UNIVERSITAT DE BARCELONA

El Trastorno Bipolar: Cambios cerebrales asociados con el estado de ánimo y el deterioro cognitivo

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Tesi presentada per

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CERTIFICAN que han guiado y supervisado la tesis doctoral titulada "El Trastorno Bipolar: Cambios cerebrales asociados con el estado de ánimo y el deterioro cognitivo" y que ésta cumple los requerimientos para su defensa y para la obtención del título de doctor.

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There is a silence where hath been no sound,
There is a silence where no sound may be,
In the cold grave—under the deep deep sea,
Or in the wide desert where no life is found,
Which hath been mute, and still must sleep profound;
No voice is hush'd—no life treads silently,
But clouds and cloudy shadows wander free,
That never spoke, over the idle ground:
But in green ruins, in the desolate walls
Of antique palaces, where Man hath been,
Though the dun fox, or wild hyena, calls,
And owls, that flit continually between,
Shriek to the echo, and the low winds moan,
There the true Silence is, self-conscious and alone.

Silence – Thomas Hood

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Listado de siglas

RM	Resonancia Magnética
fMRI	Functional Magnetic Resonance Imaging (resonancia magnética funcional)
DSM	Diagnostic and Statistical Manual of Mental Disorders (manual diagnóstico y estadístico de los trastornos mentales)
SNP	Single Nucleotide Polymorphism (polimorfismo de nucleótido simple)
GWAS	Genome-Wide Association Study (asociación genética a nivel de todo el genoma)
CNV	Copy Number Variation (variación en el número de copias)
VBM	Voxel Based Morphometry (morfometría basada en voxel)
ENIGMA	Enhancing Neuro Imaging Genetics through Meta-Analysis
FA	Fractional Anisotropy (anisotropía fraccional)
PET	Positron Emission Tomography (tomografía por emisión de positrones)
ROI	Region Of Interest (región de interés)
DMN	Default Mode Network (red neuronal por defecto)
YMRS	Young Mania Rating Scale
HDRS	Hamilton Depression Rating Scale
TAP	Test de Acentuación de Palabras
WAIS-III	Wechsler Adult Intelligence Scale – 3a version
BOLD	Blood-Oxygen-Level Dependent (señal dependiente del nivel de oxigeno en sangre)
FWHM	Full Width at Half Maximum (amplitud máxima a media altura)
AAL	Automated Anatomical Labeling

Listado de figuras y tablas

Prólogo

Esta tesis, presentada para obtener el grado académico de Doctor por la Universidad de Barcelona, está formada por tres artículos publicados en revistas internacionales indexadas y desarrollados a lo largo de mi formación en el Programa de Doctorado de Medicina, bajo la dirección de la Dra. Edith Pomarol-Clotet y el Dr. Eduard Vieta.

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Brain functional changes across the different phases of bipolar disorder. Pomarol-Clotet E, Alonso-Lana S, Moro N, Sarró S, Bonnin CM, Goikolea JM, Fernández-Corcuera P, Amann BL, Romaguera A, Vieta E, Blanch J, McKenna PJ, Salvador R. *Br J Psychiatry*. 2015; 206(2), 136-144. doi: 10.1192/bjp.bp.114.152033.

Brain functional changes in first-degree relatives of patients with bipolar disorder: evidence for default mode network dysfunction. Alonso-Lana S, Valentí M, Romaguera A, Sarri C, Sarró S, Rodríguez-Martínez A, Goikolea JM, Amann BL, Maristany T, Salvador R, Vieta E, McKenna PJ, Pomarol-Clotet E. *Psychological Medicine*. 2016; 46(12): 2513-2521. doi: 10.1017/S0033291716001148.

Structural and functional brain correlates of cognitive impairment in euthymic patients with bipolar disorder. Alonso-Lana S, Goikolea JM, Bonnin CM, Sarro S, Segura B, Amann BL, Monté GC, Moro N, Fernandez-Corcuera P, Maristany T, Salvador R, Vieta E, Pomarol-Clotet E, McKenna PJ. *PloS One*. 2016; 11(7). doi: 10.1371/journal.pone.0158867.

Justificación

El trastorno bipolar es una enfermedad crónica, recurrente e incapacitante, con una prevalencia de alrededor del 1% y asociada con una elevada tasa de morbilidad y mortalidad. Sin embargo, todavía hoy en día no se conoce de forma precisa su etiología y fisiopatología debido principalmente a que son numerosos los factores que contribuyen a su desarrollo y al mantenimiento de sus síntomas.

