functionally defined region that can be subdivided in different portions (Mars et al., 2012): the most posterior and dorsal parts of the TPJ (i.e. angular gyrus) seem to be more linked with social information processing and tend to co-activate with other regions involved in self-reflection and theory of mind, while anterior parts are associated with externally cued attention (Scholz et al., 2009). There also seems to be a hemispheric asymmetry in the TPJ, since social cognition has been especially linked to the right TPJ while the left has been attributed a more general role in meta-representation (for a review, see Saxe, 2010). However, this remains an open issue since the left TPJ is sometimes also activated in social processing tasks (Krall et al., 2015).

Alterations in self/other differentiation in schizophrenia may be observed in the comparison between self- and other-reflection. For example, Jardri et al. (2011), using a task where participants heard their own pre-recorded voice alternated with someone else's voice, found that the 'self' and 'non-self' cortical maps were more overlapped in patients with schizophrenia than controls, affecting the medial frontal cortex and PCC/precuneus, the right middle temporal cortex and the right inferior parietal cortex (adjacent to the TPJ). This was interpreted as impairment for self/other differentiation in the patient group. Bedford et al. (2012) found an alteration in the dorsomedial prefrontal cortex in patients, who showed similar levels of activity in this region for self and other-processing, while the controls significantly increased its activity for self-reflection compared to other-reflection. However, other studies have reported no differences between patients

and controls (Holt et al., 2011; Tan et al., 2015; van der Meer et al., 2013; Zhang et al., 2015), or found differences outside the typical self/other-reflection areas (e.g., the precentral gyrus in Pauly et al., 2014).

The studies reviewed above reveal that, although self/other processing and differentiation are proposed as a basis for several symptoms in schizophrenia, consistent deficits in the neural correlates of these cognitive processes are yet to be characterized. This heterogeneity in previous studies might be a result of the combination of different factors: first, most of the studies on self/other reflection in schizophrenia have used tasks where trait adjectives or sentences are presented to the participants, who have to decide whether these traits apply to themselves or to another person. However, the control conditions against which self- and other-reflection are contrasted vary from affect labeling (i.e. judging whether the adjective is positive or negative) (Holt et al., 2011; Murphy et al., 2010; Tan et al., 2015), semantic knowledge (i.e. answering Yes or No to sentences about general facts) (van der Meer et al., 2013; Zhang et al., 2015) or perceptual tasks (Bedford et al., 2012; Pauly et al., 2014). Contrasting self- or other-reflection against conditions that might impose different cognitive demands (e.g. semantic knowledge is likely to be more demanding than perceptual tasks) may result in differences in the self and other activation maps. Secondly, the degree of familiarity with the individual chosen for other-reflection also ranges from close relatives and friends (Holt et al., 2011; Murphy et al., 2010; Pauly et al., 2014; van der Meer et al., 2013) to public figures (Bedford et al., 2012; Tan et al., 2015), which could also affect activation patterns (e.g. reflecting upon close relatives may rely more in autobiographical memory, while reflecting upon public figures may involve more semantic memory, and involve different brain regions, see Murray et al., 2012). Finally, significant differences in patient status and small sample sizes might also explain the lack of consistency among results.

The present study aims to further examine self- and other-processing in schizophrenia, with an emphasis on self/other differentiation (i.e. the direct comparison between self- and other-reflection). We will use a self/other-reflection task based on previous studies (Modinos et al., 2009; van der Meer et al., 2013) that we have already used successfully in healthy subjects (Fuentes-Claramonte et al., 2019), where we observed significant differences between self- and other-reflection in DMN regions with the specific involvement of the right posterior TPJ (angular gyrus) in other, but not self-reflection. Considering the variability in the tasks used in the previous literature, we have selected this task to best isolate the components of interest for our study. We consider that the present work will allow us to broaden the knowledge on the neural basis of self/other reflection in schizophrenia. Although there is no consistent pattern of findings in the existing schizophrenia literature, we expect that alterations will arise in relevant DMN areas involved in self/other differentiation, namely the mPFC, the PCC and the TPJ.

2. Methods

2.1. Subjects

Thirty-two patients with a DSM-IV-TR diagnosis of schizophrenia recruited from three psychiatric hospitals (Benito Menni CASM, Sagrat Cor de Martorell and Hospital Sant Rafael) in Barcelona participated in the study. They all underwent diagnostic evaluation by trained raters using the Spanish version of the Structured Clinical Interview for DSM Disorders (SCID). Psychotic symptoms were also scored using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) and the The Clinical Global Impressions Scale (CGI, Guy, 1976). Patients were excluded if they (a) were younger than 18 or older than 65 years, (b) had a history of brain trauma or neurological disease, and (c) had shown alcohol/substance abuse within 12 months prior to participation. With respect to the last criterion, all participants were questioned about alcohol and drug use during the previous year by a psychiatrist. As well as excluding patients who showed evidence of substance abuse/

dependence, we also excluded those who reported habitual use of cannabis. All patients were right-handed and all were taking antipsychotic medication.

The control sample consisted of 33 right-handed healthy individuals recruited from non-medical staff working in the hospital, their relatives and acquaintances, plus independent sources in the community. They were selected to be similar to the patients in age, sex and IQ (premorbid IQ in the patients). This last was estimated using the Word Accentuation Test (Test de acentuación de palabras (TAP) Del Ser et al., 1997; Gomar et al., 2011), which requires pronunciation of Spanish words whose accents have been removed. This test is conceptually similar to the UK National Adult Reading Test (NART) (Nelson, 1982) and the US Wide Range of Achievement Test used in the USA (Jastak and Wilkinson, 1984). Scores can be converted into full scale IQ estimates (Gomar et al., 2011). The control sample met the same exclusion criteria as the patients. They were also questioned and excluded if they reported a history of mental illness and/or treatment with psychotropic medication and the SCID was also used to exclude current psychiatric disorders.

All participants gave written informed consent prior to participation. All the study procedures had been previously approved by the Research Ethics Committee FIDMAG Sisters Hospitallers (Comité de Ética de la Investigación de FIDMAG Hermanas Hospitalarias) and complied with its ethical standards on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Healthy controls received a gift-card as a compensation for their participation in the study.

2.2. Self-other task

The task used in the present study was adapted from the one described in Modinos et al. (2009) and has already been used in healthy subjects by our group (Fuentes-Claramonte et al., 2019) to investigate the processing of information related to the self and another known person, compared to general semantic knowledge. To best isolate the components of interest for our study, this task uses (1) a semantic control condition (matched in perceptual and motor requirements and in statement complexity with the conditions of interest) to separate self- and other-reflection from processing of externally-oriented information, and (2) an 'other' condition aimed to compare reflection upon oneself to reflection on other individuals within the participant's environment, for which we selected an 'other' personally known by the participant (so responses might be based on previous interactions and not so much on semantic knowledge, and so exposure to this 'other' might be more uniform across participants than with public figures), but not a very close 'other' to avoid strong emotional investment.

Before scanning, participants were given detailed task instructions and were asked to choose an acquaintance to think about inside the scanner for the other-reflection condition. The chosen individual had to be familiar to the participant, but not too close in order to avoid eliciting strong feelings towards them (valid examples were classmates or co-workers), similar to the original implementation of the task (Modinos et al., 2009). The final choice of acquaintance was made in consultation with one of the researchers to ensure the degree of closeness was similar for all participants.

During the task, participants viewed a series of statements which were either about themselves (Self), about an acquaintance (Other) or about general knowledge (Facts), which were similar in length and complexity in the three conditions. Participants had to respond whether they considered the sentence to be true or false with a button press. In the Self condition, sentences referring to personal qualities, attributes or attitudes were presented (e.g. "In general, I like order", "I am a tense or very nervous person"). Similarly, in the Other condition sentences referred to the personality traits and behavior of the chosen acquaintance. Examples of sentences included in the Other condition are "OTHER often makes decisions without thinking" or "OTHER usually

has very good ideas", where OTHER was substituted by the chosen person's name. In the Facts condition, sentences referred to general knowledge, such as "A decade is a period of ten years" or "Insects only have four legs". As in the original version, half of the sentences in the Self and Other conditions had a positive valence and the rest had a negative quality, while in the Facts condition half of the sentences were true and the other half were false. Different from the original, the Self and Other conditions only included statements referring to personality, behavior and attitudes, but not physical appearance (these were a minority in Modinos et al., 2009). All statements were written in Spanish, and all participants were fluent Spanish speakers.

The task consisted of 54 trials (18 per condition) arranged in a block design. Each block started with an instruction screen indicating the condition that corresponded to that block ("Sentences about Me", "Sentences about Other", "Sentences about Facts"), which lasted 3s. After a 1s delay, three trials were presented, each lasting 9s, where the sentence appeared in the center of the screen and the options "Yes" and "No" appeared at the bottom-right and bottom-left corners, respectively, to act as a reminder of the required response ("Yes" with the right index finger, and "No" with the left index finger). Trials were separated by a 1s blank screen. After the three trials, the next block started, for a total of 6 blocks per condition. Every 3 blocks there was a resting period of 16s in which only a crosshair was presented as fixation point. Block order was pseudorandomized, with each of the three conditions occurring once between resting periods. Total task duration was 12 min and 12 s. This design deviates from the task design used by Modinos et al. (2009) in that the trials were longer, resulting in fewer trials overall, but with a similar amount of time spent in each condition. This change was made to ensure participants had time to read and reflect on each statement before responding. As demonstrated in Fuentes-Claramonte et al. (2019), this version of the task is able to elicit activation of relevant DMN brain regions in self and other-reflection.

2.3. Image acquisition

Images were acquired with a 3T Philips Achieva scanner (Philips Medical Systems, Best, the Netherlands). Functional data were acquired using a $T2^*$-weighted echo-planar imaging (EPI) sequence with 364 volumes and the following acquisition parameters: TR = 2000 ms, TE = 30 ms, Flip angle = 78°, in-plane resolution = 3×3 mm, FOV = 240 mm, slice thickness = 3 mm, inter-slice gap = 1mm. Slices (32 per volume) were acquired with an interleaved order parallel to the AC-PC plane. Before the functional sequence, a high-resolution anatomical 3D volume was acquired using a TFE (Turbo Field Echo) sequence for anatomical reference and inspection (TR = 8.15ms; TE = 3.73ms; Flip angle = 8°; voxel size = 0.9375×0.9375 mm; slice thickness = 1mm; slice number = 160; FOV = 240 mm).

2.4. Image preprocessing and analysis

Preprocessing and analysis was carried out with the FEAT module included in the FSL (FMRIB Software Library) software, version 5.0 (Smith et al., 2004). The first 20 s (10 volumes) of the sequence, corresponding to signal stabilization, were discarded. Preprocessing included motion correction (using the MCFLIRT algorithm) and co-registration and normalization to a common stereotactic space (Montreal Neurological Institute template). Before group analyses, normalized images were spatially filtered with a Gaussian filter (FWHM = 5 mm). To minimize unwanted movement-related effects, individuals with an estimated maximum absolute movement >3.0 mm or an average absolute movement >0.3 mm were excluded from the study.

Statistical analysis was performed by means of a General Linear Model (GLM) approach. At the first level, three regressors of interest were defined in the GLM corresponding to the three task conditions (Self, Other, Facts) in a block-design fashion. Instruction screens were modeled by an additional nuisance regressor. Fixation periods were not

3

Table 1
Demographic and clinical sample characteristics.

	Patients (N = 23)	Controls (N = 27)	Significance
Sex (M/F)	16/7	17/10	p = 0.623
Age	37.00 (8.06)	38.74 (10.20)	p = 0.512
	range 22-55	range 23-61	
Estimated pre-morbid IQ (TAP)	100.64 (10.23)	104.07 (6.34)	p = 0.178
	range 81-114	range 91-114	
PANSS Total score	69 (18.19)		
	range 39-115		
PANSS Positive	16.04 (5.49)		
	range 8-28		
PANSS Negative	19.74 (5.79)		
	range 11-33		
PANSS General	33.22 (9.08)		
	range 18-59		
CGI	4.17 (0.89)		
	range 3-6		
Treatment (chlorpromazine equivalent, daily dose in mg)	498.77 (490.27) range 62.5-2400		

Measures are means (SD). Group differences were tested with a Chi-square test for sex and unpaired two sample t-tests for age and pre-morbid IQ.

modeled and thus acted as an implicit baseline. GLMs were fitted to generate activation maps for each of the three conditions of interest compared to baseline and for the comparisons between conditions (Self vs. Facts, Other vs. Facts, Other vs. Self). Second level analyses and group comparisons between patients and controls were performed within the FEAT module, with mixed-effects GLMs (Beckmann et al., 2003). All statistical tests were carried out at the cluster level with a corrected p value of 0.05 using Gaussian random field methods. The default threshold of $z = 2.3$ was used to define the initial set of clusters.

3. Results

Demographic and clinical characteristics of the final samples included in the analyses are detailed in Table 1. As can be seen, the patients and the controls did not differ significantly in terms of age, sex and estimated premorbid IQ. Nine patients and 6 controls were excluded from the analyses due to excessive head movement. All patients were on antipsychotic treatment (21 on atypical neuroleptics and 2 on both typical and atypical) and were admitted to inpatient (14 patients) or outpatient (9 patients) units.

3.1. Self vs. facts mean group results

Brain activity associated to self-reflection was identified by the Self > Facts contrast, where both patients and controls showed similar regions of activation in the medial prefrontal cortex, the PCC and precuneus, the left angular gyrus and TPJ area, the middle temporal cortex (bilateral), and parts of the visual cortex (calcarine cortex and lingual gyrus, see Fig. 1 and Supplementary Table S1 for details).

3.2. Self vs. facts group comparison

Group comparison in the Self vs. Facts contrast showed a cluster of differences in the left DLFPC/middle frontal gyrus (MNI coordinates $x = -52$, $y = 14$, $z = 36$; $Z = 3.94$; cluster size = 527 voxels; $p = 0.008$). As seen in Fig. 2, the patients hyperactivated this region in self-reflection. Moreover, controls increased activity in the DLPFC in Facts with respect to Self, but this increase was not observed in the patients, who displayed similar (heightened) levels of activation in both conditions.
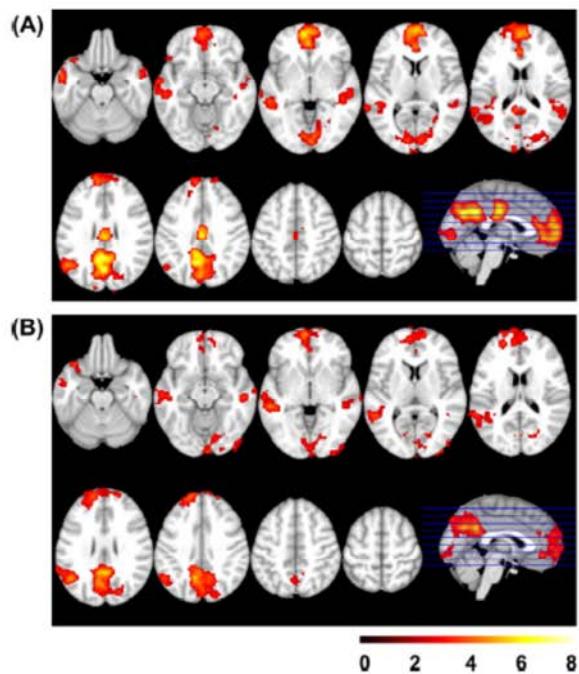
Fig. 1. Mean activation in Self > Facts control group (A) and in the patient group (B). Images are displayed in neurological convention (right is right). Color bar depicts z values.
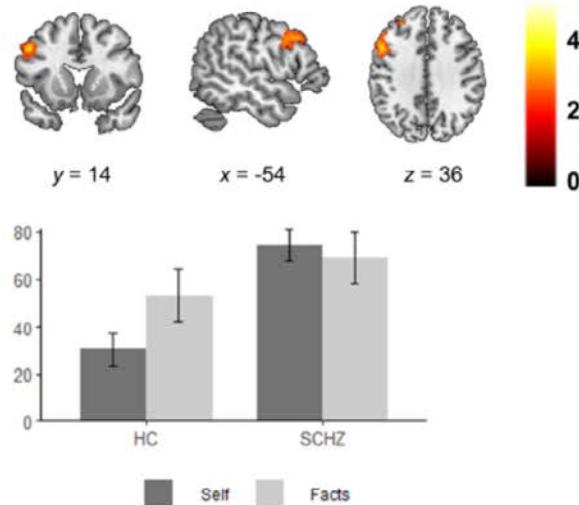
Fig. 2. Group differences between healthy subjects and schizophrenic patients in the Self vs. Facts contrast. Plot shows the mean parameter estimates (average of all beta weights in the cluster) for the left DLFPC in the Self and Facts conditions (respective to baseline) for each group in the cluster of group differences. Error bars represent standard error of the mean. Images are displayed in neurological convention (right is right). Color bar depicts z values.

3.3. Other vs. facts mean group results

Other-reflection (Other > Facts contrast) yielded a very similar pattern of activation to that of Self-reflection, involving mostly the same regions plus the right angular gyrus in the control group. In
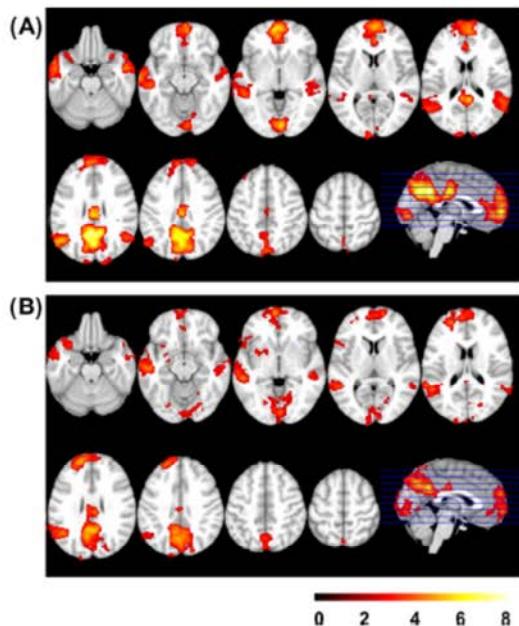
Fig. 3. Mean activation in Other > Facts in the control group (A) and in the patient group (B). Images are displayed in neurological convention (right is right). Color bar depicts z values.

patients, other-reflection also activated the left insula and putamen (see Fig. 3 and Supplementary Table S2 for details).

3.4. Other vs. facts group comparison

This group comparison showed three clusters of differences between patients and controls: one in the precuneus (MNI coordinates $x = 22$, $y = -46$, $z = 18$; $Z = 3.94$; cluster size = 502 voxels; $p = 0.02$), one in the left DLPFC (MNI coordinates $x = -42$, $y = 50$, $z = 14$; $Z = 4.06$; cluster size = 594 voxels; $p = 0.008$), and one in the left precentral gyrus (MNI coordinates $x = -54$, $y = 8$, $z = 34$; $Z = 4.21$; cluster size = 552 voxels; $p = 0.01$). We observed that patients deactivated the precuneus during the Other condition while controls did not (although both groups deactivated this region in the Facts condition, as shown in Fig. 4). In the DLPFC and precentral gyrus, we observed increased activation in the patient group in Other-processing (while activation in the Facts condition was similar in both groups). Interestingly, these last two clusters were located very close to the area of differences found in the Self vs. Facts contrast and displayed a similar pattern of alteration in the patient group.

3.5. Self vs. other mean group results

No region showed increased activity in Self trials when compared to the Other condition (Self > Other contrast), neither in the patients nor in the controls. On the other hand, several brain areas were more active in the Other than in the Self condition: healthy subjects showed activation in the precuneus and PCC, mPFC extending into the right hemisphere, angular gyrus, temporal pole and amygdalae, and right superior frontal cortex (Supplementary Table S3, Fig. 5). Patients with schizophrenia, however, only showed activation in the PCC and the left temporal pole (Supplementary Table S3, Fig. 5).

3.6. Self vs. other group comparison

This group comparison showed a cluster of differences in the right angular gyrus (MNI coordinates $x = 48$, $y = -64$, $z = 30$; $Z = 4.54$; cluster size = 547 voxels; $p = 0.007$), which was activated for other-reflection in the control group, but not in the patients (Fig. 5).

4. Discussion

This study aimed to examine the brain correlates of self/other differentiation in schizophrenia by comparing brain activation during self- and other-reflection. We report, for the first time, a significant alteration in right TPJ activity in patients with schizophrenia in other-reflection. In healthy controls, self- and other-reflection activated a similar set of brain regions when compared with a semantic control condition, although direct comparison of self and other revealed that some of them were relatively more active in other-reflection. However, the right TPJ was not activated for self, but only for other-reflection, which is consistent with the role attributed to this area in self/other differentiation and social cognition (Eddy, 2016; Sowden and Shah, 2014). In contrast, patients with schizophrenia did not activate right TPJ for either self- or other-reflection. TPJ hypoactivation in schizophrenia has been previously described with social cognition tasks (Benedetti et al., 2009; de Achával et al., 2012; Makowski et al., 2016; Thakkar et al., 2014; but see also Kronbichler et al. (2017), which shows meta-analytic evidence of both aberrant hypo and hyperactivation of the TPJ in mentalizing tasks). The present finding supports the hypothesis that TPJ dysfunction may underlie a disturbance in self/other differentiation processes in schizophrenia (Eddy, 2016).