El presente estudio tiene como objetivo profundizar en el conocimiento de las alteraciones en el funcionamiento cerebral presentes en el trastorno bipolar y su relación con las distintas fases afectivas y de remisión clínica que caracterizan la enfermedad. Esto permitirá determinar qué alteraciones están relacionadas con las fases agudas de la enfermedad y, por tanto, consideradas marcadores de estado, en contraposición con otras alteraciones que siguen presentes a pesar de la remisión clínica y que por tanto, son marcadores rasgo. Estas alteraciones persistentes pueden, a su vez, reflejar la carga genética asociada a la enfermedad y por ello, mediante una muestra de hermanos sanos de pacientes bipolares se pretende también determinar qué alteraciones pueden además considerarse endofenotipos de la enfermedad. Por último, se determinará si estas posibles alteraciones consideradas potencialmente como marcadores rasgo y/o endofenotipos de la enfermedad pueden estar asociadas con el deterioro cognitivo presente a pesar de la remisión clínica en al menos un porcentaje de estas personas. Este conocimiento es esencial para entender la patogénesis y las particularidades sintomatológicas que caracterizan la enfermedad, reflejo de las estructuras y redes neurales subyacentes.

La aparición de la Resonancia Magnética (RM) y el posterior desarrollo de las técnicas de RM funcional (fMRI, por sus siglas en inglés) han supuesto un avance importante para estudiar la estructura y el funcionamiento cerebral *in vivo* y de manera segura. Se ha convertido en una excelente herramienta para conocer los circuitos y redes neuronales relacionados con la cognición, la emoción y el comportamiento; implicados no sólo en los trastornos mentales severos, sino esenciales para la comprensión de la función cerebral general. Por lo tanto, las técnicas de fMRI tienen el potencial de convertirse en herramientas de diagnóstico y de detección de regiones diana que podrían derivar nuevos tratamientos de terapia farmacológica u otros tratamientos innovadores como el neurofeedback, la

estimulación cerebral profunda o la estimulación magnética transcraneal, en definitiva, tratamientos más adecuados y específicos a las alteraciones cerebrales subyacentes.

1 Introducción

1.1. INTRODUCCIÓN GENERAL AL TRASTORNO BIPOLAR

El trastorno bipolar ha sido clásicamente definido como un trastorno en el que se alternan periodos de remisión y recaídas caracterizadas por cambios en el estado de ánimo que van desde la manía o hipomanía a la depresión. Estas recaídas tienen una afectación significativa en todas las esferas de la vida de la persona, pudiendo desembocar en consecuencias graves y duraderas.

1.1.1 Características clínicas

Sintomatología clínica

Los episodios de manía o hipomanía se caracterizan por una exaltación del estado de ánimo así como por un aumento de la actividad y la energía que se mantienen al menos una semana o cuatro días respectivamente (American Psychiatric Association 2013). Es habitual que disminuyan las horas de sueño, aumente la participación en conductas de riesgo, exista aceleración del pensamiento y del habla, presencia de fuga de ideas y distraibilidad, aumento de la autoestima y sensación de grandeza y, en ocasiones, se pueden presentar síntomas psicóticos asociados como delirios congruentes o no congruentes con el estado de ánimo y/o alucinaciones. Por el contrario, los episodios de depresión se caracterizan por un estado de ánimo decaído y/o por la pérdida del interés y placer mantenido durante al menos dos semanas. Se puede acompañar de aumento o disminución significativa de peso o de horas de sueño, de alteraciones atencionales y de la concentración, así como por sentimientos o delirios de inutilidad, culpa o de muerte (American Psychiatric Association 2013). La severidad de estos síntomas o la presencia de síntomas psicóticos pueden obligar a una hospitalización para lograr la estabilización clínica y minimizar o evitar posibles daños.

Intercalados entre estos episodios, existen periodos de remisión clínica o eutimia pero que, a diferencia de lo que se pensaba con anterioridad, hoy en día se ha evidenciado que no es invariablemente sinónimo de recuperación total. Durante la eutimia pueden persistir síntomas afectivos subsindrómicos (Joffe et al 2004), un funcionamiento psicosocial deteriorado (Coryell et al 1993) y deterioro cognitivo (Bourne et al 2013).

Prevalencia

La prevalencia del trastorno bipolar es del 1-2% para el tipo I y el tipo II, en el que los episodios de depresión se intercalan con episodios de hipomanía, y es relativamente uniforme a través de las diferentes culturas y regiones así como entre hombres y mujeres (Ferrari et al 2011, Goodwin et al 2008a, Merikangas et al 2011). A nivel local, en un estudio reciente llevado a cabo en Cataluña con los criterios de la 5ª edición del Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM-V, por sus siglas en inglés), se estableció una prevalencia general del 3.0%, siendo de 0.3% para el tipo I, 0.9% para el tipo II y de 1.8% para otros tipos de trastorno bipolar (Calvo-Perxas et al 2015).

No obstante, estos valores epidemiológicos aumentan considerablemente, hasta aproximadamente un 5%, cuando se tiene en cuenta el concepto de "espectro bipolar", según el cual, las manifestaciones del trastorno se producen en un continuo de gravedad, desde manifestaciones no completas del trastorno hasta los tipos incluidos en los manuales diagnósticos como el DSM-V (Akiskal et al 2000).

Inicio y curso

La edad de inicio puede variar considerablemente, si bien típicamente se inicia en la juventud, siendo el 50% de los casos diagnosticados antes de los 25 años (Kessler et al 2005). La duración de los episodios puede variar ampliamente desde días hasta meses aunque, por lo general, los episodios depresivos suelen ser más largos y recurrentes que los episodios maníacos (Judd et al 2002).

Además, existe cierta evidencia de un aumento del número de episodios, y por tanto, una disminución del tiempo en remisión clínica, conforme la enfermedad avanza en el tiempo (Kessing et al 1998, Peters et al 2014, Roy-Byrne et al 1985). Esto ha llevado a que muchos autores planteen el concepto de progresión y se hayan propuesto modelos de estadiaje según los cuales el trastorno evoluciona desde periodos asintomáticos y prodrómicos hasta la aparición del primer episodio afectivo, tras lo cual los individuos pueden alternar nuevos episodios y periodos de remisión clínica hasta etapas refractarias donde la remisión ya no es evidente (Berk et al 2007, Kapczinski et al 2009, Reinares et al 2013).

Morbilidad y mortalidad

El trastorno bipolar presenta una alta prevalencia de comorbilidad con otros diagnósticos del eje I y II del DSM como los trastornos de ansiedad, de abuso de sustancias y de la conducta alimentaria y con trastornos de la personalidad (George et al 2003, Grant et al 2005). Además, se ha asociado con un mayor riesgo de sufrir enfermedades somáticas, sin que éstas puedan explicarse o ser causadas únicamente por el tratamiento farmacológico, y de las cuales son de especial importancia las relacionadas con el sistema cardiovascular y endocrino (Beyer et al 2005, Forty et al 2014, Krishnan 2005). De hecho, en los últimos años diversos estudios epidemiológicos han puesto de manifiesto una mayor prevalencia de síndrome metabólico (Vancampfort et al 2013), y en concreto en España se ha encontrado que este síndrome es un 60% más prevalente en el caso de pacientes con trastorno bipolar en comparación con la población general (Garcia-Portilla et al 2008).

La presencia de estas comorbilidades supone un factor de riesgo añadido al ya de por sí alto riesgo de mortalidad, siendo éste de entre dos o tres veces mayor que la población general (Carlborg et al 2015). Esto es debido en parte al alto índice de intentos de suicidio, ya que en torno al 25-50% de las personas con trastorno bipolar cometen tentativas de suicidio y alrededor del 15% muere por ello, especialmente en los primeros años tras el diagnóstico del trastorno (Osby et al 2001, Tondo & Baldessarini 2005).

Tratamiento

A día de hoy, el tratamiento del trastorno bipolar es principalmente farmacológico. Dada la naturaleza episódica y crónica de la enfermedad, el objetivo es tanto tratar los episodios específicos como prevenir la aparición de nuevos episodios o recaídas. De manera profiláctica se hace uso de estabilizadores del ánimo como el litio y los anticonvulsivos, y durante los episodios de manía o depresión se pautan antipsicóticos atípicos o antidepresivos, para tratar de resolver lo más rápido posible estos episodios (National Institute for Health and Care Excellence (NICE) 2014). A pesar de un tratamiento continuo farmacológico, el 75% de los pacientes recaen durante los primeros cinco años, y dos terceras partes de éstos presentan varios episodios durante este intervalo (Gitlin et al 1995).

Como tratamientos coadyuvantes al farmacológico se han desarrollado psicoterapias complementarias que actualmente se están estudiando, como la psicoeducación, la terapia cognitivo-conductual, la terapia familiar o la terapia interpersonal y del ritmo social (para una revisión ver Yatham et al (2005) y Yatham et al (2006)) o más recientemente la remediación funcional (Torrent et al 2013).