Self/other differentiation is believed to initially involve motor mechanisms underpinning imitation and recognition of action goals, as well as interpretation of facial emotions and non-verbal communication; followed by mentalizing processes that include inferring the mental state of the other or reasoning about their beliefs and emotions (Eddy, 2018). Successfully decoupling the self and other may aid higher level perspective taking. In contrast, when these processes are impaired, self/other blending can occur and the person may have reduced ability in perspective taking, or may not be able to suppress imitation and this could lead to confusion, personal distress and depersonalization (Eddy, 2016). The right TPJ is associated with decoupling mechanisms, referring to the ability to dissociate an agent's mental state from one's own beliefs and to differentiate between belief and reality (van Veluw and Chance, 2014). This could conceivably provide a basis for patients with schizophrenia being impaired in identifying the origin of beliefs, intentions, or actions, and so having difficulties testing them against reality, resulting not only in difficulties in social interaction but also in delusional explanations of others' behavior (e.g. ideas/delusions of reference or persecution, grandiosity).

It should be noted that the TPJ is not a unitary region, and at least two subdivisions have been found using resting-state functional connectivity: a more anterior part that shows connectivity with attentional regions (ventral PFC and anterior insula) and a more posterior subdivision connected with DMN regions (mPFC, PCC/precuneus) (Mars et al., 2012). In the present study, group differences were found in the angular gyrus, which belongs to the posterior subdivision of the TPJ, and is usually described as belonging to the DMN (Buckner et al., 2008). Interestingly, though, there was a laterality effect: the left angular gyrus was activated both by self- and other-reflection (although BOLD signal was higher in the second), but the right was only active during other-reflection. This adds specificity to our results, since the right TPJ has been more strongly linked to self/other differentiation and social cognition in the previous literature than the left (Eddy, 2016). Consistently, there were no group differences in the left TPJ.

The findings concerning the TPJ are also relevant because this region has been proposed as a target for therapeutic intervention. Several
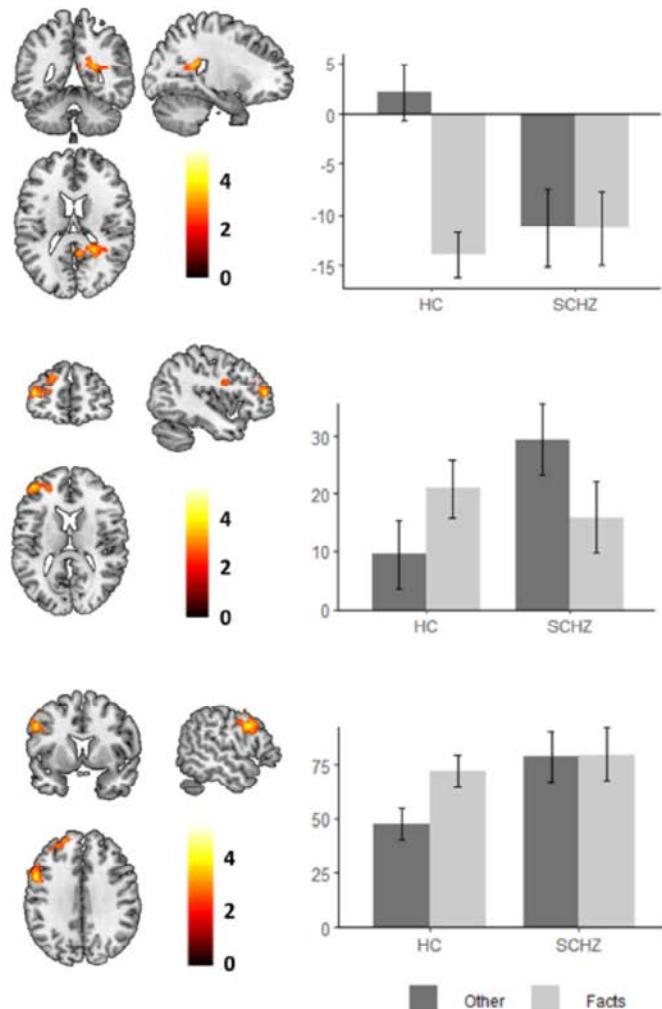
Fig. 4. Group differences between healthy subjects and schizophrenic patients in the Other vs. Facts contrast. Plots show the mean parameter estimates (beta weights) for the precuneus (upper row), the DLPFC (middle row) and the precentral gyrus (lower row) in the Other and Facts conditions (respect to baseline) for each group. Error bars represent standard error of the mean. Images are displayed in neurological convention (right is right). Color bars depict z values.

drugs may affect its function, for instance, drugs that alter norepinephrine (Strange and Dolan, 2007), selective serotonin reuptake inhibitors (Cremers et al., 2016) and intranasal oxytocin (Hu et al., 2016). In addition, the TPJ is a promising target for neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) (Donaldson et al., 2015).

In the present study, we also observed hyperactivation of the left lateral frontal cortex (including the DLPFC and the precentral gyrus) during self- and other-reflection. Detailed examination of the activation pattern in this area revealed that hyperactivation was specific to self/other processing, while activation levels were similar between groups in the semantic condition. Given the attentional role that the lateral frontal cortex has been assigned (Badre, 2008), and its involvement in semantic memory (Raposo et al., 2012), activation of this region would arguably be expected during semantic processing (i.e. Facts condition), but not in self- and other-reflection. Moreover, we observed that the patients deactivated a cluster in the precuneus for both semantic and other processing, while controls only did so for semantic processing.

Deactivation of the precuneus is characteristic of tasks that place cognitive demands on the subject, such as classical attention or working memory tasks (Cavanna and Trimble, 2006), even in schizophrenic patients (Pomarol-Clotet et al., 2008). In the patients in our study, self- and other-reflection seem to have imposed greater cognitive demands than in controls, leading to hyperactivity of the lateral prefrontal cortex and deactivation of the precuneus in conditions that should not require these changes (more akin to cognitive, attention-demanding tasks). An alternative, or perhaps complementary interpretation of this finding, would be that healthy participants treat self- and other-related information differently from semantic knowledge, as evidenced by the obvious differences in patterns of brain activity between these conditions. In schizophrenia, however, the ability to distinguish between these two kinds of information may be disturbed, leading to difficulties in the management of social information.

This activation pattern is also interesting because DMN regions involved in self/other-reflection tend to decrease their activation when attention is externally focused, which in turn involves an increase in activity of attentional or executive networks, where the lateral
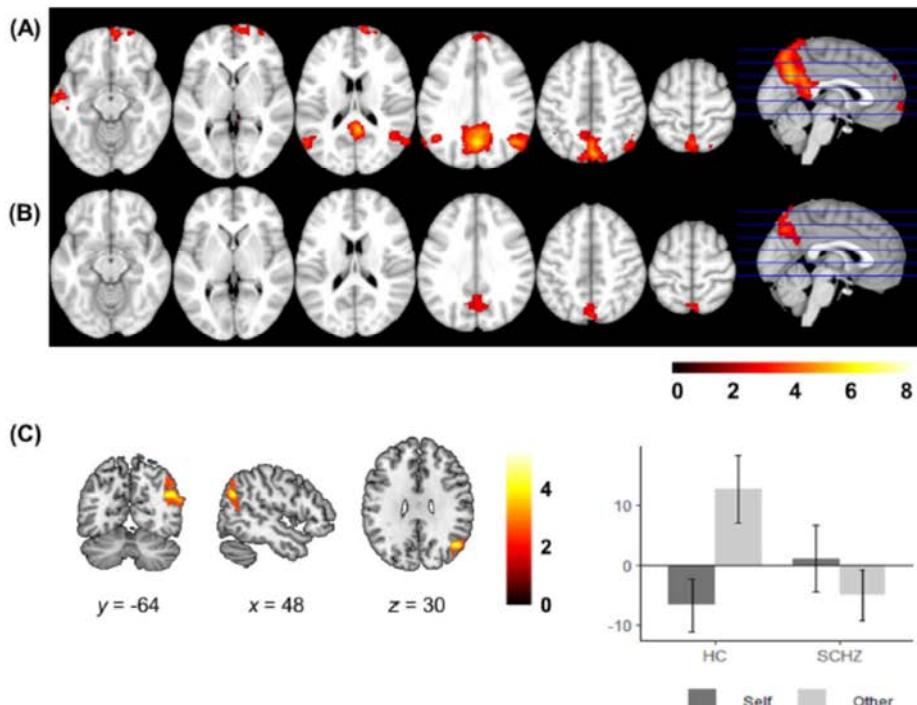
Fig. 5. Mean activation in Other > Self in the control group (A) and in the patient group (B). (C) Group differences between healthy subjects and schizophrenic patients in the Other vs. Self contrast. Plot shows the mean parameter estimates (beta weights) for the cluster in the right angular gyrus in the Self and Other conditions (respect to baseline) for each group. Patients fail to activate the right angular gyrus in the Other condition. Error bars represent standard error of the mean. Images are displayed in neurological convention (right is right). Color bars depict z values.

prefrontal cortex is a relevant node (Fox et al., 2005). Thus, adequate balance between these intrinsic networks seems necessary for adaptive cognitive functioning, and a failure in its regulation might be linked to psychiatric symptoms. Alterations in the DMN are well-established in schizophrenia (Dreher et al., 2012; Haatveit et al., 2016; Pomarol-Clotet et al., 2008; Salgado-Pineda et al., 2011; Schneider et al., 2011). Some authors have proposed that there is a stable difference in the DMN structure and its connections with the salience network and the central executive network (Menon, 2011; Woodward et al., 2011). Given that healthy subjects showed activation differences between task conditions in the lateral prefrontal cortex, the precuneus and the right angular gyrus, and these changes were not found in patients, our results could also be linked to a failure in network balance between the DMN and the executive network in schizophrenia. These results may suggest that the process of functional specialization of the DMN may be altered in schizophrenia.

The present results add evidence to the range of alterations in self/other-reflection reported in schizophrenia. However, our findings converge only partially with previous results. In the Other vs. Facts contrast, we found altered activation of a region close to the PCC as also found by Tan et al. (2015) and van der Meer et al. (2013), but other findings have not been replicated. Our task was based on the design used by van der Meer et al. (2013); however, we did not include sentences about physical attributes in the Self or the Other conditions. A second reason for differences might be the degree of familiarity with the individual chosen as 'other' in the Other condition (Murray et al., 2012). In our study, participants were instructed to choose a known person but not someone with a close relationship with them, so that the 'other' was personally known and had a history of past interactions with the participant, but not as close as in other studies where the 'other' was

required to be a close friend or family member. Other studies have used a public 'other'; however, this may impose significant variation in the amount of exposure to such individuals. Although we tried to control the level of closeness between the participant and the 'other', it is important to keep in mind that there is some degree of variability that could not be controlled. It might also be important to bear in mind that relationships and attachments might be different in schizophrenia patients than in controls. It is also of course possible that discrepancies between studies could be explained in terms of prevalence of positive and negative symptoms in the schizophrenia samples, stage of the disorder, or medication use.

4.1. Conclusions

The present study is the first to reveal diminished activation of the right TPJ, a brain region with a relevant proposed role for self/other differentiation and social cognition, in patients with schizophrenia during other-reflection. Additionally, it found evidence that schizophrenic patients rely more on cognitive control areas (i.e. left lateral prefrontal cortex) for self- and other-reflection, suggesting that this type of cognitive process might place greater cognitive demands in patients with this disorder. Taken together, the results support a failure in self- and other-related information processing in schizophrenia and provide evidence for disturbances in self/other differentiation, which might lead to altered judgments of others' behavior and personality. An alteration in the right TPJ activity is a potential neural mechanism for this disturbance. This latter finding may be relevant for future studies, particularly those aiming to examine psychosocial treatments and neuromodulation techniques in schizophrenia.

Financial support

This work was supported by Generalitat de Catalunya (2017 SGR 01271 to EP-C and 2017 SGR 1265 to PF-C from AGAUR). Also by grants from Ministerio de Ciencia, Innovación y Universidades: Juan de la Cierva-formación contract (FJCI-2015-25278 to PF-C) and from Ministerio de Economía y Competitividad (FFI2016-77647-C2-2-P to PS-P). And by the Instituto de Salud Carlos III, co-funded by European Regional Development Fund/European Social Fund "Investing in your future": Miguel Servet Research contract (CPII16/00018 to EP-C), Rio Hortega contract (CM15/00024 to MM-S), and Research Project Grants (PI14/01151 to RS, PI14/01148 to EP-C, PI18/00810 to EP-C, PI18/00877 to RS and PI18/00880 to PM).

CRediT authorship contribution statement

Paola Fuentes-Claramonte: Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization. Marta Martin-Subero: Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization. Pilar Salgado-Pineda: Conceptualization, Methodology, Investigation, Data curation. Aniol Santo-Angles: Investigation. Isabel Argila-Plaza: Investigation. Josep Salavert: Investigation. Antoni Arévalo: Investigation. Clara Bosque: Investigation. Carmen Sarri: Investigation. Amalia Guerrero-Pedraza: Investigation. Antoni Capdevila: Investigation, Resources. Salvador Sarró: Resources, Project administration, Funding acquisition, Supervision. Peter J. McKenna: Conceptualization, Funding acquisition, Writing - review & editing. Edith Pomarol-Clotet: Conceptualization, Funding acquisition, Writing - review & editing, Supervision. Raymond Salvador: Conceptualization, Methodology, Software, Writing - original draft, Writing - review & editing, Funding acquisition.

Declaration of Competing Interest

None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2019.102134.

References

Andrews-Hanna, J.R., Smallwood, J., Spreng, R.N., 2014. The default network and self-generated thought: component processes, dynamic control, and clinical relevance. Ann. N. Y. Acad. Sci. 1316, 29–52. https://doi.org/10.1111/nyas.12360.

Badre, D., 2008. Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. Trends Cogn. Sci. 12, 193–200. https://doi.org/10.1016/j.tics.2008.02.004.

Beckmann, C.F., Jenkinson, M., Smith, S.M., 2003. General multilevel linear modeling for group analysis in FMRI. Neuroimage 20, 1052–1063. https://doi.org/10.1016/S1053-8119(03)00435-X.

Bedford, N.J., Surguladze, S., Giampietro, V., Brammer, M.J., David, A.S., 2012. Self-evaluation in schizophrenia: an fMRI study with implications for the understanding of insight. BMC Psychiatry 12. https://doi.org/10.1186/1471-244X-12-106.

Benedetti, F., Bernasconi, A., Bosia, M., Cavallaro, R., Dallaspezia, S., Falini, A., Poletti, S., Radaelli, D., Riccaboni, R., Scotti, G., Smeraldi, E., 2009. Functional and structural brain correlates of theory of mind and empathy deficits in schizophrenia. Schizophr. Res. 114, 154–160. https://doi.org/10.1016/j.schres.2009.06.021.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann. N. Y. Acad. Sci. 1124, 1–38. https://doi.org/10.1196/annals.1440.011.

Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129, 564–583. https://doi.org/10.1093/brain/awl004.

Cremers, H., Lee, R., Keedy, S., Phan, K.L., Coccaro, E., 2016. Effects of escitalopram administration on face processing in intermittent explosive disorder: an fMRI Study. Neuropsychopharmacology 41, 590–597. https://doi.org/10.1038/npp.2015.187.

de Achával, D., Villarreal, M.F., Costanzo, E.Y., Douer, J., Castro, M.N., Mora, M.C., Nemeroff, C.B., Chu, E., Bär, K.J., Guinjoan, S.M., 2012. Decreased activity in right-hemisphere structures involved in social cognition in siblings discordant for schizophrenia. Schizophr. Res. 134, 171–179. https://doi.org/10.1016/j.schres.2011.11.010.

Del Ser, T., Gonzalez-Montalvo, J., Martinez-Espinosa, S., Delgado-Villapalos, C., Bermejo, F., 1997. Estimation of premorbid intelligence in spanish people with the word accentuation test and its application to the diagnosis of dementia. Brain Cogn 33, 343–356. https://doi.org/10.1006/brcg.518948.

Denny, B.T., Kober, H., Wager, T.D., Ochsner, K.N., 2012. A meta-analysis of functional neuroimaging studies of self and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. J. Cogn. Neurosci. 24, 1742–1752. https://doi.org/10.1162/jocn.

Donaldson, P.H., Rinehart, N.J., Enticott, P.G., 2015. Noninvasive stimulation of the temporoparietal junction: a systematic review. Neurosci. Biobehav. Rev. 55, 547–572. https://doi.org/10.1016/j.neubiorev.2015.05.017.

Dreher, J.C., Koch, P., Kohn, P., Apud, J., Weinberger, D.R., Berman, K.F., 2012. Common and differential pathophysiological features accompany comparable cognitive impairments in medication-free patients with schizophrenia and in healthy aging subjects. Biol. Psychiatry 71, 890–897. https://doi.org/10.1016/j.biopsych.2012.01.002.

Eddy, C.M., 2018. Social cognition and self-other distinctions in neuropsychiatry: insights from schizophrenia and Tourette syndrome. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 82, 69–85. https://doi.org/10.1016/j.pnpbp.2017.11.026.

Eddy, C.M., 2016. The junction between self and other? Temporo-parietal dysfunction in neuropsychiatry. Neuropsychologia 89, 465–477. https://doi.org/10.1016/j.neuropsychologia.2016.07.030.

Elk, M.Van, Duizer, M., Sligte, I., Schie, H.Van, 2016. Transcranial direct current stimulation of the right temporoparietal junction impairs third-person perspective taking. Cogn. Affect. Behav. Neurosci. 9–23. https://doi.org/10.3758/s13415-016-0462-z.

Fett, A.K.J., Viechtbauer, W., Dominguez, M., de, G., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. 35, 573–588. https://doi.org/10.1016/j.neubiorev.2010.07.001.

Fuentes-Claramonte, P., Martín-Subero, P., Alonso-Lana, S., Moreno-Alcázar, A., Argila-Plaza, I., Santo-Angles, A., Albajes-Eizagirre, A., Anguera-Camós, M., Capdevila, A., Sarró, S., McKenna, P.J., Pomarol-Clotet, E., Salvador, R., 2019. Shared and differential default-mode related patterns of activity in an autobiographical, a self-referential and an attentional task. PLoS One 14, 1–21. https://doi.org/10.1371/journal.pone.0209376.

Gomar, J.J., Ortiz-Gil, J., McKenna, P.J., Salvador, R., Sans-Sansa, B., Sarró, S., Guerrero, A., Pomarol-Clotet, E., 2011. Validation of the Word Accentuation Test (TAP) as a means of estimating premorbid IQ in Spanish speakers. Schizophr. Res. 128, 175–176. https://doi.org/10.1016/j.schres.2010.11.016.

Green, M.F., Horan, W.P., Lee, J., 2015. Social cognition in schizophrenia. Nat. Rev. Neurosci. 16, 620–631. https://doi.org/10.1093/schbul/sbn045.

Guy, W., 1976. Clinical Global Impression. ECDEU Assessment Manual for Psychopharmacology. National Institute of Mental Health, Rockville, MD.

Haatveit, B., Jensen, J., Alnes, D., Kaufmann, T., Brandt, C.L., Thoresen, C., Andreassen, O.A., Melle, I., Ueland, T., Westlye, L.T., 2016. Reduced load-dependent default mode network deactivation across executive tasks in schizophrenia spectrum disorders. NeuroImage Clin. 12, 389–396. https://doi.org/10.1016/j.nicl.2016.08.012.

Holt, D.J., Cassidy, B.S., Andrews-Hanna, J.R., Lee, S.M., Coombs, G., Goff, D.C., Gabrieli, J.D., Moran, J.M., 2011. An anterior-to-posterior shift in midline cortical activity in schizophrenia during self-reflection. Biol. Psychiatry 69, 415–423. https://doi.org/10.1016/j.biopsych.2010.10.003.An.

Hu, Y., Scheele, D., Becker, B., Voos, G., David, B., Hurlemann, R., Weber, B., 2016. The effect of oxytocin on third-party altruistic decisions in unfair situations: an fMRI study. Sci. Rep. 6, 1–10. https://doi.org/10.1038/srep20236.

Jardri, R., Pins, D., Lafargue, G., Very, E., Ameller, A., Delmaire, C., Thomas, P., 2011. Increased overlap between the brain areas involved in self-other distinction in schizophrenia. PLoS One 6. https://doi.org/10.1371/journal.pone.0017500.

Jastak, S., Wilkinson, G.S., 1984. WRAT-R : wide range achievement test-revised administration manual. Jastak Associates, Wilmington, Del.

Kay, S.R., Fiszbein, A., Opfer, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Krall, S.C., Rottschy, C., Oberwelland, E., Bzdok, D., Fox, P.T., Eickhoff, S.B., Fink, G.R., Konrad, K., 2015. The role of the right temporoparietal junction in attention and social interaction as revealed by ALE meta-analysis. Brain Struct. Funct. 220, 587–604. https://doi.org/10.1007/s00429-014-0803-z.

Kronbichler, L., Tschernegg, M., Martin, A.I., Schurz, M., Kronbichler, M., 2017. Abnormal brain activation during theory of mind tasks in schizophrenia: a meta-analysis. Schizophr. Bull. 43, 1240–1250. https://doi.org/10.1093/schbul/sbx073.

Makowski, C.S., Lepage, M., Harvey, P.-O., 2016. Functional neural correlates of social approval in schizophrenia. Soc. Cognit. Affect. Neurosci. 11, 445–457. https://doi.org/10.1093/scan/nsv125.

Mars, R.B., Sallet, J., Schüffelgen, U., Jbabdi, S., Toni, I., Rushworth, M.F.S., 2012. Connectivity-based subdivisions of the human right "temporoparietal junction area": Evidence for different areas participating in different cortical networks. Cereb. Cortex 22, 1894–1903. https://doi.org/10.1093/cercor/bhr268.

Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cognit. Sci. 15, 483–506. https://doi.org/10.1016/j.tics.2011.08.003.

Modinos, G., Ormel, J., Aleman, A., 2009. Activation of anterior insula during self-reflection. PLoS One 4, e4618. https://doi.org/10.1371/journal.pone.0004618.

Molnar-Szakacs, I., Uddin, L.Q., 2013. Self-processing and the default mode network: interactions with the mirror neuron system. Front. Hum. Neurosci. 7, 571. https://doi.org/10.3389/fnhum.2013.00571.

Murphy, E.R., Brent, B.K., Benton, M., Pruitt, P., Diwadkar, V., Rajarethinam, R.P., Keshavan, M.S., 2010. Differential processing of metacognitive evaluation and the neural circuitry of the self and others in schizophrenia: a pilot study. Schizophr. Res. 116, 252–258. https://doi.org/10.1016/j.schres.2009.11.009.

Murray, R.J., Schaer, M., Debbané, M., 2012. Degrees of separation: a quantitative neuroimaging meta-analysis investigating self-specificity and shared neural activation between self- and other-reflection. Neurosci. Biobehav. Rev. 36, 1043–1059. https://doi.org/10.1016/j.neubiorev.2011.12.013.

Nelson, H.E., 1982. The National Adult Reading Test (NART): Test Manual. Wind. NFER-Nelson, UK https://doi.org/Thesis_references-Converted#319.

Pauly, K.D., Kircher, T.T.J., Schneider, F., Habel, U., 2014. Me, myself and I: Temporal dysfunctions during self-evaluation in patients with schizophrenia. Soc. Cogn. Affect. Neurosci. 9, 1779–1788. https://doi.org/10.1093/scan/nst174.

Pomarol-Clotet, E., Salvador, R., Sarró, S., Gomar, J., Vila, F., Martínez, Á., Guerrero, A., Ortiz-Gil, J., Sans-Sansa, B., Capdevila, A., Cebamanos, J.M.M., McKenna, P.J.P.J., Sarro, S., Gomar, J., Vila, F., Martinez, A., Guerrero, A., Ortiz-Gil, J., Sans-Sansa, B., Capdevila, A., Cebamanos, J.M.M., McKenna, P.J.P.J., 2008. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? Psychol. Med. 38, 1185–1193. https://doi.org/10.1017/S0033291708003565.

Raposo, A., Mendes, M., Marques, J.F., 2012. The hierarchical organization of semantic memory: executive function in the processing of superordinate concepts. Neuroimage 59, 1870–1878. https://doi.org/10.1016/j.neuroimage.2011.08.072.

Salgado-Pineda, P., Fakra, E., Delaveau, P., McKenna, P.J., Pomarol-Clotet, E., Blin, O., 2011. Correlated structural and functional brain abnormalities in the default mode network in schizophrenia patients. Schizophr. Res. 125, 101–109. https://doi.org/10.1016/j.schres.2010.10.027.

Saxe, R., 2010. The right temporo-parietal junction: a specific brain region for thinking about thoughts. Handb. Theory Mind. 1–35. https://doi.org/10.1016/S1053-8119(03)00230-1.

Schneider, F.C., Royer, A., Grosselin, A., Pellet, J., Barral, F.G., Laurent, B., Brouillet, D., Lang, F., 2011. Modulation of the default mode network is task-dependant in chronic schizophrenia patients. Schizophr. Res. 125, 110–117. https://doi.org/10.1016/j.schres.2010.11.013.

Scholz, J., Triantafyllou, C., Whitfield-Gabrieli, S., Brown, E.N., Saxe, R., 2009. Distinct regions of right temporo-parietal junction are selective for theory of mind and exogenous attention. PLoS One 4. https://doi.org/10.1371/journal.pone.0004869.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K.,

Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23, 208–219. https://doi.org/10.1016/j.neuroimage.2004.07.051.

Sowden, S., Shah, P., 2014. Self-other control: a candidate mechanism for social cognitive function. Front. Hum. Neurosci. 8, 1–5. https://doi.org/10.3389/fnhum.2014.00789.

Strange, B.A., Dolan, R.J., 2007. B-adrenergic modulation of oddball responses in humans. Behav. Brain Funct. 3, 1–5. https://doi.org/10.1186/1744-9081-3-29.

Tan, S., Zhao, Y., Fan, F., Zou, Y., Jin, Z., Zen, Y., Zhu, X., Yang, F., Tan, Y., Zhou, D., 2015. Brain correlates of self-evaluation deficits in schizophrenia: a combined functional and structural MRI study. PLoS One 10, 1–12. https://doi.org/10.1371/journal.pone.0138737.

Thakkar, K.N., Peterman, J.S., Park, S., 2014. Altered brain activation during action imitation and observation in schizophrenia: a translational approach to investigating social dysfunction in schizophrenia. Am. J. Psychiatry 171, 539–548. https://doi.org/10.1176/appi.ajp.2013.13040498.Altered. 2.

van der Meer, L., Costafreda, S., Aleman, A., David, A.S., 2010. Self-reflection and the brain: a theoretical review and meta-analysis of neuroimaging studies with implications for schizophrenia. Neurosci. Biobehav. Rev. 34, 935–946. https://doi.org/10.1016/j.neubiorev.2009.12.004.

van der Meer, L., De Vos, A.E., Stiekema, A.P.M., Pijnenborg, G.H.M., Van Tol, M.J., Nolen, W.A., David, A.S., Aleman, A., 2013. Insight in schizophrenia: involvement of self-reflection networks? Schizophr. Bull. 39, 1352–1362. https://doi.org/10.1093/schbul/sbs122.

van der Weiden, A., Prikken, M., van Haren, N.E.M., 2015. Self-other integration and distinction in schizophrenia: a theoretical analysis and a review of the evidence. Neurosci. Biobehav. Rev. 57, 220–237. https://doi.org/10.1016/j.neubiorev.2015.09.004.

van Veluw, S.J., Chance, S.A., 2014. Differentiating between self and others: an ALE meta-analysis of fMRI studies of self-recognition and theory of mind. Brain Imaging Behav 8, 24–38. https://doi.org/10.1007/s11682-013-9266-8.

Woodward, N.D., Rogers, B., Heckers, S., 2011. Functional resting-state networks are differentially affected in schizophrenia. Schizophr. Res. 130, 86–93. https://doi.org/10.1016/j.schres.2011.03.010.

Zhang, L., Opmeer, E.M., Ruhé, H.G., Aleman, A., Van Der Meer, L., 2015. Brain activation during self- and other-reflection in bipolar disorder with a history of psychosis: comparison to schizophrenia. NeuroImage Clin. 8, 202–209. https://doi.org/10.1016/j.nicl.2015.04.010.

5.   DISCUSIÓN

5.1. Estudio 1: Correlatos de neuroimagen funcional del recuerdo autobiográfico en esquizofrenia

Autobiographical memory and default mode network function in schizophrenia: an fMRI study

El objetivo principal de este estudio es examinar la actividad funcional cerebral en relación al recuerdo autobiográfico en esquizofrenia mediante la técnica de fMRI. Se utiliza una tarea que compara una condición de memoria autobiográfica con una condición control: una condición de visualizado de palabras que no evocan recuerdo autobiográfico y además una línea base que consiste en visualizar una cruz fija.

En ambos casos, los controles sanos muestran una activación de las regiones de la DMN; especialmente de sus dos regiones corticales mediales (mPFC y PCC). Los pacientes muestran un patrón de activación similar al de los controles en estas regiones. No obstante, se observa que presentan un fallo de desactivación en regiones fuera de la DMN.

El patrón de activaciones que presentan los controles sanos en nuestro estudio es consistente con el descrito en el meta-análisis de Svoboda y colaboradores en el que se analizaron 24 estudios sobre recuerdo autobiográfico (Svoboda, McKinnon, & Levine, 2006).

En cuanto a los estudios previos en esquizofrenia, nuestros hallazgos son divergentes respecto al único estudio publicado hasta la fecha (Cuervo-Lombard et al., 2012). Estos autores encontraron una reducción de la activación en la corteza frontal medial, el precuneus, en la corteza prefrontal lateral y en el lóbulo temporal medial izquierdo en los pacientes. Sin embargo, estos resultados sólo fueron obtenidos a partir de la utilización de una máscara con umbrales no corregidos; el análisis corregido de todo el cerebro únicamente reveló diferencias en pequeños clústeres situados en regiones no corticales.

En cambio, en nuestro estudio los pacientes afectos de esquizofrenia sí que presentan alteraciones en el funcionamiento cerebral en el análisis corregido de todo el cerebro. De hecho, en el contraste entre la condición de recuerdo autobiográfico versus la condición de

reposo aparecen 7 clústeres de diferencias (corteza parietal derecha e izquierda, giro postcentral, corteza temporal medial izquierda, corteza temporal inferior izquierda, corteza occipital superior izquierda, ínsula); de los cuales, seis representan un fallo de desactivación (todas las regiones anteriores excepto la corteza occipital superior). Todos estos clústeres se encuentran fuera de las regiones consideradas constituyentes de la DMN (Buckner et al., 2008; Thomas Yeo et al., 2011). Todo ello nos lleva a interpretar que los pacientes con esquizofrenia presentan un fallo de desactivación fuera de la DMN durante la realización de una tarea destinada a activarla.

Existen pocos estudios en la literatura que reporten desactivaciones en relación al recuerdo autobiográfico en controles sanos. Ino y colaboradores en su estudio de 21 controles sanos encontraron desactivaciones en la siguientes regiones: polos temporales, corteza orbitofrontal, ínsula posterior, corteza occipital, corteza temporal media y corteza temporal superior durante la realización de una condición de "no pensar" versus una condición de recuerdo autobiográfico (Ino, Nakai, Azuma, Kimura, & Fukuyama, 2011). Además, también observaron desactivaciones en la corteza cingulada medial y precuneus. Bado y colaboradores en su estudio de 18 controles sanos observaron una mayor activación durante la realización de una condición de "estado de reposo pero despierto" respecto a la condición de recuerdo autobiográfico en la corteza cingulada subgenual anterior, el estriado ventral, el hipotálamo y el lóbulo parietal inferior de manera bilateral (Bado et al., 2014). De manera conjunta, estos resultados apoyan la idea de que el recuerdo autobiográfico está asociado a desactivaciones y hay indicios de superposición de estas regiones con las reportadas en nuestro estudio. Hay un tercer estudio llevado a cabo por Dupre y colaboradores en el que se utiliza una tarea con tres condiciones experimentales, una de memoria autobiográfica, una de prospección y una de teoría de la mente sobre 31 sujetos sanos (DuPre, Luh, & Spreng, 2016). Durante el contraste entre las tres condiciones combinadas frente a una condición de línea base, estos autores reportan clústeres de desactivación en regiones parietales y temporales de manera consistente con nuestros resultados; además de en la corteza occipital.

El hallazgo principal de este estudio es la evidencia de una función intacta de la DMN en esquizofrenia durante el desarrollo de una tarea normalmente destinada a activarla, como es el recuerdo autobiográfico. Adicionalmente se observan indicios de alteraciones en el patrón de actividad asociado a la memoria autobiográfica que, en cualquier caso, afectarían a otros circuitos cerebrales externos a la DMN.

5.2. Estudio 2: Correlatos de neuroimagen funcional de la autorreflexión y reflexión sobre el otro en esquizofrenia

Brain imaging correlates of self- and other-reflection in schizophrenia

El objetivo principal de este estudio es examinar la actividad funcional cerebral en relación a la auto-reflexión y la reflexión sobre el otro en esquizofrenia mediante la técnica de fMRI. Para ello, se utiliza una tarea con tres condiciones experimentales: una de reflexión sobre uno mismo, una de reflexión sobre una tercera persona y una condición semántica de control, además de una de línea base consistente en el visionado de una cruz fija.

En el contraste de autorreflexión versus la condición semántica de control los sujetos sanos presentan un patrón de activación en las regiones de la DMN; especialmente de sus dos regiones corticales mediales (mPFC y PCC). De manera interesante, en el contraste de reflexión sobre el otro los sujetos sanos mostraron un patrón de activación similar al anterior en las regiones de la DMN además del giro angular derecho. Los pacientes, por otro lado, muestran un patrón de activación muy parecido al de los controles sanos en estas regiones de la DMN en el contraste de autorreflexión y en el de reflexión sobre el otro; aunque en éste último desactivan un clúster en el precuneus. Pero además, observamos que presentan un clúster de hiperactivación en la DLPFC izquierda y el giro precentral. Estos hallazgos sugieren que los pacientes son capaces de activar las regiones de la DMN involucradas en los procesos de pensamiento y reflexión sobre uno mismo y reflexión sobre el otro y mentalización aunque con un mayor nivel de esfuerzo cognitivo; puesto que la corteza prefrontal lateral es un nodo importante de la CEN (Fox et al., 2005). Además, siguiendo esta hipótesis, la desactivación del precuneus es característica de tareas que imponen una elevada demanda cognitiva para el sujeto (Cavanna & Trimble, 2006; Pomarol-Clotet, E., Salvador, R., Sarro, S., Gomar, J., Vila, F., Martinez, A., Guerrero, A., Ortiz-Gil, J., Sans-Sansa, B., Capdevila, A. et al., 2008).

En cuanto a la comparación directa entre las condiciones de reflexión sobre el otro y auto-reflexión, nuestro estudio muestra por primera vez que los pacientes con esquizofrenia presentan una disminución de la activación en la TPJ derecha durante la reflexión sobre una tercera persona. La hipoactivación de la TPJ ya había sido reportada en esquizofrenia durante la realización de tareas de cognición social (Benedetti et al., 2009; de Achával et al., 2012; Makowski, Lepage, & Harvey, 2016; Thakkar, Peterman, & Park, 2014); aunque en el meta-análisis de Kronbicher y colaboradores se observan hiper e hipoactivación en esta región

durante la realización de tareas de mentalización (Kronbichler, Tschernegg, Martin, Schurz, & Kronbichler, 2017).

Nuestro hallazgo apoya la idea de que existe una disfunción en la TPJ en esquizofrenia que se relacionaría con alteraciones en la diferenciación entre el yo y el otro en esta enfermedad (Eddy, 2016). Esta diferenciación involucraría mecanismos motores como la imitación; la interpretación de las expresiones faciales y la comunicación no verbal. Además, incluiría procesos de mentalización como son inferir el estado mental de los otros o razonar sobre sus creencias y emociones (Eddy, 2018). Por lo tanto, la capacidad de desacoplar mentalmente el yo del otro dota al individuo de la habilidad de tomar perspectiva. La TPJ derecha está asociada a los mecanismos de desacoplamiento entre el yo y el otro (van Veluw & Chance, 2014). Cuando esta capacidad para desacoplar el yo del otro está alterada, puede resultar imposible suprimir la imitación o separar las creencias sobre los intereses e intenciones del otro de la realidad y todo ello conducir a confusión, estrés interpersonal y despersonalización (Eddy, 2016).

Es importante recalcar que la TPJ no es una región unitaria, sino que se han identificado por lo menos dos subdivisiones: una más anterior que se conecta funcionalmente con regiones atencionales como la corteza prefrontal ventral y la ínsula anterior, y una subdivisión más posterior que se conecta con regiones de la DMN (mPFC, PCC/PCUN) (Mars et al., 2012). En nuestro estudio, las diferencias se obtuvieron en el giro angular derecho, el cual pertenece a la subdivisión posterior de la TPJ y se considera como parte constituyente de la DMN (Buckner et al., 2008). Además, observamos lateralidad en este resultado puesto que no observamos diferencias en la activación de la TPJ izquierda. Esto añade especificidad a nuestros resultados porque la TPJ derecha se ha asociado de manera más robusta en la literatura a los procesos de cognición social y de diferenciación entre el yo y el otro (Eddy, 2016).

Este hallazgo resulta de especial interés dado que la TPJ ha sido propuesta como diana terapéutica por diversos autores. En este sentido, distintos fármacos pueden influir en su funcionamiento, desde los inhibidores selectivos de la recaptación de serotonina (Cremers, Lee, Keedy, Phan, & Coccaro, 2016), los fármacos que alteran los niveles de noradrenalina (Strange & Dolan, 2007) hasta la oxitocina intranasal (Y. Hu et al., 2016). Además, la TPJ podría ser una diana para las novedosas técnicas de neuromodulación (Donaldson, Rinehart, & Enticott, 2015).

6. CONCLUSIONES FINALES

Esta tesis demuestra que durante los procesos de memoria autobiográfica, la DMN se activa con normalidad en la esquizofrenia pero existe un fallo en la desactivación de regiones externas a la DMN. Si se replica, este hallazgo podría tener una implicación principal en la fisiopatología de la esquizofrenia: en primer lugar implicaría que en lugar de existir una disfunción en la DMN en esquizofrenia, se trataría de una disfunción más global en la capacidad de desactivar distintas regiones cerebrales en función de la tarea a desarrollar. Este hecho apoyaría las teorías que defienden la existencia de un desequilibrio en esquizofrenia entre las redes neuronales orientadas a tareas (CEN, SN) y la DMN que normalmente actuarían de manera anticorrelacionada.

En esta línea, se encuentra también el siguiente hallazgo de la tesis, puesto que en nuestro segundo estudio los pacientes son capaces de activar la DMN al mismo nivel que los controles sanos durante la realización de una tarea de autorreflexión; pero presentan un fallo en la desactivación de la DLPFC izquierda y el giro precentral, siendo éstas regiones externas a la DMN y pertenecientes a la CEN.

De manera conjunta, los resultados de ambas publicaciones muestran que los pacientes afectos de esquizofrenia son capaces, en general, de activar las regiones de la DMN a un nivel similar al de los controles sanos durante la ejecución de las tareas destinadas a activar dicha red. Estos resultados se contraponen por lo tanto a estudios anteriores realizados con tareas cognitivas como la tarea n-back que encontraron un fallo claro en desactivación de la DMN. Esto podría sugerir que el fallo que observamos en estos pacientes está más en las dinámicas de las redes cerebrales y en su interacción; y no tanto en una red concreta o una región específica. A favor de esta hipótesis, en ambos estudios observamos que los pacientes activan de manera significativamente más intensa las regiones cerebrales que participan en el control atencional, sugiriendo que requieren de un mayor esfuerzo cognitivo para su realización.

La presente tesis contiene el primer estudio publicado en revelar una disminución en la activación de la TPJ derecha en esquizofrenia; en concreto en el giro angular derecho, un área conocida por su papel clave en los procesos de diferenciación entre el yo y el otro y de cognición social. El giro angular es una estructura que sí forma parte de la DMN; aunque no es considerada una región central de dicha red como son las áreas de la línea media (mPFC y PCUN). Tampoco es una región que haya mostrado fallos en desactivación tan claros en la

esquizofrenia como sí ha hecho el mPFC. Además, encontramos evidencia de que los pacientes afectos de esquizofrenia requieren mantener activas las áreas de control cognitivo (DLPFC) durante la realización de las tareas de autorreflexión y reflexión sobre el otro; cosa que podría conducir a alteraciones en la diferenciación entre el yo y el otro que implicarían juicios aberrantes acerca de las creencias e intenciones de los demás. La alteración en la actividad de la TPJ derecha constituiría un potencial mecanismo neuronal detrás de este problema.

7. LIMITACIONES, PUNTOS FUERTES Y LÍNEAS DE FUTURO

Existen algunas limitaciones en los estudios llevados a cabo. En primer lugar, las muestras en ambos estudios son relativamente pequeñas y esto podría influir en la potencia de los estudios. Además, se debe tener en cuenta que todos los pacientes estaban bajo tratamiento antipsicótico; algo que puede afectar a la estructura y funcionalidad cerebral. Aunque cabe recalcar que esta limitación es común a la mayoría de estudios en esquizofrenia, ya que muy pocos pacientes diagnosticados se encuentran sin tratamiento. Y, finalmente, en el estudio de memoria autobiográfica no se midió el rendimiento de los pacientes; por lo que los resultados podrían estar influidos por un bajo desempeño durante la realización de la tarea. Además, en el estudio de autorreflexión y reflexión sobre el otro, aunque intentamos controlar el grado de intimidad entre los participantes y la persona que escogían como el "otro"; es posible que las relaciones y los apegos en esquizofrenia sean diferentes a los de las personas sanas y esto pueda añadir cierta variabilidad a los resultados obtenidos.