1.1.2. Deterioro cognitivo en el trastorno bipolar

Otra de las características del trastorno bipolar es la presencia de deterioro cognitivo persistente a pesar de la remisión clínica, lo cual ha sido confirmado y replicado por diversos meta-análisis publicados en los últimos diez años (Arts et al 2008, Bourne et al 2013, Mann-Wrobel et al 2011, Robinson et al 2006, Torres et al 2007). Estos meta-análisis han puesto de relieve la afectación de las funciones ejecutivas y la memoria, junto con la preservación de las medidas de inteligencia cristalizada, aunque también se ha reportado un patrón más generalizado de afectación (Mann-Wrobel et al 2011) y en el último meta-análisis publicado hasta la fecha, a pesar de que se encontró un rendimiento disminuido, los valores del tamaño del efecto fueron más moderados que los reportados en meta-análisis anteriores (d=0.26-0.63 vs. d=0.5-1) (Bourne et al 2013).

Este deterioro cognitivo se asocia con un peor pronóstico (Mann-Wrobel et al 2011) y con afectación de la capacidad funcional (Depp et al 2012); no parece ser atribuible a los efectos de la medicación (Balanza-Martinez et al 2010) o a la presencia de síntomas afectivos residuales (Bonnin et al 2012); y se observa en aproximadamente un 40% de los pacientes (Altshuler et al 2004, Bora et al 2010b, Burdick et al 2014, Volkert et al 2015). En comparación con otros trastornos psiquiátricos, la presencia de deterioro cognitivo es menos prevalente que en la esquizofrenia o el trastorno esquizoafectivo, pero ligeramente mayor en relación al trastorno depresivo mayor (Iverson et al 2011, Reichenberg et al 2009).

1.2. LA FISIOPATOLOGÍA DEL TRASTORNO BIPOLAR

Son numerosos los factores que están implicados en la etiología y fisiopatología del trastorno bipolar y por ello, ningún gen o alteración cerebral puede explicar la condición por sí solos. Además, una compleja enfermedad psiquiátrica como el trastorno bipolar no depende sólo de

la vulnerabilidad que estos factores confieren a su origen, sino también, de cómo éstos interaccionan entre sí y con los factores ambientales en la recurrencia y la progresión de la enfermedad. La evidencia proveniente de diversas disciplinas pone en evidencia alteraciones existentes en todos los niveles, desde alteraciones moleculares y bioquímicas, de la integridad glial y neuronal, afectación de diferentes sistemas fisiológicos como el sistema inmune, endocrino, el sistema nervioso periférico, y por supuesto, el sistema nervioso central (ver **Figura 1**) (Maletic & Raison 2014, Miller & Raison 2016).