Como puntos fuertes de los dos estudios y de la tesis en general, cabe destacar que se trata del primer trabajo orientado a estudiar la DMN en esquizofrenia a partir de tareas diseñadas para su activación; en contraposición a la corriente general en los trabajos previos que se enfocaron en la desactivación de esta red. Los paradigmas experimentales se han basado en otros utilizados en estudios previos, pero con un diseño que permitía superar algunas de las limitaciones previas y examinar los procesos cognitivos específicos de interés para esta tesis. A nivel de análisis, se han seguido con rigor los estándares actuales en fMRI, utilizando valores de p corregidos por múltiples comparaciones, el hecho de utilizar tareas nobeles destinadas a activar la DMN y probarlas por primera vez en una cohorte de pacientes con esquizofrenia y el uso de valores de p corregidos por múltiples comparaciones. Añadir que el escáner que se ha utilizado para obtener las imágenes de fMRI es de 3 Teslas. Además, el segundo estudio es el primero en revelar una disminución en la activación de la TPJ derecha durante la realización de una tarea de reflexión sobre el otro en esquizofrenia.

El papel que puede estar jugando la DMN en la fisiopatología de la esquizofrenia es un tema de debate en la actualidad. Esta tesis aporta evidencia para apoyar la teoría de que existe un desequilibrio entre la DMN y la CEN y las redes atencionales. En este sentido, serían interesantes estudios de conectividad capaces de analizar la relación entre las redes y su

interacción; como los que utilizan técnicas de análisis derivadas de la teoría de grafos, como por ejemplo el análisis de componentes independientes. Esto se puede hacer tanto a nivel de reposo como con tareas específicas. Por otro lado, siguiendo el mismo tipo de estudio de la tesis, se podrían diseñar tareas destinadas a co-activar la DMN junto con redes atencionales. Además, el hallazgo de una alteración en el funcionamiento de la TPJ podría ser relevante para futuros estudios destinados a explorar los tratamientos psicosociales y las técnicas de neuromodulación en esquizofrenia.

De manera conjunta, los resultados de estas investigaciones ayudan a alcanzar una mayor comprensión de la esquizofrenia desde un punto de vista neurobiológico y pueden contribuir incluso al desarrollo de nuevos tratamientos para algunos de sus síntomas.

BIBLIOGRAFÍA

Addis, D. R., Wong, A. T., & Schacter, D. L. (2007). Remembering the past and imagining the future: Common and distinct neural substrates during event construction and elaboration. *Neuropsychologia*, *45*(7), 1363–1377.

Aguilar-Ortiz, S., Salgado-Pineda, P., Vega, D., Pascual, J. C., Marco-Pallarés, J., Soler, J., … Pomarol-Clotet, E. (2020). Evidence for default mode network dysfunction in borderline personality disorder. *Psychological Medicine*, *50*(10), 1746–1754.

Aleman, A., Kahn, R. S., & Selten, J. P. (2003). Sex differences in the risk of schizophrenia: Evidence from meta-analysis. *Archives of General Psychiatry*, *60*(6), 565–571.

Andreasen, N. C. (1989). The Scale for the Assessment of Negative Symptoms (SANS): Conceptual and theoretical foundations. *British Journal of Psychiatry*, *155*(NOV. SUPPL. 7), 49–52.

Andreasen, Nancy C., Arndt, S., Alliger, R., Miller, D., & Flaum, M. (1995). Symptoms of Schizophrenia: Methods, Meanings, and Mechanisms. *Archives of General Psychiatry*, *52*(5), 341–351.

Andreasen, Nancy C., & Olsen, S. (1982). Negative v Positive Schizophrenia: Definition and Validation. *Archives of General Psychiatry*, *39*(7), 789–794.

Andreasen, Nancy C., Swayze, V. W., Flaum, M., Yates, W. R., Arndt, S., & Mcchesney, C. (1990). Ventricular Enlargement in Schizophrenia Evaluated with Computed Tomographic Scanning: Effects of Gender, Age, and Stage of Illness. *Archives of General Psychiatry*, *47*(11), 1008–1015.

Andrews-Hanna, J. R. (2012). The brain's default network and its adaptive role in internal mentation. *Neuroscientist*, Vol. 18, pp. 251–270.

Andrews-Hanna, J. R., Reidler, J. S., Huang, C., & Buckner, R. L. (2010). Evidence for the default network's role in spontaneous cognition. *Journal of Neurophysiology*, *104*(1), 322–335.

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-Anatomic Fractionation of the Brain's Default Network. *Neuron*, *65*(4), 550–562.

Andrews-Hanna, J. R., Saxe, R., & Yarkoni, T. (2014). Contributions of episodic retrieval and mentalizing to autobiographical thought: Evidence from functional neuroimaging, resting-state connectivity, and fMRI meta-analyses. *NeuroImage*, *91*, 324–335.

APA. (1994). *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* (4th Edition). Washington DC: American Psychiatric Association.

APA. (2002). *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-R)* (4th Edition Revised). Washington DC: American Psychiatric Association.

APA. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (5th Edition). Washington DC: American Psychiatric Association.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T. E. (2002). Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. *British Medical Journal*, *325*(7374), 1212–1213.

Bado, P., Engel, A., de Oliveira-Souza, R., Bramati, I. E., Paiva, F. F., Basilio, R., … Moll, J. (2014). Functional dissociation of ventral frontal and dorsomedial default mode network components during resting state and emotional autobiographical recall. *Human Brain Mapping*, *35*(7), 3302–3313.

Barrera, A., McKenna, P. J., & Berrios, G. E. (2005). Formal thought disorder in schizophrenia: An executive or a semantic deficit? *Psychological Medicine*, *35*(1), 121–132.

Beckmann, C. F., Jenkinson, M., Woolrich, M. W., Behrens, T. E. J., Flitney, D. E., Devlin, J. T., & Smith, S. M. (2006). Applying FSL to the FIAC data: Model-based and model-free analysis of voice and sentence repetition priming. *Human Brain Mapping*, Vol. 27, pp. 380–391.

Benedetti, F., Bernasconi, A., Bosia, M., Cavallaro, R., Dallaspezia, S., Falini, A., … Smeraldi, E. (2009). Functional and structural brain correlates of theory of mind and empathy deficits in schizophrenia. *Schizophrenia Research*, *114*(1–3), 154–160.

Berrios, G. E., & Fernández, L. (1996). Problemas conceptuales en la investigación de trastornos esquizofrénicos. *Revista de La Asociación Española de Neuropsiquiatría.*, *16*(59), 451–468.

Blackwood, D. H. R., Fordyce, A., Walker, M. T., St Clair, D. M., Porteous, D. J., & Muir, W. J. (2001). Schizophrenia and affective disorders - Cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: Clinical and P300 findings in a family. *American Journal of Human Genetics*, *69*(2), 428–433.

Bleuler, E. (1987). *Dementia Praecox, Or, The Group of Schizophrenias*. New York: International Universities Press.

Bluhm, R. L., Miller, J., Lanius, R. A., Osuch, E. A., Boksman, K., Neufeld, R. W. J., … Williamson, P. (2007). Spontaneous low-frequency fluctuations in the BOLD signal in schizophrenic patients: Anomalies in the default network. *Schizophrenia Bulletin*, *33*(4), 1004–1012.

Boonstra, G., Van Haren, N. E. M., Schnack, H. G., Cahn, W., Burger, H., Boersma, M., … Kahn, R. S. (2011). Brain volume changes after withdrawal of atypical antipsychotics in patients with first-episode schizophrenia. *Journal of Clinical Psychopharmacology*, *31*(2), 146–153.

Bourque, F., Van Der Ven, E., & Malla, A. (2011). A meta-analysis of the risk for psychotic disorders among first- and second-generation immigrants. *Psychological Medicine*, *41*(5), 897–910.

Braga, R. M., & Buckner, R. L. (2017). Parallel Interdigitated Distributed Networks within the Individual Estimated by Intrinsic Functional Connectivity. *Neuron*, *95*(2), 457-471.e5.

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. S. (2009). Default-mode brain dysfunction in mental disorders: A systematic review. *Neuroscience and Biobehavioral Reviews*, Vol. 33, pp. 279–296.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, Vol. 1124, pp. 1–38.

Callicott, J. H., Bertolino, A., Mattay, V. S., Langheim, F. J. P., Duyn, J., Coppola, R., … Weinberger, D. R. (2000). Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cerebral Cortex*, *10*(11), 1078–1092.

Callicott, J. H., Mattay, V. S., Verchinski, B. A., Marenco, S., Egan, M. F., & Weinberger, D. R. (2003). Complexity of prefrontal cortical dysfunction in schizophrenia: More than up or down. *American Journal of Psychiatry*, *160*(12), 2209–2215.

Cannon, M., Jones, P. B., & Murray, R. M. (2002). Obstetric complications and schizophrenia: Historical and meta-analytic review. *American Journal of Psychiatry*, Vol. 159, pp. 1080–1092.

Cardno, A. G., & Gottesman, I. I. (2000). Twin studies of schizophrenia: From bow-and-arrow concordances to star wars Mx and functional genomics. *American Journal of Medical Genetics - Seminars in Medical Genetics*, Vol. 97, pp. 12–17.

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: A review of its functional anatomy and behavioural correlates. *Brain*, Vol. 129, pp. 564–583.

Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G., … Whiteford, H. A. (2018). Global epidemiology and burden of schizophrenia: Findings from the global burden of disease study 2016. *Schizophrenia Bulletin*, *44*(6), 1195–1203.

Chua, S. E., & McKenna, P. J. (1995). Schizophrenia - A brain disease? A critical review of structural and functional cerebral abnormality in the disorder. *British Journal of Psychiatry*, Vol. 166, pp. 563–582.

Correction Collins, P. Y., Patel, V., Joestl, S. S., March, D., Insel, T. R., Daar, A. S., … Walport, M. (2011). Grand challenges in global mental health. *Nature*, Vol. 475, pp. 27–30.

Corripio, I., Roldán, A., Sarró, S., McKenna, P. J., Alonso-Solís, A., Rabella, M., … Portella, M. J. (2020). Deep brain stimulation in treatment resistant schizophrenia: A pilot randomized cross-over clinical trial. *EBioMedicine*, *51*.

Cooper, J. E. (1972). *Psychiatric diagnosis in New York and London: A comparative study of mental hospital admissions.*Oxford: Oxford University Press.

Cremers, H., Lee, R., Keedy, S., Phan, K. L., & Coccaro, E. (2016). Effects of escitalopram administration on face processing in intermittent explosive disorder: An fMRI Study. *Neuropsychopharmacology*, *41*(2), 590–597.

Crovitz, H. F., & Schiffman, H. (1974). Frequency of episodic memories as a function of their age. In *Bulletin of the Psychonomic Society* (Vol. 4).

Crow, T. J. (1982). Neurohumoural and Structural Changes in Schizophrenia: Two Dimensions of Pathology. *Progress in Brain Research*, *55*(C), 407–417.

Cuervo-Lombard, C., Lemogne, C., Gierski, F., Béra-Potelle, C., Tran, E., Portefaix, C., … Limosin, F. (2012). Neural basis of autobiographical memory retrieval in schizophrenia. *British Journal of Psychiatry*, *201*(6), 473–480.

Cuesta MJ, Peralta V, & Serrano JF. (2000). Nuevas perspectivas en la psicopatología de los trastornos esquizofrénicos. *Anales Sistema Sanitario Navarra*, *23*, 37–50.

de Achával, D., Villarreal, M. F., Costanzo, E. Y., Douer, J., Castro, M. N., Mora, M. C., … Guinjoan, S. M. (2012). Decreased activity in right-hemisphere structures involved in social cognition in siblings discordant for schizophrenia. *Schizophrenia Research*, *134*(2–3), 171–179.

Del Ser, T., González-Montalvo, J. I., Martínez-Espinosa, S., Delgado-Villapalos, C., & Bermejo, F. (1997). Estimation of premorbid intelligence in Spanish people with the word accentuation test and its application to the diagnosis of dementia. *Brain and Cognition*, *33*(3), 343–356.

DeLisi, L. E. (2008). Reviewing the "Facts about Schizophrenia": A possible or impossible task? *Schizophrenia Research*, Vol. 102, pp. 19–20.

Denny, B. T., Kober, H., Wager, T. D., & Ochsner, K. N. (2012). A meta-analysis of functional neuroimaging studies of self- and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. *Journal of Cognitive Neuroscience*, *24*(8), 1742–1752.

Dixon, L. B., Dickerson, F., Bellack, A. S., Bennett, M., Dickinson, D., Goldberg, R. W., … Kreyenbuhl, J. (2010). The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophrenia Bulletin*, *36*(1), 48–70.

Donaldson, P. H., Rinehart, N. J., & Enticott, P. G. (2015). Noninvasive stimulation of the temporoparietal junction: A systematic review. *Neuroscience and Biobehavioral Reviews*, Vol. 55, pp. 547–572.

Dreher, J. C., Koch, P., Kohn, P., Apud, J., Weinberger, D. R., & Berman, K. F. (2012). Common and differential pathophysiological features accompany comparable cognitive impairments in medication-free patients with schizophrenia and in healthy aging subjects. *Biological Psychiatry*, *71*(10), 890–897.

DuPre, E., Luh, W. M., & Spreng, R. N. (2016). Multi-echo fMRI replication sample of autobiographical memory, prospection and theory of mind reasoning tasks. *Scientific Data*, *3*.

Eddy, C. M. (2016). The junction between self and other? Temporo-parietal dysfunction in neuropsychiatry. *Neuropsychologia*, Vol. 89, pp. 465–477.

Eddy, C. M. (2018). Social cognition and self-other distinctions in neuropsychiatry: Insights from schizophrenia and Tourette syndrome. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, Vol. 82, pp. 69–85.

Fan, J. B., Zhang, C. S., Gu, N. F., Li, X. W., Sun, W. W., Wang, H. Y., … He, L. (2005). Catechol-O-methyltransferase gene Val/Met functional polymorphism and risk of schizophrenia: A large-scale association study plus meta-analysis. *Biological Psychiatry*, *57*(2), 139–144.

Fernández-Corcuera, P., Salvador, R., Monté, G. C., Salvador Sarró, S., Goikolea, J. M., Amann, B., … Pomarol-Clotet, E. (2013). Bipolar depressed patients show both failure to activate and failure to de-activate during performance of a working memory task. *Journal of Affective Disorders*, *148*(2–3), 170–178.

First, M. (2002). *Structured clinical interview for DSM-IV-TR axis I disorders SCID-I: clinical version.* Washington DC: New York State Psychiatric Institute.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–9678.

Fransson, P. (2006). How default is the default mode of brain function?. Further evidence from intrinsic BOLD signal fluctuations. *Neuropsychologia*, *44*(14), 2836–2845.

Fuentes-Claramonte, P., Martín-Subero, M., Salgado-Pineda, P., Alonso-Lana, S., Moreno-Alcázar, A., Argila-Plaza, I., … Salvador, R. (2019). Shared and differential default-mode related patterns of activity in an autobiographical, a self-referential and an attentional task. *PLoS ONE*, *14*(1).

Fuentes-Claramonte, P., Martin-Subero, M., Salgado-Pineda, P., Santo-Angles, A., Argila-Plaza, I., Salavert, J., … Salvador, R. (2020). Brain imaging correlates of self- and other-reflection in schizophrenia. *NeuroImage: Clinical*, *25*.

Fusar-Poli, P., Smieskova, R., Kempton, M. J., Ho, B. C., Andreasen, N. C., & Borgwardt, S. (2013). Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neuroscience and Biobehavioral Reviews*, Vol. 37, pp. 1680–1691.

Garrity, A. G., Pearlson, G. D., McKiernan, K., Lloyd, D., Kiehl, K. A., & Calhoun, V. D. (2007). Aberrant "default mode" functional connectivity in schizophrenia. *American Journal of Psychiatry*, *164*(3), 450–457.

Gilbert, C. D., & Sigman, M. (2007). Brain States: Top-Down Influences in Sensory Processing. *Neuron*, Vol. 54, pp. 677–696.

Gilbert, S. J., Dumontheil, I., Simons, J. S., Frith, C. D., & Burgess, P. W. (2007). Comment on "Wandering minds: the default network and stimulus-independent thought". *Science (New York, N.Y.)*, Vol. 317.

Gomar, J. J., Ortiz-Gil, J., McKenna, P. J., Salvador, R., Sans-Sansa, B., Sarró, S., … Pomarol-Clotet, E. (2011). Validation of the Word Accentuation Test (TAP) as a means of estimating premorbid IQ in Spanish speakers. *Schizophrenia Research*, Vol. 128, pp. 175–176.

Grover, S., Sahoo, S., Rabha, A., & Koirala, R. (2019, June 1). ECT in schizophrenia: A review of the evidence. *Acta Neuropsychiatrica*, Vol. 31, pp. 115–127.

Guerrero-Pedraza, A., McKenna, P. J., Gomar, J. J., Sarró, S., Salvador, R., Amann, B., … Pomarol-Clotet, E. (2012). First-episode psychosis is characterized by failure of deactivation but not by hypo- or hyperfrontality. *Psychological Medicine*, *42*(01), 73–84.

Gusnard, D. A. (2005). Being a self: Considerations from functional imaging. *Consciousness and Cognition*, *14*(4), 679–697.

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews Neuroscience*, *2*(10), 685–694.

Guy, W. (1976). *ECDEU Assessment Manual for Psychopharmacology—Revised*. Rockville, MD: U.S. Department of Health, Education, and Welfare; Public Health Service, Alcohol; Drug Abuse, and Mental Health Administration; National Institute of Mental Health; Psychopharmacology Research Branch; Division of Extramural Research Programs.

Häfner, H., An Der Heiden, W., Behrens, S., Gattaz, W. F., Hambrecht, M., Löffler, W., … Stein, A. (1998). Causes and consequences of the gender difference in age at onset of schizophrenia. *Schizophrenia Bulletin*, Vol. 24, pp. 99–113.

Haijma, S. V., Van Haren, N., Cahn, W., Koolschijn, P. C. M. P., Hulshoff Pol, H. E., & Kahn, R. S. (2013). Brain volumes in schizophrenia: A meta-analysis in over 18 000 subjects. *Schizophrenia Bulletin*, *39*(5), 1129–1138.

Harrison, P. J., & Weinberger, D. R. (2005). Schizophrenia genes, gene expression, and neuropathology: On the matter of their convergence. *Molecular Psychiatry*, Vol. 10, pp. 40–68.

Hill, K., Mann, L., Laws, K. R., Stephenson, C. M. E., Nimmo-Smith, & McKenna, P. J. (2004). Hypofrontality in schizophrenia: A meta-analysis of functional imaging studies. *Acta Psychiatrica Scandinavica*, Vol. 110, pp. 243–256.

Howes, O. D., Montgomery, A. J., Asselin, M. C., Murray, R. M., Valli, I., Tabraham, P., … Grasby, P. M. (2009). Elevated striatal dopamine function linked to prodromal signs of schizophenia. *Archives of General Psychiatry*, *66*(1), 13–20.

Howes, O., McCutcheon, R., & Stone, J. (2015). Glutamate and dopamine in schizophrenia: An update for the 21st century. *Journal of Psychopharmacology*, Vol. 29, pp. 97–115.

Hu, M. L., Zong, X. F., Mann, J. J., Zheng, J. J., Liao, Y. H., Li, Z. C., … Tang, J. S. (2017). A Review of the Functional and Anatomical Default Mode Network in Schizophrenia. *Neuroscience Bulletin*, Vol. 33, pp. 73–84.

Hu, Y., Scheele, D., Becker, B., Voos, G., David, B., Hurlemann, R., & Weber, B. (2016). The Effect of Oxytocin on Third-Party Altruistic Decisions in Unfair Situations: An fMRI Study. *Scientific Reports*, *6*.

Ingvar, D. H., & Franzén, G. (1974). Distribution of cerebral activity in chronic schizophrenia. *The Lancet*, *304*(7895), 1484–1486.

Ino, T., Nakai, R., Azuma, T., Kimura, T., & Fukuyama, H. (2011). Brain Activation During Autobiographical Memory Retrieval with Special Reference to Default Mode Network. *The Open Neuroimaging Journal*, *5*, 14–23.

Jääskeläinen, E., Juola, P., Hirvonen, N., McGrath, J. J., Saha, S., Isohanni, M., … Miettunen, J. (2013). A systematic review and meta-analysis of recovery in schizophrenia. *Schizophrenia Bulletin*, *39*(6), 1296–1306.

Jablensky, A. (2010). El concepto diagnóstico de la esquizofrenia: su historia, evolución y perspectivas futuras. *Dialogues in Clinical Neuroscience*, *12*(3), 271–287.
Jaspers, K. (2006). *Psicopatología General*. Ciudad de México: Fondo de Cultura Económica.

Jauhar, S., McKenna, P. J., Radua, J., Fung, E., Salvador, R., & Laws, K. R. (2014). Cognitive-behavioural therapy for the symptoms of schizophrenia: Systematic review and meta-analysis with examination of potential bias. *British Journal of Psychiatry*, Vol. 204, pp. 20–29.

Johnstone, E. C., Frith, C. D., Crow, T. J., Husband, J., & Kreel, L. (1976). Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *The Lancet*, *308*(7992), 924–926.

Jones, S. R., & Fernyhough, C. (2007). A new look at the neural diathesis-stress model of schizophrenia: The primacy of social-evaluative and uncontrollable situations. *Schizophrenia Bulletin*, *33*(5), 1171–1177.

Jongsma, H. E., Turner, C., Kirkbride, J. B., & Jones, P. B. (2019). International incidence of psychotic disorders, 2002–17: a systematic review and meta-analysis. *The Lancet Public Health*, *4*(5), e229–e244.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261–276.