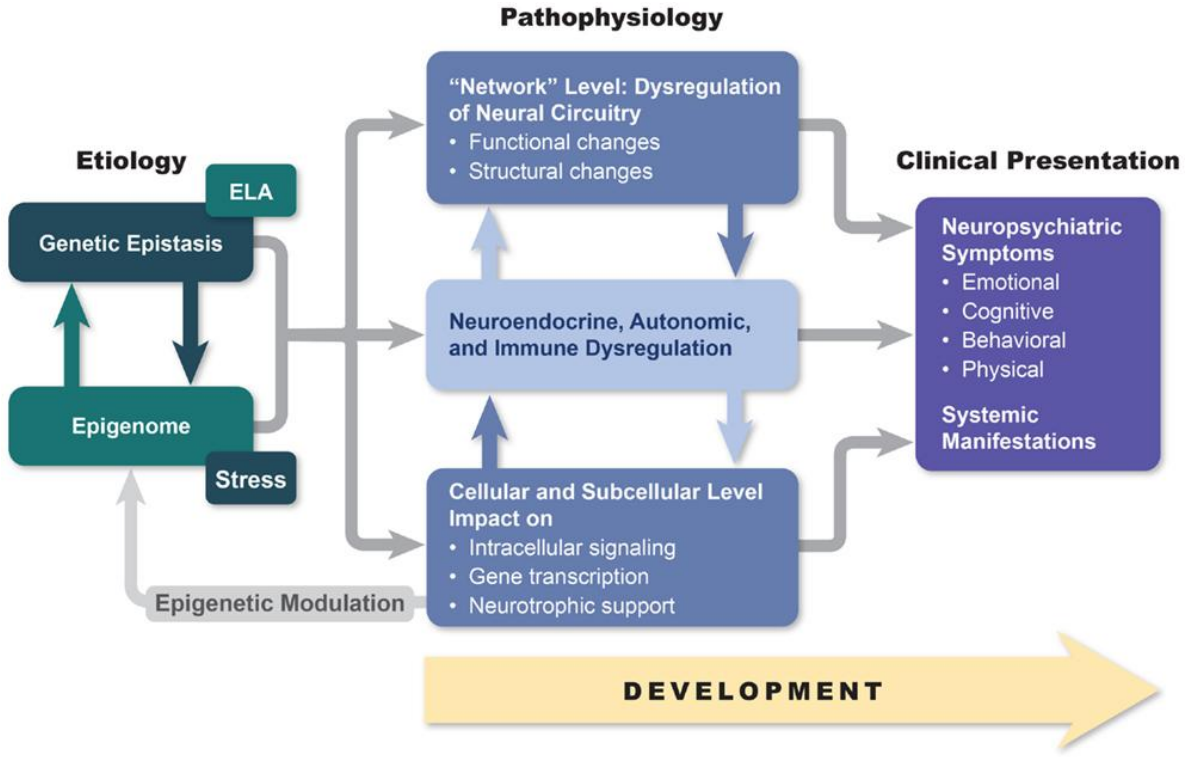

Figura 1. Modelo etiopatogénico que refleja los diferentes sistemas biológicos implicados en el trastorno bipolar (Maletic & Raison 2014).

1.2.1. Base genética en el trastorno bipolar

Actualmente nadie pone en duda la base genética del trastorno, principalmente por la evidencia proveniente de los estudios epidemiológicos genéticos realizados en familias y gemelos y, en menor medida, los estudios de adopción. A través de ellos se ha determinado que los familiares de primer grado de personas con trastorno bipolar presentan un riesgo de hasta 10 veces mayor de desarrollar el trastorno; la concordancia entre gemelos es mayor cuando éstos son monocigóticos, es decir, genéticamente idénticos, en comparación con los

gemelos dicigóticos, estando la concordancia en torno a un 40% y un 5% respectivamente; y la heredabilidad (proporción de la varianza para el desarrollo de un trastorno que es debida a factores genéticos) se situaría entre el 60-93% (Craddock & Jones 1999, Kieseppa et al 2004, Lichtenstein et al 2009, McGuffin et al 2003, Smoller & Finn 2003).

Dada la evidencia de esta base genética, se ha invertido un considerable tiempo y esfuerzo en determinar los genes implicados, así como los procesos biológicos subyacentes. Los resultados provenientes de los estudios basados en genes candidatos, a pesar de su limitada replicación, han mostrado algunos hallazgos consistentes en relación a genes implicados en el riesgo para el trastorno o la expresión de algunos rasgos clínicos o cognitivos más específicos, como por ejemplo el SLC6A4, BDNF, DAOA, DTNBP1, NRG1, DISC1 o el DRD4[1] (Seifuddin et al 2012, Szczepankiewicz 2013). Con el desarrollo de la tecnología, en los últimos años se han llevado a cabo análisis de variantes genéticas como los polimorfismos de nucleótido simple (SNPs, por sus siglas en inglés) a gran escala, a través de los llamados estudios de asociación genética a nivel de todo el genoma (GWAS, por sus siglas en inglés). Los resultados de estos estudios han permitido confirmar la arquitectura poligénica del trastorno e identificar diferentes *loci* como el CACNA1C, ZNF804A, ANK3, NCAN, ODZ4 y ADCY2[2] (Chen et al 2013, Cichon et al 2011, Ferreira et al 2008, Muhleisen et al 2014, Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011, Sklar et al 2008, Wellcome Trust Case Control 2007). La variación en el número de copias (CNV, por sus siglas en inglés) es otro tipo de variante genética muy poco frecuente y consistente en pequeñas adiciones, supresiones o pequeños cambios en la posición del ADN. Varios estudios han encontrado pruebas de su implicación en diferentes trastornos como el autismo, el trastorno por déficit de atención e hiperactividad, la esquizofrenia, y también, en el trastorno bipolar (Malhotra & Sebat 2012), si bien aún son necesarios más estudios para establecer qué CNVs son compartidos entre diferentes trastornos y cuáles son específicos para el trastorno bipolar (Chen et al 2016).

No obstante, no hay que olvidar que la influencia genética no actúa de forma aislada ni en un punto concreto del desarrollo de los individuos. En este sentido, el estudio de la compleja

[1] SLC6A4: gen transportador de serotonina; BDNF: factor neurotrófico derivado del cerebro; DAOA: activador de la D-aminoácido oxidasa; DTNBP1: dysbindin-1; NRG1: neuregulin-1; DISC1: disruptivo en esquizofrenia 1; DRD4: receptor de dopamina D4.

[2] CACNA1C: gen voltaje-bloqueado del canal de calcio; ZNF804A: proteína dedo de zinc 804A; ANK3: ankyrin-3; NCAN: neurocan; ODZ4: proteína de la transmembrana del teneurin-4; ADCY2: adenilato ciclasa-2.

arquitectura genética del trastorno debe comprender las interacciones genéticas (o epistasis) y proteicas, así como la interacción con factores ambientales a través de complejos mecanismos como la epigenética, entre otros. Algunos de los factores ambientales que han sido estudiados por su posible rol como factores de riesgo para el desarrollo del trastorno han sido los factores del neurodesarrollo prenatales y perinatales, la exposición a estrés físico o psicológico o el abuso de sustancias, si bien la evidencia es aún escasa y limitada (Marangoni et al 2016, Tsuchiya et al 2003).

1.2.2. Otras alteraciones neurobiológicas

Las alteraciones en la función del eje hipotalámico-hipofisario-adrenal del sistema neuroendocrino han sido documentadas en relación al trastorno bipolar en forma de elevación de cortisol y una menor sensibilidad de los receptores de glucocorticoides (Belvederi Murri et al 2016). Esta hiperactividad neuroendocrina se ha asociado con la supresión de la hormona estimulante de la tiroides y con la alteración en el patrón circadiano de secreción de cortisol, ampliamente documentadas en el trastorno bipolar (Cowdry et al 1983, Dallaspezia & Benedetti 2009, Harvey 2008). Además, esta mayor resistencia de los receptores de glucocorticoides ha sido ligada a una elevación de citoquinas proinflamatorias y por lo tanto, a alteraciones del sistema inmunológico (Pace & Miller 2009, Rosenblat et al 2014). De hecho, el trastorno depresivo mayor y más recientemente el trastorno bipolar, han sido asociados con una respuesta inflamatoria crónica de bajo grado (Munkholm et al 2013). Estas citoquinas activan la microglía del cerebro, lo que aumenta las señales inflamatorias, el estrés oxidativo, la disminución de factores neurotróficos, el aumento de glutamato con su consiguiente excitotoxicidad, y disminuye el metabolismo de los sistemas monoaminérgicos de neurotransmisión (dopamina y serotonina) (Felger & Lotrich 2013).

Esta reacción en cadena de disminución de factores neurotróficos y sobreactivación microglial son algunos de los factores involucrados en el deterioro neuronal y glial que de hecho se observa en pacientes con trastorno bipolar. Estudios histológicos postmortem han evidenciado cambios en la densidad, el número y en la morfología de células gliales y neuronales en regiones fronto-límbicas, aunque en el caso de las neuronas, las alteraciones detectadas parecen ser menos extensas (Rajkowska 2002). Estas regiones son de especial interés en relación al trastorno bipolar ya que son en gran medida responsables de la regulación de estos sistemas fisiológicos comentados (Dedovic et al 2009), por lo tanto, están

implicadas de forma muy directa, pero a través de mecanismos muy amplios, en la regulación del humor y la respuesta al estrés, y como veremos en la próxima sección, su alteración es de hecho uno de los hallazgos más reportados en los estudios de neuroimagen estructural y funcional.

Por tanto, el trastorno bipolar es un trastorno multifactorial, probablemente resultado de complejas interacciones genéticas y ambientales, que se reflejan en afectación de diversos sistemas fisiológicos y circuitos cerebrales, lo que tiene como resultado el amplio espectro de síntomas observables en los pacientes.

1.3. NEUROIMAGEN EN EL TRASTORNO BIPOLAR

1.3.1. Cambios cerebrales estructurales

Cambios en sustancia gris

En los primeros estudios de volumetría, las alteraciones estructurales cerebrales asociadas con el trastorno bipolar se relacionaron principalmente con un aumento del tamaño de los ventrículos laterales (Arnone et al 2009, Kempton et al 2008, McDonald et al 2004) y Arnone et al (2009) encontraron además una ligera reducción del volumen total del cerebro y del lóbulo frontal en comparación con controles. En los estudios más recientes se han empleado técnicas de análisis de todo el cerebro, tales como la morfometría basada en voxel (VBM, por sus siglas en inglés), capaces de detectar cambios sutiles y que no se ajustan a límites anatómicos (Ashburner & Friston 2000). Estos estudios han encontrado principalmente evidencia de reducción de sustancia gris en la corteza cingulada anterior, la ínsula y la corteza frontal inferior (Bora et al 2010a, Ellison-Wright & Bullmore 2010, Houenou et al 2011, Selvaraj et al 2012, Wise et al 2016b). Dado que estos cambios de volumen dependen tanto del grosor como del área de superficie cortical, un cambio en el volumen puede deberse a cambios en uno o ambos parámetros. En este sentido se han encontrado cambios en el grosor cortical en la corteza cingulada anterior izquierda y regiones prefrontales y superiores temporales bilaterales (para una revisión ver Hanford et al (2016)), mientras que no parece haber cambios en el área de superficie cortical (Rimol et al 2012).