Kay, Stanley R., Fiszbein, A., Vital-Herne, M., & Fuentes, L. S. (1990). The positive and negative syndrome scale-spanish adaptation. *Journal of Nervous and Mental Disease*, *178*(8), 505–517.

Kopelman, M. D., Wilson, B. A., & Baddeley, A. D. (1989). The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. *Journal of Clinical and Experimental Neuropsychology : Official Journal of the International Neuropsychological Society*, *11*(5), 724–744.

Kraepelin, E. (1909). *Dementia praecox. Trans in J. Cutting and m. shepherd (Eds). (1987), The clinical roots pf the schizophrenia concept*. Cambridge: Cambridge University Press.

Kreyenbuhl, J., Buchanan, R. W., Dickerson, F. B., & Dixon, L. B. (2010). The schizophrenia patient outcomes research team (PORT): Updated treatment recommendations 2009. *Schizophrenia Bulletin*, Vol. 36, pp. 94–103.

Kronbichler, L., Tschernegg, M., Martin, A. I., Schurz, M., & Kronbichler, M. (2017). Abnormal Brain Activation during Theory of Mind Tasks in Schizophrenia: A Meta-Analysis. *Schizophrenia Bulletin*, *43*(6), 1240–1250.

Landin-Romero, R., McKenna, P. J., Salgado-Pineda, P., Sarró, S., Aguirre, C., Sarri, C., … Pomarol-Clotet, E. (2015). Failure of deactivation in the default mode network: a trait marker for schizophrenia? *Psychological Medicine*, *45*(6), 1315–1325.

Laursen, T. M., Nordentoft, M., & Mortensen, P. B. (2014). Excess early mortality in schizophrenia. *Annual Review of Clinical Psychology*, Vol. 10, pp. 425–448.

Lawrie, S. M., & Abukmeil, S. S. (1998). Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. *British Journal of Psychiatry*, Vol. 172, pp. 110–120.

Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Örey, D., Richter, F., … Davis, J. M. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. *The Lancet*, *382*(9896), 951–962.

Leung, M., Cheung, C., Yu, K., Yip, B., Sham, P., Li, Q., … McAlonan, G. (2011). Gray matter in first-episode schizophrenia before and after antipsychotic drug treatment. Anatomical likelihood estimation meta-analyses with sample size weighting. *Schizophrenia Bulletin*, *37*(1), 199–211.

Lewine, R. R., Fogg, L., & Meltzer, H. Y. (1983). Assessment of negative and positive symptoms in schizophrenia. *Schizophrenia Bulletin*, *9*(3), 368–376.

Liddle, P. F. (1987). Schizophrenic syndromes, cognitive performance and neurological dysfunction. *Psychological Medicine*, *17*(1), 49–57.

Liu, H., Kaneko, Y., Ouyang, X., Li, L., Hao, Y., Chen, E. Y. H., … Liu, Z. (2012). Schizophrenic patients and their unaffected siblings share increased resting-state connectivity in the task-negative network but not its anticorrelated task-positive network. *Schizophrenia Bulletin*, *38*(2), 285–294.

Macher, J. P. (2010). Schizophrenia. *Dialogues in Clinical Neuroscience*, Vol. 12, p. 265.

Madre, M., Pomarol-Clotet, E., McKenna, P., Radua, J., Ortiz-Gil, J., Panicali, F., … Amann, B. L. (2013). Brain functional abnormality in schizo-affective disorder: An fMRI study. *Psychological Medicine*, *43*(1), 143–153.

Makowski, C. S., Lepage, M., & Harvey, P. O. (2016). Functional neural correlates of social approval in schizophrenia. *Social Cognitive and Affective Neuroscience*, *11*(3), 445–457.

Malla, A., & Payne, J. (2005). First-episode psychosis: Psychopathology, quality of life, and functional outcome. *Schizophrenia Bulletin*, Vol. 31, pp. 650–671.

Manoach, D. S., Press, D. Z., Thangaraj, V., Searl, M. M., Goff, D. C., Halpern, E., … Warach, S. (1999). Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. *Biological Psychiatry*, *45*(9), 1128–1137.

Marder, S. R., & Cannon, T. D. (2019). Schizophrenia. *New England Journal of Medicine*, *381*(18), 1753–1761.

Mars, R. B., Sallet, J., Schüffelgen, U., Jbabdi, S., Toni, I., & Rushworth, M. F. S. (2012). Connectivity-based subdivisions of the human right "temporoparietal junction area": Evidence for different areas participating in different cortical networks. *Cerebral Cortex*, *22*(8), 1894–1903.

Martin-Subero, M., Fuentes-Claramonte, P., Salgado-Pineda, P., Salavert, J., Arevalo, A., Bosque, C., … Pomarol-Clotet, E. (2019). Autobiographical memory and default mode network function in schizophrenia: an fMRI study. *Psychological Medicine*, 1–8.

Marwaha, S., & Johnson, S. (2004). Schizophrenia and employment: A review. *Social Psychiatry and Psychiatric Epidemiology*, Vol. 39, pp. 337–349.

Marwaha, S., Johnson, S., Bebbington, P., Stafford, M., Angermeyer, M. C., Brugha, T., … Toumi, M. (2007). Rates and correlates of employment in people with schizophrenia in the UK, France and Germany. *British Journal of Psychiatry*, *191*(JULY), 30–37.

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews*, Vol. 30, pp. 67–76.

McKiernan, K. A., D'Angelo, B. R., Kaufman, J. N., & Binder, J. R. (2006). Interrupting the "stream of consciousness": An fMRI investigation. *NeuroImage*, *29*(4), 1185–1191.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function*, Vol. 214, pp. 655–667.

Milanovic, S. M., Thermenos, H. W., Goldstein, J. M., Brown, A., Gabrieli, S. W., Makris, N., … Seidman, L. J. (2011). Medial prefrontal cortical activation during working memory differentiates schizophrenia and bipolar psychotic patients: A pilot FMRI study. *Schizophrenia Research*, Vol. 129, pp. 208–210.

Minzenberg, M. J., Laird, A. R., Thelen, S., Carter, C. S., & Glahn, D. C. (2009). Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Archives of General Psychiatry*, *66*(8), 811–822.

Mirnics, K., & Lewis, D. A. (2001). Genes and subtypes of schizophrenia. *Trends in Molecular Medicine*, Vol. 7, pp. 281–283.

Modinos, G., Ormel, J., & Aleman, A. (2009). Activation of anterior insula during self-reflection. *PloS One*, *4*(2), e4618.

Mueser, K. T., & McGurk, S. R. (2004). Schizophrenia. *Lancet*, *363*(9426), 2063–2072.

Murray, R. M., Lewis, S. W., & Reveley, A. M. (1985). Towards an aetiological classification of schizophrenia. *The Lancet*, *325*(8436), 1023–1026.

Nekovarova, T., Fajnerova, I., Horacek, J., & Spaniel, F. (2014). Bridging disparate symptoms of schizophrenia: A triple network dysfunction theory. *Frontiers in Behavioral Neuroscience*, *8*(171), 1-10.

Oertel-Knöchel, V., Reinke, B., Hornung, A., Knöchel, C., Matura, S., Knopf, M., … Linden, D. E. J. (2012). Patterns of autobiographical memory in bipolar disorder examined by psychometric and functional neuroimaging methods. *Journal of Nervous and Mental Disease*, *200*(4), 296–304.

Organización Mundial de la Salud. (1995). *Clasificación estadística internacional de enfermedades y problemas relacionados con la salud. (CIE-10)*. Washington DC: Organización Panamericana de la Salud.

Owen, M. J., Sawa, A., & Mortensen, P. B. (2016). Schizophrenia. *The Lancet*, Vol. 388, pp. 86–97.

Pardiñas, A. F., Holmans, P., Pocklington, A. J., Escott-Price, V., Ripke, S., Carrera, N., … Walters, J. T. R. (2018). Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nature Genetics*, *50*(3), 381–389.

Pomarol-Clotet, E., Salvador, R., Sarro, S., Gomar, J., Vila, F., Martinez, A., Guerrero, A., Ortiz-Gil, J., Sans-Sansa, B., Capdevila, A., et al., Pomarol-Clotet, E., Salvador, R., Sarró, S., Gomar, J., Vila, F., … McKenna, P. J. (2008). Failure To Deactivate in the Prefrontal Cortex in Schizophrenia: Dysfunction of the Default Mode Network? *Psychological Medicine*, *38*(8), 1185–1193.

Raichle, M E. (2015). The brain's default mode network. *Annu Rev Neurosci*, *38*, 433–447.

Raichle, Marcus E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(2), 676–682.

Raz, S., & Raz, N. (1990). Structural Brain Abnormalities in the Major Psychoses: A Quantitative Review of the Evidence From Computerized Imaging. *Psychological Bulletin*, *108*(1), 93–108.

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K. H., Holmans, P. A., … O'Donovan, M. C. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, *511*(7510), 421–427.

Rodríguez-Cano, E., Sarró, S., Monté, G. C., Maristany, T., Salvador, R., McKenna, P. J., & Pomarol-Clotet, E. (2014). Evidence for structural and functional abnormality in the subgenual anterior cingulate cortex in major depressive disorder. *Psychological Medicine*, *44*(15), 3263–3273.

Rosen, W. G., Mohs, R. C., Johns, C. A., Small, N. S., Kendler, K. S., Horvath, T. B., & Davis, K. L. (1984). Positive and negative symptoms in schizophrenia. *Psychiatry Research*, *13*(4), 277–284.

Salavert, J., Ramos-Quiroga, J. A., Moreno-Alcázar, A., Caseras, X., Palomar, G., Radua, J., … Pomarol-Clotet, E. (2018). Functional Imaging Changes in the Medial Prefrontal Cortex in Adult ADHD. *Journal of Attention Disorders*, *22*(7), 679–693.

Salgado-Pineda, P., Fakra, E., Delaveau, P., McKenna, P. J., Pomarol-Clotet, E., & Blin, O. (2011). Correlated structural and functional brain abnormalities in the default mode network in schizophrenia patients. *Schizophrenia Research*, *125*(2–3), 101–109.

Salvador, R., Anguera, M., Gomar, J. J., Bullmore, E. T., & Pomarol-Clotet, E. (2010). Conditional mutual information maps as descriptors of net connectivity levels in the brain. *Frontiers in Neuroinformatics*, *4*, (115), 1-8.

Schneider, F. C., Royer, A., Grosselin, A., Pellet, J., Barral, F. G., Laurent, B., … Lang, F. (2011). Modulation of the default mode network is task-dependant in chronic schizophrenia patients. *Schizophrenia Research*, *125*(2–3), 110–117.

Schneider, K. (1950). *Klinische Psychopathologie*. Stuttgart: Thieme.

Schwab, S. G., Knapp, M., Mondabon, S., Hallmayer, J., Borrmann-Hassenbach, M., Albus, M., … Wildenauer, D. B. (2003). Support for association of schizophrenia with genetic variation in the 6p22.3 gene, dysbindin, in sib-pair families with linkage and in an additional sample of triad families. *American Journal of Human Genetics*, *72*(1), 185–190.

Shorter, E. (2015). The history of nosology and the rise of the diagnostic and statistical manual of mental disorders. *Dialogues in Clinical Neuroscience*, *17*(1), 59–67.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*(SUPPL. 1).

Spreng, R. N., & Grady, C. L. (2010). Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *Journal of Cognitive Neuroscience*, *22*(6), 1112–1123.

Stilo, S. A., & Murray, R. M. (2010). La epidemiología de la esquizofrenia: Reemplazar el dogma con el conocim. *Dialogues in Clinical Neuroscience*, *12*(3), 305–315.

Stilo, S. A., & Murray, R. M. (2019). Non-Genetic Factors in Schizophrenia. *Current Psychiatry Reports*, Vol. 21.

Strange, B. A., & Dolan, R. J. (2007). β-adrenergic modulation of oddball responses in humans. *Behavioral and Brain Functions*, *3*.

Strauss, J. S., Carpenter, W. T., & Bartko, J. J. (1974). The diagnosis and understanding of schizophrenia. Summary and conclusions. *Schizophrenia Bulletin*, pp. 70–80.

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a Complex Trait: Evidence from a Meta-analysis of Twin Studies. *Archives of General Psychiatry*, *60*(12), 1187–1192.

Svoboda, E., McKinnon, M. C., & Levine, B. (2006). The functional neuroanatomy of autobiographical memory: A meta-analysis. *Neuropsychologia*, Vol. 44, pp. 2189–2208.

Tan, H. Y., Sust, S., Buckholtz, J. W., Mattay, V. S., Meyer-Lindenberg, A., Egan, M. F., … Callicott, J. H. (2006). Dysfunctional prefrontal regional specialization and compensation in schizophrenia. *American Journal of Psychiatry*, *163*(11), 1969–1977.

Tandon, R., Keshavan, M. S., & Nasrallah, H. A. (2008). Schizophrenia, "Just the Facts" What we know in 2008. 2. Epidemiology and etiology. *Schizophrenia Research*, *102*(1–3), 1–18.

Thakkar, K. N., Peterman, J. S., & Park, S. (2014). Altered brain activation during action imitation and observation in schizophrenia: A translational approach to investigating social dysfunction in schizophrenia. *American Journal of Psychiatry*, *171*(5), 539–548.

Thomas Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., … Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165.

Thompson, P. A., & Meltzer, H. Y. (1993). Positive, negative, and disorganisation factors from the schedule for affective disorders and schizophrenia and the present state examination. A three-factor solution. *British Journal of Psychiatry*, *163*(SEPT.), 344–351.

Tiihonen, J., Mittendorfer-Rutz, E., Majak, M., Mehtälä, J., Hoti, F., Jedenius, E., … Taipale, H. (2017). Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. *JAMA Psychiatry*, *74*(7), 686–693.

Tiwari, A. K., Zai, C. C., Müller, D. J., & Kennedy, J. L. (2010). Genética en la esquizofrenia: ¿dónde estamos y qué viene? *Dialogues in Clinical Neuroscience*, *12*(3), 289–303.

Uchida, H., Takeuchi, H., Graff-Guerrero, A., Suzuki, T., Watanabe, K., & Mamo, D. C. (2011). Dopamine D2 receptor occupancy and clinical effects: A systematic review and pooled analysis. *Journal of Clinical Psychopharmacology*, Vol. 31, pp. 497–502.

van Erp, T. G. M., Walton, E., Hibar, D. P., Schmaal, L., Jiang, W., Glahn, D. C., … Turner, J. A. (2018). Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. *Biological Psychiatry*, *84*(9), 644–654.

Van Horn, J. D., & McManus, I. C. (1992). Ventricular enlargement in schizophrenia. A meta-analysis of studies of the ventricle:brain ratio (VBR). *British Journal of Psychiatry*, *160*(MAY.), 687–697.

van Veluw, S. J., & Chance, S. A. (2014). Differentiating between self and others: An ALE meta-analysis of fMRI studies of self-recognition and theory of mind. *Brain Imaging and Behavior*, Vol. 8, pp. 24–38.

Vassos, E., Pedersen, C. B., Murray, R. M., Collier, D. A., & Lewis, C. M. (2012). Meta-analysis of the association of urbanicity with schizophrenia. *Schizophrenia Bulletin*, *38*(6), 1118–1123.

Walker, E. F., & Diforio, D. (1997). Schizophrenia: A Neural Diathesis-Stress Model. *Psychological Review*, *104*(4), 667–685.

Weinberger, D. R., Berman, K. F., & Zec, R. F. (1986). Physiologic Dysfunction of Dorsolateral Prefrontal Cortex in Schizophrenia: I. Regional Cerebral Blood Flow Evidence. *Archives of General Psychiatry*, *43*(2), 114–124.

Weinberger, D. R., Egan, M. F., Bertolino, A., Callicott, J. H., Mattay, V. S., Lipska, B. K., … Goldberg, T. E. (2001). Prefrontal neurons and the genetics of schizophrenia. *Biological Psychiatry*, *50*(11), 825–844.

Whitfield-Gabrieli, S., & Ford, J. M. (2012). Default mode network activity and connectivity in psychopathology. *Annual Review of Clinical Psychology*, Vol. 8.

Whitfield-Gabrieli, S., Thermenos, H. W., Milanovic, S., Tsuang, M. T., Faraone, S. V., McCarley, R. W., … Seidman, L. J. (2009). Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(4), 1279–1284.

Williams, N. M., Preece, A., Spurlock, G., Norton, N., Williams, H. J., Zammit, S., … Owen, M. J. (2003). Support for genetic variation in neuregulin 1 and susceptibility to schizophrenia. *Molecular Psychiatry*, *8*(5), 485–487.

Wright, I. C., Rabe-Hesketh, S., Woodruff, P. W. R., David, A. S., Murray, R. M., & Bullmore, E. T. (2000). Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry*, *157*(1), 16–25.

Wu, D., & Jiang, T. (2020). Schizophrenia-related abnormalities in the triple network: a meta-analysis of working memory studies. *Brain Imaging and Behavior*, *14*(4), 971–980.

Zhou, Y., Liang, M., Tian, L., Wang, K., Hao, Y., Liu, H., … Jiang, T. (2007). Functional disintegration in paranoid schizophrenia using resting-state fMRI. *Schizophrenia Research*, *97*(1–3), 194–205.

ANEXO 1

Artículo publicado en la revista PLOS ONE

Shared and differential default-mode related patterns of activity in an autobiographical, a self-referential and an attentional task

Referencia:

Fuentes-Claramonte, P., Martín-Subero, M., Salgado-Pineda, P., Alonso-Lana, S., Moreno-Alcázar, A., Argila-Plaza, I., … Salvador, R. (2019). Shared and differential default-mode related patterns of activity in an autobiographical, a self-referential and an attentional task. *PLoS ONE*, *14*(1).

Acceso Pubmed: 10.1371/journal.pone.0209376.

Shared and differential default-mode related patterns of activity in an autobiographical, a self-referential and an attentional task

Paola Fuentes-Claramonte[1,2], Marta Martín-Subero[1,2,3], Pilar Salgado-Pineda[1,2], Silvia Alonso-Lana[1,2], Ana Moreno-Alcázar[2,4,5], Isabel Argila-Plaza[1], Aniol Santo-Angles[1], Anton Albajes-Eizagirre[1,2], Maria Anguera-Camós[1], Antoni Capdevila[6,7], Salvador Sarró[1,2], Peter J. McKenna[1,2], Edith Pomarol-Clotet[1,2]*, Raymond Salvador[1,2]

1 FIDMAG Germanes Hospitalàries Research Foundation, Barcelona, Spain, 2 CIBERSAM (Centro de Investigación Biomédica en Red de Salud Mental), Barcelona, Spain, 3 Universitat Autònoma de Barcelona, Barcelona, Spain, 4 Institut de Neuropsiquiatria i Addiccions, Centre Fòrum Research Unit, Parc de Salut Mar, Barcelona, Spain, 5 IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain, 6 Radiology Unit, Hospital de la Santa Creu i Sant Pau (HSCSP), Barcelona, Spain, 7 CIBER-BBN (Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina), Barcelona, Spain

* epomarol-clotet@fidmag.com

Abstract

The default-mode network (DMN) comprises a set of brain regions that show deactivations during performance of attentionally demanding tasks, but also activation during certain processes including recall of autobiographical memories and processing information about oneself, among others. However, the DMN is not activated in a homogeneous manner during performance of such tasks, so it is not clear to what extent its activation patterns correspond to deactivation patterns seen during attention-demanding tasks. In this fMRI study we compared patterns of activation in response to an autobiographical memory task to those observed in a self/other-reflection task, and compared both to deactivations observed during the n-back working memory task. Autobiographical recall and self-reflection activated several common DMN areas, which were also deactivated below baseline levels by the n-back task. Activation in the medial temporal lobe was seen during autobiographical recall but not the self/other task, and right angular gyrus activity was specifically linked to other-reflection. ROI analysis showed that most, but not all DMN regions were activated above baseline levels during the autobiographical memory and self-reflection tasks. Our results provide evidence for the usefulness of the autobiographical memory task to study DMN activity and support the notion of interacting subsystems within this network.

Introduction

The default mode network (DMN) is a set of brain regions that typically show synchronized activity in a variety of behavioral states including resting states but also tasks with different cognitive requirements [1–4]. Its core regions include the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC)/precuneus, and the angular gyrus in the inferior parietal

120

lobule. Parts of the temporal lobe, including its neocortex and the hippocampus and parahippocampus, are often also considered part of the network [5,6] while some specific portions of the ventrolateral (VLPFC) and dorsolateral prefrontal cortex (DLPFC), usually extending from the mPFC, have been included as well [7,8]. A considerable amount of research about the DMN has been focused on its deactivation during the performance of tasks demanding externally oriented attention (i.e. greater activity at rest or fixation than during task execution, [3,5,9,10]) that led to its initial identification as a "task-negative" network [1]. However, later work has shown its involvement in several cognitive functions [10], and its specific role is presently uncertain, with proposals ranging from low-level 'background' monitoring of the environment to internal mentation detached from the outside world, construction of mental simulations or maintenance of the self-concept [5,11]. Changes in DMN activity have also been linked to attentional fluctuations during task performance [12–14].

Highly relevant to theories of DMN function is the finding that, while many cognitive tasks produce deactivation in the DMN, others increase its activity in one or more of its parts [10]. One such task is autobiographical recall, i.e. the conscious recollection of relatively rich images from a person's past, typically evoked experimentally by a cue word or phrase. A meta-analysis of PET and fMRI studies of autobiographical recall by Svoboda et al. [15] found activations corresponding quite closely to several regions of the DMN, including the medial frontal cortex, the PCC/precuneus, the inferior parietal cortex and the hippocampus. Other studies have shown similar activation patterns [16–22]. Convergent evidence from lesion and EEG studies also highlight the involvement of DMN areas in autobiographical memory [23,24].

The DMN is also engaged in tasks that, similar to autobiographical memory, share the need to process self-relevant information, including self-reflection, making social and emotional judgments about oneself and others, envisioning the future or performing theory of mind operations [5,6,17,22]. However, despite the similarity between DMN regions and regions activated by self-reference tasks, the two are not identical as there are brain areas that also respond differentially, for example portions of the ventral mPFC or the precuneus [20,25–27]. Similarly, although it has not been studied yet, it is quite likely that the extent of the overlap between regions activated in self referential tasks and regions deactivated by standard cognitive tasks is also incomplete. More detailed consideration of the brain activations that take place in response to self-reference and other tasks which activate the DMN might also be desirable because the control conditions used in such tasks are often attention-demanding (e.g., semantic processing, arithmetic tasks), and so seem capable of producing DMN deactivation. In such circumstances it becomes unclear whether activations seen in DMN areas will be a result of activation over baseline levels in the self-relevant conditions, or rather reflect deactivation of these same regions in the control conditions, or a combination of both [3]. For example, Holt et al. [28] found significant differences in the mPFC between a self-reflection and an affect-labeling condition. However, these differences arose from a deactivation in the affect-labeling condition rather than activation in self-reflection: in the latter, activity was close to the baseline level (fixation). A similar result was found in Jenkins & Mitchell [29] for the same region. Detailed examination of the activation and deactivation patterns in different DMN regions is needed to clarify this question. In this sense, note that baseline conditions in most cognitive tasks consist of rest or fixation periods, which are examples of relatively unconstrained and low-demanding tasks against which activation or deactivation is tested. Thus, the terms 'baseline' and 'rest' are herein used to refer to those low-demanding tasks, during which several cognitive processes are probably still taking place.

Another aspect that warrants further exploration in the study of the DMN is the heterogeneity found within the network: some authors propose that the DMN is organized into subsystems linked to specific roles that interact with each other: a medial temporal lobe (hippocampal)

121

subsystem associated with autobiographical and episodic memory and a dorsal mPFC subsystem, also including the lateral temporal and inferior parietal cortex, linked to mentalizing and social processing [5,26,27,30]. This hypothesis stems from the observation that the dorsal mPFC and the medial temporal lobes do not show functional connectivity with each other but are both connected to core DMN regions, which would serve as hubs within the network, coordinating the associated subsystems [5,31]. Recent findings have shown that DMN subsystems can be identified by functional connectivity in individual brains, which have supported the existence of two subnetworks within the DMN, only one of which is functionally coupled with the hippocampal formation [32]. Such findings highlight the importance of studying the patterns of activation of the different DMN regions in response to different task conditions. Previous studies that have directly compared to what extent different self-relevant tasks overlap or differ in brain activation have found support for these two subsystems, with the medial temporal lobe linked to episodic memory, future planning and prospection, while the dorsal subsystem has been associated to mentalizing, making self-referential decisions, and theory of mind [22,26,31,33]. These studies also showed that midline structures were commonly activated in all self-referential tasks. Less studied has been, however, the degree of overlap between the activation of DMN areas in self-reference tasks and their deactivation in classical attention-demanding paradigms.

In the present study, we aim to (1) validate an autobiographical memory task as a suitable paradigm for studies targeting the DMN, and (2) examine activations and deactivations during performance of this autobiographical memory task and a self/other reflection task. We will compare these with an attention-demanding task, the n-back paradigm, which has been consistently found to produce deactivation in the DMN [34–36]. We expect that midline DMN regions (mPFC, PCC) will be activated in autobiographical memory and self reflection, but deactivated in the n-back task. We also expect the hippocampus to be preferentially activated for autobiographical memory and the inferior parietal cortex to be preferentially activated for self-reflection, while both will be deactivated in the n-back. Activity in these regions will be analyzed to explore whether it corresponds to activations or deactivations with respect to baseline levels which consist of fixation periods. An important concern that arises in studies about the DMN is that memory or self-reflection processes might be engaged not only during the task, but also during fixation, which may prevent the observation of differences between them [15]. For this reason, our study will use two different analysis approaches: first, a conventional whole-brain analysis comparing each condition of interest with a matched control condition that involves similar perceptual and linguistic demands; and second, a ROI analysis that tests activation levels against a fixation baseline. This will allow us to identify the brain regions involved in each task and examine which conditions drive activation and deactivation in the DMN.

Materials and methods

Participants

The sample consisted of 37 healthy volunteers recruited from the community. Exclusion criteria included left-handedness, neurological illness, present or past diagnosis of psychiatric disorder, first-degree relatives with a psychiatric diagnosis, alcohol or substance abuse or dependence (excluding nicotine) in the last year, head trauma with loss of consciousness, and general exclusion criteria for MRI such as presence of metals within the body or pregnancy. One participant was excluded due to anatomical abnormality found in the MRI scan, leaving 36 to be included in the analyses. Two participants were excluded from the autobiographical memory task and 3 participants were excluded from the self-reflection task due to excessive

122

Table 1. Demographic characteristics of the final samples for each task.

	Autobiographical memory task	Self-reflection task	N-back task
Total N	34	33	36
Mean age (SD)	41.97 (11.63)	41.67 (11.67)	41.19 (11.99)
Age range	23–65	23–65	18–65
Gender	19 M / 15 F	19 M / 14 F	20 M / 16 F

head movement. Demographic characteristics of the final samples used for the three tasks are shown in Table 1.

All participants gave written informed consent prior to participation in accordance to the Declaration of Helsinki. All the study procedures had been previously approved by the Clinical Research Ethics Committee of the Sisters Hospitallers (Comité de Ética de Investigación Clínica de las Hermanas Hospitalarias). Participants received a gift-card as a compensation for their participation in the study.

Experimental tasks

Autobiographical memory task. The task used in the present work was designed using as a reference the paradigm applied by Oertel-Knöchel et al. [21] which was modified to allow direct comparison between a condition where an autobiographical memory was evoked, and an otherwise similar control condition where no memory was evoked. Immediately before the fMRI session, each participant was interviewed by one of the researchers to obtain autobiographical memory-evoking and non-evoking stimuli. For this, they were administered prompts from the Autobiographical Memory Interview (AMI) [37], which take the form of phrases, and the Crovitz test [38], which take the form of words. During the interview, participants were required to provide memories of specific incidents from their past based on these prompts; between four and six memories for each time period were provided: childhood (until age 11), adolescence (age 12–18), adulthood (age 19 and above) and recent events (the last year). For each memory, a pair of two words was constructed in agreement with the participant, able to evoke its associated memory upon presentation. This interview lasted approximately 1 hour. The stimuli finally used in the fMRI paradigm consisted of groups of three words personalized for each participant. The first word referred to one of four possible time periods ("childhood", "adolescence", "adult" and "recently"), and the other two words corresponded to one of the pairs that had evoked autobiographical memories in the prior testing (e.g. "childhood grandmother cake", "adult car robbery"). Following the scoring system of the AMI, to be included as stimuli, memories were required to be given the maximum score of 3, based on the descriptive richness of the account of the incident and its specificity in time and place.

For the control condition, we generated similar groups of three words for each participant that did not correspond to any of the retrieved memories and for which no association with a specific memory was reported. This control condition differs from Oertel-Knöchel et al.'s [21] original paradigm, where the control condition was a semantic completion task. It was chosen to be similar to the autobiographical condition at the perceptual and linguistic levels (e.g. semantic word processing), but unable to evoke personal memories.

The paradigm was a block design with 10 blocks of control stimuli alternated with 10 blocks of autobiographical stimuli; all blocks lasted 20s. Each block contained two word groups of control and autobiographical stimuli from the same time period, lasting 10s each. Between blocks, a fixation cross was presented during 16s providing the baseline (total baseline time = 5

123

min and 4 s). Participants were instructed to silently read the words and to recall the memory associated with them if there was one.

Self-reflection task. This task was adapted from the one described in Modinos et al. [39] and consisted of a personalized self-other judgment task. Before scanning, participants were asked to choose an acquaintance to think about inside the scanner. The chosen individual had to be familiar to the participant but not too close to avoid eliciting strong feelings towards them (for example, a classmate or a co-worker).

During the task, participants viewed a series of affirmations about themselves (self), an acquaintance (other), or about general knowledge (facts)–the last was the control condition. They had to respond with a button press indicating whether they considered the sentence to be true or false. In the self condition, the sentences referred to personal qualities, attributes or attitudes, such as "In general, I like order" or "I am a tense or very nervous person". Similarly, in the other condition sentences referred to the personality traits and behavior of the chosen acquaintance. Examples of sentences here were "OTHER often makes decisions without thinking" or "OTHER usually has very good ideas" (OTHER being replaced in the task by the chosen person's name). In the facts condition, sentences referred to general knowledge such as "A decade is a period of ten years" or "Insects only have four legs". In the self and other conditions half of the sentences had a positive valence and half had a negative valence, while in the facts condition half of the sentences were true and the other half were false.

The task consisted of 54 trials (18 per condition) arranged in a block design. Each block started with an instruction screen indicating the condition type ("Sentences about me", "Sentences about OTHER" and "Sentences about facts"), which lasted 3s. After a 1s delay, three trials were presented, each lasting 9s, where the sentence appeared in the center of the screen and the options "Yes" and "No" appeared at the bottom-right and bottom-left corners, respectively, to act as a reminder of the required response ("Yes" with the right index finger, and "No" with the left index finger). Trials were separated by a 1s blank screen. After three trials, the next block started, with a total of 6 blocks per condition. Every 3 blocks there was a baseline period of 16s in which a fixation cross was presented (total baseline time = 1 min 20 s). Block order was pseudorandomized, with each of the three conditions occurring once between baseline periods.

N-back task. The task consisted of two levels of memory load (1-back and 2-back) presented in a blocked design manner; in the 1-back condition, participants had to respond with a key press when the letter shown on the screen was the same as the one that was presented immediately before, whereas in the 2-back condition they had to respond when the letter was the same as that presented two letters previously. Each block consisted of 24 letters which were shown every two seconds (1 second on, 1 second off) and all blocks contained 5 repetitions (1-back and 2-back depending on the block) located randomly within the block. In order to identify which task had to be performed, letters were shown in green in the 1-back blocks and in red in the 2-back blocks. Four 1-back and four 2-back blocks were presented in an interleaved way, and between them, a baseline stimulus (an asterisk flashing with the same frequency as the letters) was presented for 16 seconds (total baseline time = 1 min 52 s). All individuals went through a training session before entering the scanner.

All tasks were administered in the same fMRI session and in the same order (n-back, autobiographical memory and self-reflection) to ensure the procedure was identical for all participants. During the fMRI session, participants were asked whether they had been attending the task and stimuli after each task. The three experimental tasks were programmed with the Tcl programming language and executed in an Alienware (Alienware Corporation, Miami, Florida, USA) laptop running on Windows 10. In the scanner, stimuli were presented on Visual-System goggles mounted on the head coil, and responses were made and registered with the

124

MRI-compatible response device Response-grip. Stimulus presentation was synchronized with the scanner through a SyncBox (VisualSystem goggles, Response-grip and SyncBox are manufactured by NordicNeurolab, AS, Bergen, Norway).

Image acquisition

Images were acquired with a 3T Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands). Functional data were acquired using a T2*-weighted echo-planar imaging (EPI) sequence with the following acquisition parameters: TR = 2000ms, TE = 30ms, Flip angle = 78°, in-plane resolution = 3 × 3mm, FOV = 240mm, slice thickness = 3mm, inter-slice gap = 1mm. The autobiographical memory task consisted of 370 volumes, the self-reflection task consisted of 364 volumes, and the n-back task consisted of 266 volumes. Slices (32 per volume) were acquired with an ascending order parallel to the AC-PC plane. The first 10 volumes were discarded to avoid T1 saturation effects. Before the functional sequences, a high-resolution anatomical 3D volume was acquired using a TFE (Turbo Field Echo) sequence for anatomical reference and inspection (TR = 8.15ms; TE = 3.73ms; Flip angle = 8°; voxel size = 0.9375 × 0.9375mm; slice thickness = 1mm; slice number = 160; FOV = 240mm).

Image preprocessing and analysis

Preprocessing and analyses were carried out with the FEAT module included in the FSL (FMRIB Software Library) software [40]. Preprocessing was identical for the three paradigms and included motion correction (using the MCFLIRT algorithm with 6 degrees of freedom) and co-registration and normalization to a common stereotactic space (Montreal Neurological Institute template with 2 × 2 × 2mm resolution) using linear transformations with 12 degrees of freedom. Before group analyses, normalized images were spatially filtered with a Gaussian filter (FWHM = 5mm). Individuals with an estimated maximum absolute movement >3.0mm or an average absolute movement >0.3mm were excluded from analyses to minimize unwanted movement-related effects.

Statistical analyses were performed by means of General Linear Models (GLMs) designed independently for each task. For the autobiographical memory task two regressors of interest were defined at the single-subject level analysis (memory blocks vs. control blocks) and the GLM was fitted to generate activation maps of each condition compared to baseline and for the comparison between conditions. For the n-back task, the same procedure was applied, defining the two task conditions as regressors of interest (1-back and 2-back). Given our interest in the deactivation of DMN regions in this task, we specifically compared the 2-back condition with baseline. For the self-reflection task, three regressors of interest were defined in the GLMs corresponding to the three task conditions (self, other, facts). Instruction screens were modeled through an additional nuisance regressor. GLMs were fitted to generate activation maps for each of the three conditions of interest compared to baseline and for the comparisons between conditions (self vs. facts, other vs. facts, self vs. other).

For the three models, temporal derivatives for each regressor of interest, as well as movement parameters (six in total, three rotations and three translations) were also included as additional regressors. Fixation periods were not modeled and thus acted as implicit baseline (i.e. to compare a condition of interest of any given task with its baseline periods, the average BOLD signal from all the baseline periods across the whole task is subtracted from that of the blocks corresponding to the condition of interest). Images were high-pass filtered with a 130s cutoff. At the group level, activations and deactivations were assessed with one-sample t-tests on the contrasts defined at the subject level with mixed-effects models [41]. Statistical tests were carried out at the cluster level with a corrected $p < 0.05$ using Gaussian random field

125

methods and considering a gray matter mask to restrict analyses to gray matter areas. A threshold of $z = 3.1$ at the voxel level was used to define the initial set of clusters.

Apart from obtaining maps of significant activations for each task, we performed region of interest (ROI) analyses to examine the activation and deactivation patterns of relevant DMN regions individually and across tasks. To define the ROIs, we used the Neurosynth package [42] to retrieve an automated meta-analysis of 516 studies using the term "default mode" (see http://neurosynth.org/analyses/terms/default%20mode/ for the original meta-analysis map). This meta-analysis provided a reverse-inference map of brain regions preferentially linked with the default mode network, FDR-corrected at $p < 0.001$. The map was smoothed with a Gaussian kernel (sigma = 3), thresholded with a minimum z value of 1.5, and binarized, to obtain the set of ROIs that were finally included in the analysis: mPFC, PCC/precuneus, right and left angular gyri, right and left medial temporal lobes, and right and left inferior temporal cortex. From each ROI we extracted average parameter estimates for each task condition compared to its corresponding baseline. This allowed us to compare the activation or deactivation levels of relevant DMN regions and to check if the differences between conditions in BOLD response found in the whole-brain analyses were mainly due to activation in the condition of interest, to deactivation in the control condition, or both.

Results

Autobiographical memory task

In the autobiographical memory condition, compared to the control condition, the participants showed extensive activation in the mPFC and PCC, the left angular gyrus, and the medial temporal lobe bilaterally, including hippocampus and parahippocampus. Other regions showing increased activity in the memory condition were the VLPFC and DLPFC, the temporal poles and the cerebellum (see Table 2 and Fig 1). Regions showing greater activity in the control than in the autobiographical memory condition included areas of the occipital and parietal cortices, superior temporal cortex and right frontal pole.

Self-reflection task

Contrasts revealed broadly similar activation maps for the self and other conditions relative to the facts condition. Both activated the mPFC and frontal pole, the left angular gyrus, the bilateral middle temporal gyrus and temporal poles, the mid-cingulate cortex, the PCC, the precuneus and the calcarine cortex. The other condition, but not the self condition, also activated the right angular gyrus (Table 3, Fig 2).

The facts condition was associated with increased activity with respect to both the self and other conditions in a set of areas that included the lateral frontal cortex bilaterally and the medial superior frontal cortex. Bilateral activity was also seen in the superior parietal cortex extending to the inferior parietal area as well as in the insula, the fusiform gyrus, and the thalamus.

While no region showed increased activity in the self compared to the other condition, several brain areas were more active in the other than in the self condition. These included the precuneus and PCC, the left and right angular gyri, the middle temporal cortex, the right frontal pole and both temporal poles.

N-back task

Because in this and in previous studies by our group (e.g. [34]), activations and deactivations were considerably more pronounced in the 2-back vs. baseline than in the 1-back vs. baseline

126

Table 2. Significant activation in the autobiographical memory task.

Region	Hemisphere	x	y	z	Z-value	Cluster size	Sig.
Memory > Control							
Cerebellum	R	36	-62	-30	7.08	14853	$p < 0.001$
Precuneus	R	8	-56	20	6.35		
PCC	L	-6	-52	34	6.12		
Hippocampus	L	-18	-14	-22	5.67		
	R	24	-20	-16	5.18		
Caudate	R	18	2	14	5.41		
Frontal pole	L	-24	52	18	5.78	8759	$p < 0.001$
SMA	L	-2	10	60	5.58		
Medial prefrontal cortex	L	-2	64	4	5.56		
DLPFC	L	-38	10	52	5.49		
Angular gyrus/Middle occipital	L	-46	-76	34	5.53	1317	$p < 0.001$
Insula	R	48	12	-8	4.66	200	$p = 0.007$
Control > Memory							
Occipital cortex	R	26	-72	38	6.1	18370	$p < 0.001$
	L	-44	-82	8	5.9		
Fusiform gyrus	L	-34	-54	-16	5.25		
	R	36	-60	-14	4.91		
Lingual gyrus	L	-22	-64	-10	5.22		
Cuneus	L	-14	-90	24	5.7		
Superior temporal cortex	L	-50	-10	0	5.2		
Inferior parietal cortex	R	54	-52	36	4.99		
Angular gyrus	R	30	-54	46	5.26		
Superior parietal	R	20	-56	60	5.11		
Superior occipital cortex	R	26	-72	38	6.11		
Middle frontal gyrus	R	42	60	-8	5.12	301	$p < 0.001$

Coordinates are shown in MNI space. Cluster size shows the number of voxels. R: Right; L: Left; PCC: Posterior cingulate cortex; SMA: Supplementary motor area, DLPFC: Dorsolateral prefrontal cortex.

https://doi.org/10.1371/journal.pone.0209376.t002

contrast, the analyses reported here are focused in the 2-back condition (activations and deactivations in the 1-back condition were highly similar but with lower intensity). Activation in the 2-back condition compared to baseline was seen in a large cluster involving left and right lateral prefrontal cortices, the anterior cingulate cortex (ACC), lateral and medial parietal cortices, the occipital cortex, the basal ganglia and the thalamus. Deactivation (i.e. baseline > 2-back) was found in the mPFC, the medial temporal lobe including the hippocampus and extending into the temporal poles (bilaterally), the superior temporal gyrus and the posterior insula, and PCC/precuneus (see Table 4 and Fig 3).

ROI analyses

For each region, we tested whether its activation was different from baseline levels with a one-sample t-test in each task condition. Only those participants with valid data for the three tasks were included in the ROI analyses (n = 33). Results are reported in Table 5 and Fig 4. A Bonferroni corrected p value of 0.001 (= 0.05/56 tests performed) was considered to control for false positives. The PCC/precuneus ROI was activated in the autobiographical and other-reflection conditions, but not in the self condition. Oppositely, it was deactivated in the 2-back, and also slightly deactivated in the facts condition (although at an uncorrected

127

Memory vs Control
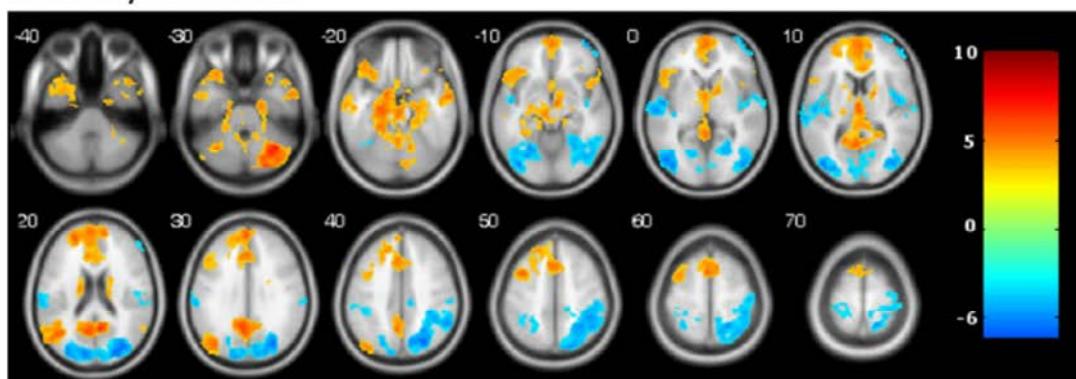
Fig 1. Activation map for the autobiographical memory task. Warm colors represent memory > control contrast, cold colors represent control > memory contrast. Numbers indicate z coordinate in MNI space. Images are displayed in neurological convention (right is right). Color bar depicts Z values.

https://doi.org/10.1371/journal.pone.0209376.g001

significance threshold). Similarly, the mPFC was activated by autobiographical memory and other-reflection, and more weakly by self-reflection (only at uncorrected level), while it was deactivated in 2-back and in the control condition from the autobiographical memory task.