Recientemente se ha publicado un mega-análisis en el que se han examinado los cambios volumétricos en estructuras subcorticales y del volumen ventricular e intracraneal en 1710 pacientes con trastorno bipolar en comparación con 2594 controles y los resultados indican una reducción en el volumen medio del hipocampo, la amígdala (sólo en el trastorno bipolar tipo I) y del tálamo, junto con un aumento del volumen de los ventrículos laterales (Hibar et al 2016). No hubo cambios en el núcleo accumbens, caudado, globo pálido o putamen, ni en el volumen intracraneal. Estos análisis han sido posibles gracias a la creación de un consorcio internacional llamado ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) y que ha permitido analizar datos a gran escala, aumentando así sustancialmente la posibilidad de detectar cambios sutiles o de evitar falsos positivos.

Cambios en sustancia blanca

Junto con estas alteraciones en la sustancia gris, existen también cambios en la sustancia blanca cerebral, principalmente caracterizados por un incremento en la presencia de hiperintensidades, pequeñas alteraciones en la sustancia blanca detectadas en las imágenes ponderadas en T2 y que probablemente reflejan alteraciones vasculares y desmielinización (Beyer et al 2009, Kempton et al 2008), o reducción de volumen de sustancia blanca en regiones prefrontales usando técnicas de VBM (Mahon et al 2010).

Más recientemente, la sustancia blanca se ha examinado a través de las imágenes de RM por difusión basadas en el proceso de difusión molecular del agua en el tejido cerebral y cuyo índice más comúnmente usado es la anisotropía fraccional (FA, por sus siglas en inglés). Este índice cuantifica la integridad de los tractos y por lo tanto es sensible a los cambios en la mielina. En el caso del trastorno bipolar se han reportado reducciones de la FA en regiones temporo-parietales derechas y de la corteza cingulada (Nortje et al 2013, Wise et al 2016a). En el caso del meta-análisis de Nortje et al (2013), estos autores encontraron reducción de FA en comparación con los controles sanos en la región temporo-parietal derecha, el cíngulo medio-posterior izquierdo y el cíngulo anterior izquierdo. Así mismo, en el último meta-análisis realizado hasta la fecha, Wise et al (2016a) encontraron afectación del genu del cuerpo calloso, también presente en pacientes con trastorno depresivo mayor, afectándose tractos que conectan ambos hemisferios de la corteza prefrontal y de esta corteza con regiones mediales temporales que incluyen el hipocampo y la amígdala. Además de estos cambios, los pacientes con trastorno bipolar mostraron una mayor disminución de FA en

regiones posteriores del cíngulo en comparación con los pacientes con trastorno depresivo mayor.

Usando técnicas más avanzadas de tractografía, Emsell et al (2013) exploraron la FA y la difusividad media en pacientes con trastorno bipolar, encontrando afectación del cuerpo calloso, del fórnix izquierdo y de la región subgenual del cíngulo. De la misma forma, en un reciente estudio multimodal a partir de imágenes de difusión de alta resolución angular y modelos más avanzados de difusión, se exploraron estos índices junto con otros adicionales y los resultados revelaron un patrón más amplio de afectación axonal (Canales-Rodriguez et al 2014). En concreto, se observaron alteraciones en varios tractos de la sustancia blanca incluyendo el cuerpo calloso, el cíngulo, la corona radiata y el fascículo fronto-occipital superior.

1.3.2. Cambios cerebrales funcionales

Los estudios de neuroimagen funcional en el trastorno bipolar han mostrado resultados heterogéneos y, en ocasiones incluso contradictorios, aunque la evidencia parece indicar que el trastorno bipolar se caracteriza por hiperactivación en estructuras subcorticales como la amígdala, el hipocampo y los ganglios basales, junto con una activación reducida en regiones prefrontales y otras regiones corticales (Green et al 2007, Savitz & Drevets 2009, Strakowski et al 2012, Strakowski et al 2005).