The angular gyrus showed a different profile: the left angular was significantly active in all self-relevant conditions (autobiographical, self-reflection and other-reflection) but was not deactivated in any condition. Its right homologue did not show any significant activation or deactivation at corrected levels, although it was active at an uncorrected level in other-reflection.

Both medial temporal lobes (MTL) were significantly active in the autobiographical memory condition, but not in self/other-reflection. The right MTL was also deactivated in the 2-back. The inferior temporal cortices were both active for autobiographical memory and self/other-reflection (the right temporal only at an uncorrected level for self-reflection), but they were not deactivated in the 2-back.

Finally, we explored if any of the ROIs was preferentially activated by autobiographical memory in contrast with self-reflection. In each ROI, we compared the parameter estimates for the two conditions using a paired samples t-test. We found that activation levels were similar in the mPFC and the temporal poles. However, the MTLs (especially the left), the PCC/precuneus and the left angular gyri were more active in autobiographical memory than in self-reflection, with differences at trend level for the right angular (Table 6).

Overlap in activation maps

As an alternative way to further explore the similarities and differences between brain areas activated by autobiographical memory and self-reflection, and deactivated by the n-back task, we examined the degree of overlap in the activation maps for each task compared to the low-level baseline (fixation). Results are displayed in Fig 5.

First we overlapped the activation maps corresponding to autobiographical memory and self-reflection vs. fixation (Fig 5A). Considerable overlap was found in the dorsomedial prefrontal cortex, left angular gyrus and temporal lobes, and also outside DMN regions such as

128

Table 3. Significant activation in the self-reflection task.

Region	Hemisphere	x	y	z	Z-value	Cluster size	Sig.
Self > Facts							
Precuneus/PCC	L	-8	-58	32	7.53	2111	p<0.001
Medial prefrontal cortex/Frontal pole	L	-8	58	-6	5.62	1745	p<0.001
Calcarine cortex	B	0	-90	-4	4.81	569	p<0.001
Middle/posterior cingulate cortex	B	0	-22	40	5.62	530	p<0.001
Angular/Middle temporal gyrus	L	-52	-62	24	5.01	508	p<0.001
Temporal pole	R	46	-4	-38	5.33	483	p<0.001
	L	-48	6	-40	4.67	479	p<0.001
Middle temporal cortex	L	-52	-36	-4	4.05	179	p = 0.006
Facts > Self							
DLPFC	R	34	14	54	7.34	5763	p<0.001
Occipital cortex	L	-28	-74	40	6.78	3602	p<0.001
Angular gyrus	R	42	-66	44	6.77	3237	p<0.001
Fusiform gyrus/Inf. Temporal cortex	L	-32	-34	-26	6.72	3027	p<0.001
	R	60	-46	-14	6.7	2303	p<0.001
Inferior frontal gyrus	L	-42	40	12	6.05	2052	p<0.001
		-48	8	30	5.86	739	p<0.001
Medial superior frontal cortex	R	4	32	40	6.11	909	p<0.001
DLPFC	L	-24	10	58	5.62	687	p<0.001
Cerebellum	L	-8	-78	-28	5.77	421	p<0.001
Thalamus	R	10	-20	8	4.57	417	p<0.001
Precuneus	R	8	-64	68	4.17	217	p = 0.002
Fusiform gyrus	L	-30	-8	-38	5.15	180	p = 0.005
Insula	L	-32	20	-2	4.36	146	p = 0.016
		-42	0	0	4.93	133	p = 0.025
ACC	L	-2	6	26	5.86	138	p = 0.021
Lingual gyrus	R	8	-52	6	4.19	124	p = 0.033
Other > Facts							
Precuneus/PCC	L	-4	-52	30	8.33	4072	p<0.001
Medial prefrontal cortex	B	0	60	0	5.51	2551	p<0.001
Inferior temporal cortex	L	-56	-8	-28	5.87	2106	p<0.001
Temporal pole	R	48	-4	-36	5.87	1276	p<0.001
		4	-86	-6	6.63	1104	p<0.001
Middle temporal/Angular gyrus	L	-52	-62	22	5.98	820	p<0.001
Angular gyrus	R	46	-56	24	5.24	620	p<0.001
Facts > Other							
Inferior temporal cortex/Fusiform gyrus	L	-52	-50	-18	6.83	2992	p<0.001
Lateral orbitofrontal cortex	R	44	54	-12	7.04	2938	p<0.001
Inferior parietal cortex/supramarginal	L	-62	-38	44	6.67	2693	p<0.001
	R	34	-78	38	5.93	2411	p<0.001
DLPFC/Inferior frontal gyrus	L	-44	46	6	6	1756	p<0.001
Inferior temporal cortex/Fusiform gyrus	R	60	-46	-18	7.34	1666	p<0.001
DLPFC	R	30	14	54	6.1	1474	p<0.001
Medial superior frontal cortex	R	2	30	44	6.32	1164	p<0.001
Inferior frontal gyrus	L	-46	8	30	5.88	754	p<0.001
Superior frontal cortex	L	-22	14	50	6.07	505	p<0.001
Insula	L	-32	24	-8	4.88	224	p = 0.001

(*Continued*)

129

Table 3. (Continued)

Region	Hemisphere	x	y	z	Z-value	Cluster size	Sig.
Fusiform gyrus	R	40	-14	-30	4.91	176	p = 0.005
	L	-30	-8	-40	4.83	114	p = 0.038
Cerebellum	R	26	-68	-32	4.68	150	p = 0.011
	L	-8	-78	-28	4.54	130	p = 0.022
Thalamus	R	2	-18	0	4.1	148	p = 0.012
ACC	B	0	6	26	5.65	122	p = 0.028
Other > Self							
Precuneus/PCC	R	2	-64	32	6.57	3326	p<0.001
Angular gyrus	R	44	-64	32	5.18	858	p<0.001
Temporal pole/Middle temporal gyrus	L	-40	16	-36	4.47	510	p<0.001
Angular/Middle temporal gyrus	L	-54	-64	18	3.99	268	p<0.001
Medial prefrontal cortex	R	4	68	-4	4.21	254	p<0.001
Middle/Inferior temporal gyrus	R	58	-6	-26	4.33	117	p = 0.025

Coordinates are shown in MNI space. Cluster size shows the number of voxels. PCC: Posterior Cingulate Cortex; ACC: Anterior Cingulate Cortex; DLPFC: Dorsolateral prefrontal cortex; R: Right; L: Left; B: Both.

the lateral prefrontal cortex, basal ganglia, thalamus and occipital cortex. Consistent with the ROI analysis, the precuneus was activated by autobiographical memory but not self-reflection.

Fig 5B depicts the overlap between autobiographical memory and deactivated areas in 2-back. Overlap is observed in the precuneus, temporal lobes and left angular gyrus. There is also overlap in the medial prefrontal cortex, however in this region deactivation in 2-back seems to be located more ventrally than activation for autobiographical memory.

Activation for self-reflection and deactivation for 2-back showed the least amount of overlap (Fig 5C). It included part of the medial prefrontal cortex (although again activation in self-reflection was more dorsal than deactivation in 2-back), a small cluster in the precuneus, left angular gyrus and temporal poles.

Discussion

The aim of this study was to analyze the activation patterns of DMN regions during the performance of an autobiographical memory task and a self-reflection task, which both activate DMN areas, and to compare these with the deactivation pattern in a conventional attention-demanding task, the n-back task. It was found that core midline DMN regions (mPFC and PCC) were activated by autobiographical memory and self-reflection but deactivated by the n-back task. We also found evidence for a MTL-hippocampus DMN subsystem preferentially linked to autobiographical memory. Our autobiographical memory task proved to be a simple and useful tool to study DMN activity relative to this process.

Current theoretical approaches to DMN function highlight its involvement in active mental states, contrary to previous accounts that considered it to be a "task-negative" network, and consider that its main function is to support self-generated thought, in contrast with other types of mental activity that are more directed towards external stimuli [5,25,30]. The present results support this view of the DMN, as it is engaged in the processing of self-relevant information and inhibited when directing attention to a cognitive task that does not contain any personal information: individually, both self-relevant tasks activated the regions classically associated to the DMN, and these same regions were deactivated in the n-back task. This pattern was confirmed by the activation maps of the whole-brain analysis and also by the ROI

130
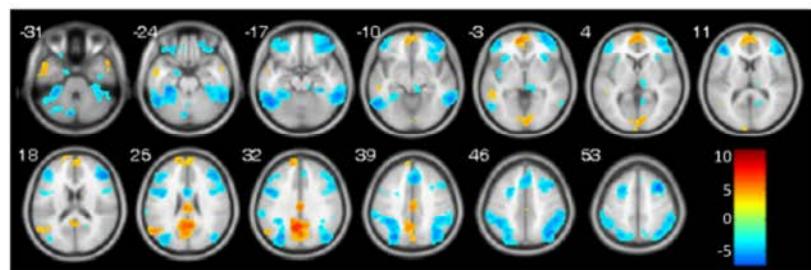
Self vs Facts
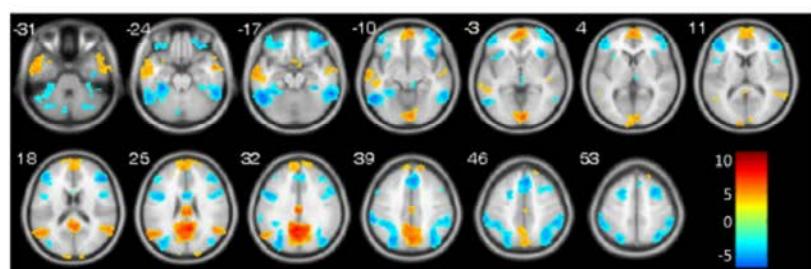
Other vs Facts

Other vs Self
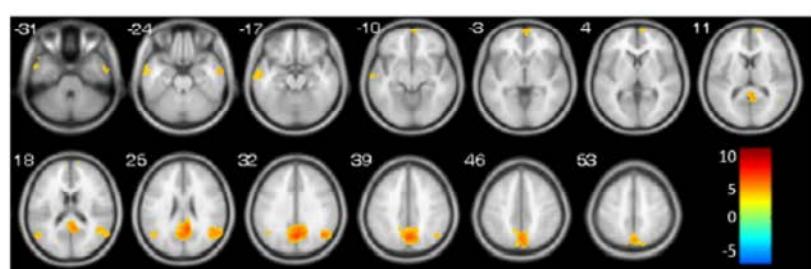
Fig 2. Activation map for the self-reflection task. Warm colors represent self > facts (upper row), other > facts (middle row) and other > self (lower row) contrasts, cold colors represent facts > self (upper row) and facts > other (middle row) contrasts. Numbers indicate z coordinate in MNI space. Images are displayed in neurological convention (right is right). Color bar depicts Z values.

analysis. Moreover, all DMN regions identified in the ROI analyses showed activation above baseline levels for autobiographical memory (some of them also for self/other reflection), which indicates that even if these regions are active during baseline or resting states (e.g. because of mind-wandering during rest periods), they activate further during tasks that involve processing self-relevant information. The ROI analysis also revealed that all the activations seen in the autobiographical > control contrast were genuine activations (i.e. activation above baseline level), and not the result of a deactivation in the control condition.

131

Table 4. Significant activation in the n-back task.

Region	Hemisphere	x	y	z	Z-value	Cluster size	Sig.
2-back > Baseline							
Cerebellum	R	30	-68	-30	8.26	45930	p<0.001
	L	-30	-66	32	7.93		
Dorsal ACC	R	2	16	48	7.82		
Inferior temporal cortex	R	58	-46	-12	5.17		
Inferior frontal cortex	R	34	28	-6	7.15		
	L	-32	24	-6	6.84		
DLPFC/Superior frontal cortex	R	36	52	10	6.15		
Inferior parietal cortex	R	56	-40	42	6.68		
Middle occipital cortex	R	30	-70	36	7.54		
Putamen	L	-16	6	2	6.45		
Baseline > 2-back							
Medial prefrontal cortex	R	4	52	-10	7.11	11747	p<0.001
Precuneus/PCC	L	-6	-56	22	6.56	4212	p<0.001
Hippocampus	L	-22	0	-26	6.33	3428	p<0.001
Angular gyrus	L	-50	-76	30	6.19	374	p<0.001
Mid-cingulate cortex	R	2	-16	48	4.22	323	p<0.001
	R	10	-36	48	4.78	173	p = 0.010
Postcentral gyrus	R	48	-20	58	4.14	187	p = 0.007
Precentral gyrus	R	24	-28	74	4.64	150	p = 0.020

Coordinates are shown in MNI space. Cluster size shows the number of voxels. PCC: Posterior Cingulate Cortex; ACC: Anterior Cingulate Cortex; DLPFC: Dorsolateral prefrontal cortex. R: Right; L: Left.

The core regions (PCC and mPFC), as expected, were active in both the autobiographical memory and the self-reflection tasks. The main difference was observed in the hippocampus and MTL, active for autobiographical memory but not self-reflection. This concurs with the proposal of Buckner et al. [5] that the hippocampus is part of a DMN subsystem linked to autobiographical recall and not to other types of self-referential processing, and with recent findings of a DMN subnetwork functionally coupled with the hippocampal formation [32]. However, we found less evidence for the second DMN subsystem (also proposed in [5]),

2-back vs Baseline
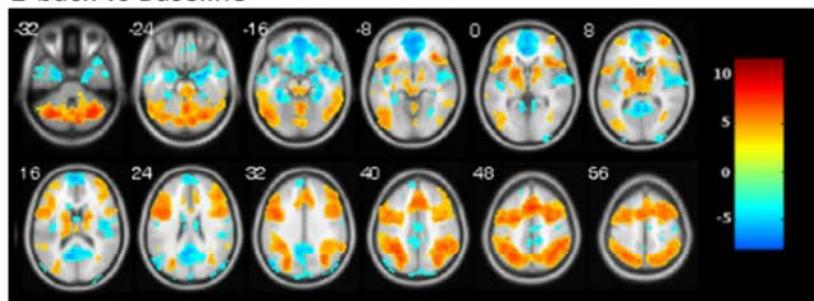
Fig 3. Activation map for the n-back task. Warm colors show activation of the 2-back condition compared to baseline, cold colors show deactivation. Numbers indicate z coordinate in MNI space. Images are displayed in neurological convention (right is right). Color bar depicts Z values.

132

Table 5. Significant activations for the ROI analyses.

Region	N-back				Autobiographical memory				Self/Other reflection					
	1-back		2-back		Memory		Control		Self		Other		Facts	
	$t_{(32)}$	p	$t_{(32)}$	p	$t_{(32)}$	p	$t_{(32)}$	p	$t_{(32)}$	p	$t_{(32)}$	p	$t_{(32)}$	p
PCC	-8.150	<0.001	-5.911	<0.001	5.444	<0.001	1.014	0.318	0.396	0.695	3.924	<0.001	-2.457	0.02
mPFC	-5.118	<0.001	-6.99	<0.001	3.478	0.001	-3.715	0.001	3.047	0.005	3.889	<0.001	0.22	0.828
Left Angular	-4.999	<0.001	-1.044	0.304	7.45	<0.001	2.834	0.008	4.166	<0.001	5.478	<0.001	2.252	0.031
Right Angular	-2.235	0.033	2.563	0.015	2.458	0.02	2.612	0.014	-0.332	0.742	2.941	0.006	1.367	0.181
Left MTL	-3.044	0.005	-2.673	0.012	6.668	<0.001	0.501	0.62	0.929	0.36	2.181	0.037	1.844	0.075
Right MTL	-5.689	<0.001	-6.328	<0.001	5.895	<0.001	-0.536	0.595	0.483	0.632	1.707	0.098	1.234	0.226
Left Inf. Temp.	-2.873	0.007	-0.608	0.547	5.484	<0.001	2.211	0.034	3.885	<0.001	5.873	<0.001	2.735	0.01
Right Inf. Temp.	-2.498	0.018	-2.095	0.044	4.463	<0.001	-0.342	0.734	2.112	0.043	3.882	<0.001	0.793	0.434

Bold shows significant activations surviving multiple comparison correction. PCC: Posterior Cingulate Cortex; mPFC: medial Prefrontal Cortex; MTL: Medial temporal lobe; Temp: Temporal.

which was hypothesized to comprise the inferior parietal cortex and to show a preferential involvement in self-reflection, as this region was significantly active for both autobiographical memory and self-reflection in the left hemisphere, while neither of them activated the right. The description of DMN subsystems has also linked the dorsal portion of the mPFC to this second subsystem, while the ventral portion corresponds to the core DMN [27]. Interestingly, our analysis of activation map overlap did show that autobiographical memory and self-reflection activated a more dorsal portion of the mPFC while deactivation in n-back was located more ventrally, although with an area of overlap between both. However, activation in dorsal mPFC was very similar in both DMN-activating tasks. Differences between mPFC subregions might therefore be more related to the need to deactivate in attention demanding tasks than to the specific self-referential process at play. As also shown by the ROI analysis, it is likely that activation in the mPFC in DMN-activating tasks arises not only from activation of this region above baseline levels in the conditions of interest but also from a deactivation in the control conditions as they usually involve some kind of cognitive processing that is not self-generated thought [3].

A novel contribution of the present study is the direct comparison of the two self-relevant tasks with the n-back, a classic cognitive task known to induce DMN deactivation [34–36]. As hypothesized, the n-back task deactivated all the DMN regions that showed increased activity in the self-relevant tasks: mPFC, PCC, left inferior parietal cortex, and MTL. It also deactivated the inferior temporal cortex, a region that has also been linked to the DMN as shown by the Neurosynth automated meta-analysis (see Methods section) and that seems to be involved in semantic processing [43]. From our results, it seems that the DMN exhibits modularity in its activation, with at least one clear subsystem involving the MTL and hippocampus, but it is deactivated as a whole when performing tasks that demand paying attention to external stimuli, although the ROI analysis indicates that deactivation is most pronounced in the core DMN regions. One question that is still a matter of debate is the meaning of these deactivations. Early work proposed that there is a baseline level of activity in the human brain, in which different cognitive processes (e.g. environment monitoring, stimulus-independent thought) take place [3]. Under this perspective, task-induced deactivation occurs when these baseline processes are suspended to perform a task that demands focused attention [9]. Recent accounts have proposed that the DMN has a role on attentional fluctuations, with deactivation occurring when the task is performed in an effortful, controlled way, but not when performance is more automatic [12,13]. Our ROI analysis shows

133
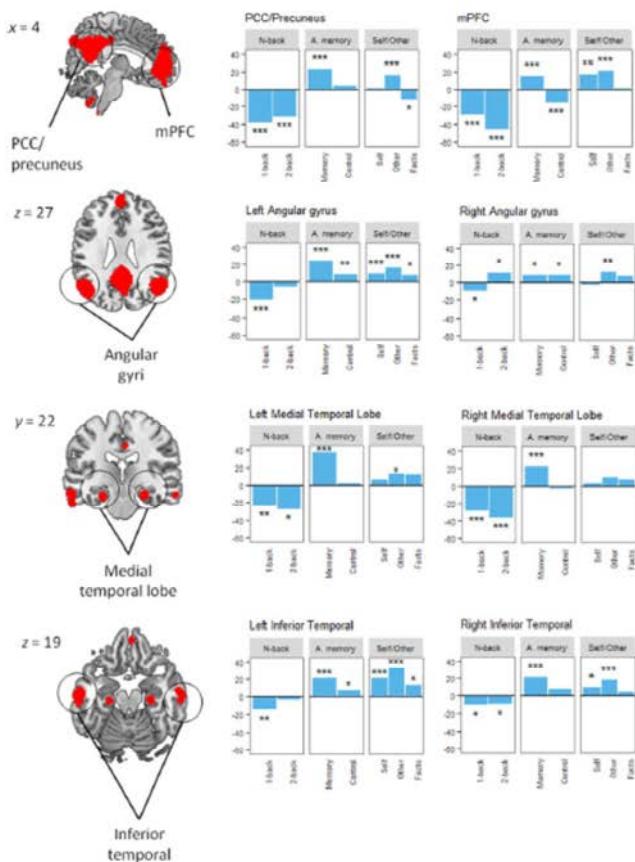
Fig 4. Activation in DMN regions in ROI analysis. Vertical axis shows parameter estimates. *p<0.05, **p<0.01, ***p<0.001 (the last being equivalent to a Bonferroni corrected p<0.05).

https://doi.org/10.1371/journal.pone.0209376.g004

Table 6. Comparison between activation levels in autobiographical memory and self-reflection conditions.

Region	Mean PE Autobigraphical memory	Mean PE Self-reflection	t(32)	p
PCC	22.639	1.553	**3.743**	**0.001**
mPFC	15.452	16.931	-0.231	0.819
Left Angular	23.719	8.917	**4.069**	**<0.001**
Right Angular	8.290	-1.264	2.053	0.048
Left MTL	36.541	5.908	**3.763**	**0.001**
Right MTL	21.642	2.796	3.406	0.002
Left Inf. Temp.	20.692	20.839	-0.023	0.981
Right Inf. Temp.	16.282	9.099	1.601	0.119

Bold shows significant activations surviving multiple comparison correction. PE: parameter estimates, MTL: Medial temporal lobe.

https://doi.org/10.1371/journal.pone.0209376.t006

134
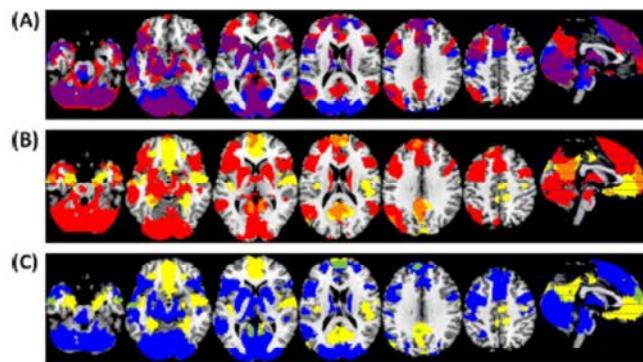
Fig 5. Overlap between activated areas in autobiographical memory and self-reflection, and deactivated areas in 2-back, compared to fixation. (A) Activation maps for autobiographical memory (red) and self-reflection (blue). Overlap is shown in purple. (B) Activation maps for autobiographical memory (red) and 2-back deactivation (yellow). Overlap is shown in orange. (C) Activation maps for self-reflection (blue) and 2-back deactivation (yellow). Overlap is shown in green.

that deactivation was clear in the 1-back (requiring sustained attention) and 2-back (requiring attention and working memory) conditions, especially in the core DMN. However, it was also possible that we had additionally observed deactivation in the control conditions of the other two tasks (reading neutral words and answering questions about the world), but this was limited or absent. While these control tasks also required goal-directed cognition, their attentional demands were far lower than those in the n-back. Thus, our results favor an interpretation of DMN deactivation as reflecting interplay between brain networks when effortful cognitive control needs to be displayed. Thus, DMN deactivation might not be only dependent on the particular task, but also on the individual's performance strategies.

The self/other task provides an additional comparison that, although secondary to the aims of the present work, is also worth considering, namely the direct comparison between self and other-reflection. Compared with the facts condition, that mostly involves semantic processing, the self and other conditions activated roughly the same brain regions (mPFC, PCC, left angular). Direct comparison of self and other revealed that these regions were more active for other than for self-reflection, which also activated the right angular gyrus. These findings contrast with previous evidence of a distinction between the ventral and dorsal portions of the mPFC for self and other-reflection, respectively [44]. A possible explanation is that self and other judgments required similar, overlapping cognitive processes in our task, given that reflection about personality and behavior of others should rely in the recall of personal interactions with the other individual. In contrast, some of the previous studies that found greater mPFC in self rather than other-reflection used a public person (e.g. a politician) as "other" [29,45]. Reflecting upon such a public figure, who is not personally known by the participant, might in fact involve semantic processing instead of self-reflection or autobiographical memory–resulting in increased mPFC activation in the self > other contrast. However, this question warrants further study because other previous works have found ACC and mPFC activity in self > other contrasts using tasks very similar to ours [39,46].

The PCC was significantly activated in other, but not in self-reflection. Greater activity in the PCC in the other rather than in the self condition had been previously reported with a very similar task [39,47,48], and this result had also been explained by the need of engaging in autobiographical memory (linked to the PCC) during other-reflection, presumably to retrieve

135

previous interactions with the individual to make a judgment [49]. Our results also support this view, as autobiographical memory but not self-reflection significantly engaged the PCC. In the case of the angular gyrus, especially in the right hemisphere, this region is part of the temporo-parietal junction, which has been proposed as a candidate for the processes of self/other differentiation based on its role in multisensory integration, action imitation and mentalizing [50,51]. A role in self/other differentiation aligns well with our result of right angular gyrus activation in other but not in self-reflection.

Limitations

Although we directly compared the autobiographical memory and self-reflection tasks in the ROI analysis, this result should be interpreted with caution given that parameter estimates come from two different paradigms. While alternatively it would have been possible to design a single task with multiple experimental conditions, using different paradigms allowed us to compare each condition of interest with a well-matched control condition and avoid the processes engaged in one task interfering in the other. On the other hand, results from the whole-brain analysis do not exactly match those from the ROI analysis, probably because the regions in each of them do not overlap completely. However, the use of independently defined ROIs was necessary to perform ROI statistics and avoid "double dipping" [52]. The two types of analyses can be seen as complementary and taking them both into account facilitates the interpretation of the results. Finally, although participants were asked about their engagement during the tasks in the periods without behavioral output, their degree of attention or engagement could not be objectively assessed. In the future, the use of eye-tracking devices during fMRI exploration could overcome this limitation.

Conclusions

The present study supports the current theoretical views of DMN function as the basis for a type of cognition that is self-generated and, even though it can be elicited by external stimuli, it is directed towards the self and personally relevant information. Our results provide evidence of the dynamics of this network: when attention is "internally oriented" (i.e. directed towards the self or towards self-related information), activity increases, and this increase overcomes even the levels of activity found in low-demanding or baseline periods, where DMN activity can also occur as a result of spontaneous mind-wandering. On the contrary, when attention is "externally oriented" (i.e. directed towards a goal-directed task that does not involve the self, such as the n-back task), this network is inhibited and its activation decreases below the resting baseline levels, while the activity of other cognitive networks rises [27]. Our study also supports the existence of task-related modularity within the DMN, with at least one subsystem preferentially linked to autobiographical memory and consisting of medial temporal areas. Future studies may combine different self-referential conditions in a single paradigm to allow more direct comparisons. It might also be interesting to use such a combined task to explore changes occurring in clinical populations with known or suspected DMN alteration, hence contributing to a better characterization of their neurobiological abnormalities.

Acknowledgments

136

Author Contributions

Conceptualization: Pilar Salgado-Pineda, Salvador Sarró, Peter J. McKenna, Edith Pomarol-Clotet, Raymond Salvador.

Data curation: Silvia Alonso-Lana, Maria Anguera-Camós, Salvador Sarró.

Formal analysis: Paola Fuentes-Claramonte, Marta Martín-Subero, Pilar Salgado-Pineda, Raymond Salvador.

Funding acquisition: Salvador Sarró, Peter J. McKenna, Edith Pomarol-Clotet.

Investigation: Paola Fuentes-Claramonte, Marta Martín-Subero, Pilar Salgado-Pineda, Silvia Alonso-Lana, Ana Moreno-Alcázar, Isabel Argila-Plaza, Aniol Santo-Angles, Antoni Capdevila.

Methodology: Paola Fuentes-Claramonte, Pilar Salgado-Pineda, Raymond Salvador.

Project administration: Salvador Sarró, Peter J. McKenna, Edith Pomarol-Clotet.

Resources: Antoni Capdevila, Salvador Sarró, Edith Pomarol-Clotet.

Software: Anton Albajes-Eizagirre, Maria Anguera-Camós, Salvador Sarró, Raymond Salvador.

Supervision: Antoni Capdevila, Salvador Sarró, Peter J. McKenna, Edith Pomarol-Clotet.

Validation: Paola Fuentes-Claramonte, Marta Martín-Subero.

Visualization: Paola Fuentes-Claramonte.

Writing – original draft: Paola Fuentes-Claramonte, Edith Pomarol-Clotet, Raymond Salvador.

Writing – review & editing: Paola Fuentes-Claramonte, Marta Martín-Subero, Pilar Salgado-Pineda, Silvia Alonso-Lana, Ana Moreno-Alcázar, Isabel Argila-Plaza, Aniol Santo-Angles, Anton Albajes-Eizagirre, Maria Anguera-Camós, Antoni Capdevila, Salvador Sarró, Peter J. McKenna, Edith Pomarol-Clotet, Raymond Salvador.

References

1. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A. 2005; 102: 9673–8. https://doi.org/10.1073/pnas.0504136102 PMID: 15976020

2. Krienen FM, Thomas Yeo BT, Buckner RL. Reconfigurable task-dependent functional coupling modes cluster around a core functional architecture. Philos Trans R Soc B Biol Sci. 2014; 369. https://doi.org/10.1098/rstb.2013.0526 PMID: 25180304

3. Gusnard DA, Raichle ME. Searching for a baseline: Functional imaging and the resting human brain. Nat Rev Neurosci. 2001; 2: 685–694. Available: http://dx.doi.org/10.1038/35094500 PMID: 11584306

4. Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, et al. Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. J Cogn Neurosci. 1997; 9: 648–663. https://doi.org/10.1162/jocn.1997.9.5.648 PMID: 23965122

5. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci. 2008; 1124: 1–38. https://doi.org/10.1196/annals.1440.011 PMID: 18400922

6. Whitfield-Gabrieli S, Ford JM. Default Mode Network Activity and Connectivity in Psychopathology. Annu Rev Clin Psychol Vol 8. 2012; 8: 49–75. https://doi.org/10.1146/Annurev-Clinpsy-032511-143049 PMID: 22224834

137

7. Thomas Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 2011; 106: 1125–1165. https://doi.org/10.1152/jn.00338.2011 PMID: 21653723

8. Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, et al. Functional Network Organization of the Human Brain. Neuron. Elsevier Inc.; 2011; 72: 665–678. https://doi.org/10.1016/j.neuron.2011.09.006 PMID: 22099467

9. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A. 2001; 98: 676–82. https://doi.org/10.1073/pnas.98.2.676 PMID: 11209064

10. Spreng RN. The fallacy of a "task-negative" network. Front Psychol. 2012; 3: 145. https://doi.org/10.3389/fpsyg.2012.00145 PMID: 22593750

11. Gusnard DA. Being a self: Considerations from functional imaging. Conscious Cogn. 2005; 14: 679–697. https://doi.org/10.1016/j.concog.2005.04.004 PMID: 16256372

12. Esterman M, Noonan SK, Rosenberg M, Degutis J. In the zone or zoning out? Tracking behavioral and neural fluctuations during sustained attention. Cereb cortex. 2013; 23: 2712–23. https://doi.org/10.1093/cercor/bhs261 PMID: 22941724

13. Kucyi A, Esterman M, Riley CS, Valera EM. Spontaneous default network activity reflects behavioral variability independent of mind-wandering. Proc Natl Acad Sci. 2016; 113: 13899–13904. https://doi.org/10.1073/pnas.1611743113 PMID: 27856733

14. Sali AW, Courtney SM, Yantis S. Spontaneous Fluctuations in the Flexible Control of Covert Attention. J Neurosci. 2016; 36: 445–454. https://doi.org/10.1523/JNEUROSCI.2323-15.2016 PMID: 26758836

15. Svoboda E, McKinnon MC, Levine B. The functional neuroanatomy of autobiographical memory: A meta-analysis. Neuropsychologia. 2006; 44: 2189–2208. https://doi.org/10.1016/j.neuropsychologia.2006.05.023 PMID: 16806314

16. Addis DR, McIntosh AR, Moscovitch M, Crawley AP, McAndrews MP. Characterizing spatial and temporal features of autobiographical memory retrieval networks: a partial least squares approach. Neuroimage. 2004; 23: 1460–71. https://doi.org/10.1016/j.neuroimage.2004.08.007 PMID: 15589110

17. Addis DR, Wong AT, Schacter DL. Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. Neuropsychologia. 2007; 45: 1363–1377. https://doi.org/10.1016/j.neuropsychologia.2006.10.016 PMID: 17126370

18. Gilboa A, Winocur G, Grady CL, Hevenor SJ, Moscovitch M. Remembering our past: Functional neuroanatomy of recollection of recent and very remote personal events. Cereb Cortex. 2004; 14: 1214–1225. https://doi.org/10.1093/cercor/bhh082 PMID: 15166099

19. Steinvorth S, Corkin S, Halgren E. Ecphory of Autobiographical Memories: an fMRI Study on Recent and Remote Memory Retrieval. Neuroimage. 2006; 30: 285–298. https://doi.org/10.1016/j.neuroimage.2005.09.025 PMID: 16257547

20. Bado P, Engel A, de Oliveira-Souza R, Bramati IE, Paiva FF, Basilio R, et al. Functional dissociation of ventral frontal and dorsomedial default mode network components during resting state and emotional autobiographical recall. Hum Brain Mapp. 2014; 35: 3302–3313. https://doi.org/10.1002/hbm.22403 PMID: 25050426

21. Oertel-Knöchel V, Reinke B, Hornung A, Knöchel C, Matura S, Knopf M, et al. Patterns of autobiographical memory in bipolar disorder examined by psychometric and functional neuroimaging methods. J Nerv Ment Dis. 2012; 200: 296–304. https://doi.org/10.1097/NMD.0b013e31824ceef7 PMID: 22456582

22. Spreng RN, Grady CL. Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. J Cogn Neurosci. 2010; 22: 1112–1123. https://doi.org/10.1162/jocn.2009.21282 PMID: 19580387

23. Philippi CL, Tranel D, Duff M, Rudrauf D. Damage to the default mode network disrupts autobiographical memory retrieval. Soc Cogn Affect Neurosci. 2014; 10: 318–326. https://doi.org/10.1093/scan/nsu070 PMID: 24795444

24. Knyazev GG, Savostyanov AN, Bocharov A V., Dorosheva EA, Tamozhnikov SS, Saprigyn AE. Oscillatory correlates of autobiographical memory. Int J Psychophysiol. Elsevier B.V.; 2015; 95: 322–332. https://doi.org/10.1016/j.ijpsycho.2014.12.006 PMID: 25523347

25. Whitfield-Gabrieli S, Moran JM, Nieto-Castañón A, Triantafyllou C, Saxe R, Gabrieli JDE. Associations and dissociations between default and self-reference networks in the human brain. Neuroimage. 2011; 55: 225–232. https://doi.org/10.1016/j.neuroimage.2010.11.048 PMID: 21111832

26. Andrews-Hanna JR, Saxe R, Yarkoni T. Contributions of episodic retrieval and mentalizing to autobiographical thought: evidence from functional neuroimaging, resting-state connectivity, and fMRI meta-analyses. Neuroimage. 2014; 91: 324–335. https://doi.org/10.1016/j.neuroimage.2014.01.032 PMID: 24486981

138

27. Andrews-Hanna JR, Smallwood J, Spreng RN. The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. Ann N Y Acad Sci. 2014; 1316: 29–52. https://doi.org/10.1111/nyas.12360 PMID: 24502540

28. Holt DJ, Cassidy BS, Andrews-Hanna JR, Lee SM, Coombs G, Goff DC, et al. An Anterior-to-Posterior Shift in Midline Cortical Activity in Schizophrenia During Self-Reflection. Biol Psychiatry. 2011; 69: 415–423. https://doi.org/10.1016/j.biopsych.2010.10.003 PMID: 21144498

29. Jenkins AC, Mitchell JP. Medial prefrontal cortex subserves diverse forms of self-reflection. Soc Neurosci. 2011; 6: 211–218. https://doi.org/10.1080/17470919.2010.507948 PMID: 20711940

30. Andrews-Hanna JR. The Brain's Default Network and Its Adaptive Role in Internal Mentation. Neurosci. 2012; 18: 251–270. https://doi.org/10.1177/1073858411403316 PMID: 21677128

31. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-Anatomic Fractionation of the Brain's Default Network. Neuron. Elsevier Ltd; 2010; 65: 550–562. https://doi.org/10.1016/j.neuron.2010.02.005 PMID: 20188659

32. Braga RM, Buckner RL. Parallel Interdigitated Distributed Networks within the Individual Estimated by Intrinsic Functional Connectivity. Neuron. Elsevier Inc.; 2017; 95: 457–471.e5. https://doi.org/10.1016/j.neuron.2017.06.038 PMID: 28728026

33. Saxe R, Moran JM, Scholz J, Gabrieli J. Overlapping and non-overlapping brain regions for theory of mind and self reflection in individual subjects. Soc Cogn Affect Neurosci. 2006; 1: 229–234. https://doi.org/10.1093/scan/nsl034 PMID: 18985110

34. Pomarol-Clotet E, Salvador R, Sarró S, Gomar J, Vila F, Martinez Á, et al. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? Psychol Med. 2008; 38: 1185–1193. https://doi.org/10.1017/S0033291708003565 PMID: 18507885

35. Gordon EM, Stollstorff M, Vaidya CJ. Using Spatial Multiple Regression to Identify Intrinsic Connectivity Networks Involved in Working Memory Performance. Hum Brain Mapp. 2012; 33: 1536–1552. https://doi.org/10.1002/hbm.21306 PMID: 21761505

36. Landin-Romero R, McKenna PJ, Salgado-Pineda P, Sarró S, Aguirre C, Sarri C, et al. Failure of deactivation in the default mode network: a trait marker for schizophrenia? Psychol Med. 2015; 45: 1315–1325. https://doi.org/10.1017/S0033291714002426 PMID: 25331916

37. Kopelman MD, Wilson BA, Baddeley AD. The autobiographical memory interview: A new assessment of autobiographical and personal semantic memory in amnesic patients. J Clin Exp Neuropsychol. Routledge; 1989; 11: 724–744. https://doi.org/10.1080/01688638908400928 PMID: 2808661

38. Crovitz HF, Sciffman H. Frequency of episodic memories as a function of their age. Bull Psychon Soc. 1974; 4: 517–518. https://doi.org/10.3758/BF03334277

39. Modinos G, Ormel J, Aleman A. Activation of anterior insula during self-reflection. PLoS One. 2009; 4: e4618. https://doi.org/10.1371/journal.pone.0004618 PMID: 19242539

40. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004; 23: 208–219. https://doi.org/10.1016/j.neuroimage.2004.07.051 PMID: 15501092

41. Beckmann CF, Jenkinson M, Smith SM. General multilevel linear modeling for group analysis in FMRI. Neuroimage. 2003; https://doi.org/10.1016/S1053-8119(03)00435-X

42. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. NeuroSynth: a new platform for large-scale automated synthesis of human functional neuroimaging data. Front Neuroinformatics Conf Abstr 4th INCF Congr Neuroinformatics. 2011; https://doi.org/10.3389/conf.fninf.2011.08.00058

43. Visser M, Jefferies E, Lambon Ralph MA. Semantic processing in the anterior temporal lobes: a meta-analysis of the functional neuroimaging literature. J Cogn Neurosci. 2010; 22: 1083–94. https://doi.org/10.1162/jocn.2009.21309 PMID: 19583477

44. Denny BT, Kober H, Wager TD, Ochsner KN. A Meta-Analysis of Functional Neuroimaging Studies of Self and Other Judgments Reveals a Spatial Gradient for Mentalizing in Medial Prefrontal Cortex. J Cogn Neurosci. 2012; 24: 1742–1752. https://doi.org/10.1162/jocn_a_00233 PMID: 22452556

45. Bergström ZM, Vogelsang DA, Benoit RG, Simons JS. Reflections of Oneself: Neurocognitive Evidence for Dissociable Forms of Self-Referential Recollection. Cereb Cortex. 2014; 25: 2648–2657. https://doi.org/10.1093/cercor/bhu063 PMID: 24700584

46. Modinos G, Mechelli A, Ormel J, Groenewold NA, Aleman A, McGuire PK. Schizotypy and brain structure: a voxel-based morphometry study. Psychol Med. 2010; 40: 1423–31. https://doi.org/10.1017/S0033291709991875 PMID: 19917146

47. Modinos G, Renken R, Ormel J, Aleman A. Self-reflection and the psychosis-prone brain: an fMRI study. Neuropsychology. 2011; 25: 295–305. https://doi.org/10.1037/a0021747 PMID: 21443341

139

48. van der Meer L, De Vos AE, Stiekema APM, Pijnenborg GHM, Van Tol MJ, Nolen WA, et al. Insight in schizophrenia: Involvement of self-reflection networks? Schizophr Bull. 2013; 39: 1352–1362. https://doi.org/10.1093/schbul/sbs122 PMID: 23104865

49. van der Meer L, Costafreda S, Aleman A, David AS. Self-reflection and the brain: A theoretical review and meta-analysis of neuroimaging studies with implications for schizophrenia. Neurosci Biobehav Rev. 2010; 34: 935–946. https://doi.org/10.1016/j.neubiorev.2009.12.004 PMID: 20015455

50. Saxe R, Wexler A. Making sense of another mind: The role of the right temporo-parietal junction. Neuropsychologia. 2005; 43: 1391–1399. https://doi.org/10.1016/j.neuropsychologia.2005.02.013 PMID: 15936784

51. Eddy CM. The junction between self and other? Temporo-parietal dysfunction in neuropsychiatry. Neuropsychologia. Elsevier; 2016; 89: 465–477. https://doi.org/10.1016/j.neuropsychologia.2016.07.030 PMID: 27457686

52. Kriegeskorte N, Simmons WK, Bellgowan PSF, Baker CI. Circular analysis in systems neuroscience– the dangers of double dipping. Nat Neurosci. 2009; 12: 535–540. https://doi.org/10.1038/nn.2303 PMID: 19396166

140