Este patrón de hipoactivación frontal e hiperactivación límbica ha servido de base a la hora de postular diversos modelos neuronales. Dada la implicación de estas regiones mencionadas en el procesamiento y regulación emocional (Ongur & Price 2000), diversos autores han determinado que la capacidad para regular la propia emoción es uno de los problemas fundamentales presentes en este trastorno (Ochsner & Gross 2008, Phillips 2006, Phillips et al 2003, Phillips et al 2008, Strakowski et al 2012, Townsend & Altshuler 2012). Según estos autores, estructuras como la amígdala, el estriado ventral y el tálamo participan en la percepción inicial emocional, mientras que la regulación depende de activaciones concurrentes de sistemas implicados en procesos de regulación emocional automáticos (sistema medial prefrontal: corteza orbitofrontal, corteza dorsomedial prefrontal, región subgenual y rostral del cingulado anterior e hipocampo/parahipocampo) o voluntarios (sistema lateral prefrontal: corteza dorsolateral y ventrolateral prefrontal) (ver **Figura 2**)

(Phillips et al 2003, Phillips et al 2008). En el caso del trastorno bipolar, proponen que la inestabilidad afectiva puede ser el resultado de una disfunción paralela en estos circuitos neurales, es decir, una combinación de aumento de la actividad subcortical y de regiones límbicas implicadas en la evaluación inicial de los estímulos emocionales, junto con una reducción de la actividad en regiones implicadas en la regulación de estas respuestas y procesos atencionales.

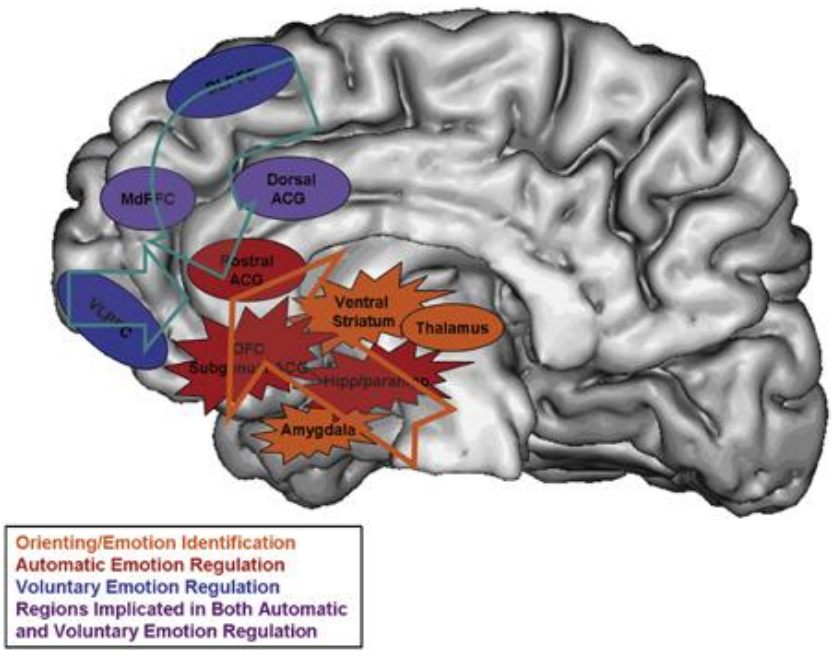

Figura 2. Modelo de regulación emocional donde se ilustran las alteraciones presentes en el trastorno bipolar en relación a las regiones implicadas en la orientación e identificación emocional (naranja), las regiones implicadas en la regulación emocional automática (rojo), las regiones implicadas en la regulación emocional voluntaria (azul) y regiones implicadas tanto en proceso automáticos como voluntarios (morado) (Phillips et al 2008).

1.3.2.1. Cambios funcionales dependientes del estado vs rasgo

Una cuestión que aún no está resuelta es la determinación de los cambios dependientes del "estado" vs "rasgo", es decir, si existen diferencias entre los episodios maníacos y depresivos y hasta qué punto los cambios observados persisten en eutimia.

Kupferschmidt y Zakzanis (2011) meta-analizaron 55 estudios de tomografía por emisión de positrones (PET, por sus siglas en inglés) y fMRI y encontraron cambios tanto en las fases agudas de la enfermedad como en eutimia, pero las diferencias observadas entre las distintas

fases y con el uso de diferentes paradigmas siguieron un patrón complejo. Cuando los análisis se restringieron a los estudios en eutimia, el uso de tareas de procesamiento emocional facial se relacionó principalmente con hiperactivación de regiones límbicas como el hipocampo, la amígdala o la ínsula, mientras que el uso de paradigmas cognitivos revelaron una hipoactivación que afectaba la corteza lateral frontal media e inferior e hipocampo junto con hiperactivación del giro temporal superior y de la corteza ventrolateral prefrontal. Contrariamente, Chen et al (2011), cuyo meta-análisis se restringió a 50 estudios de fMRI, encontraron que los pacientes bipolares mostraban una mayor activación de regiones mediales temporales (parahipocampo, hipocampo y amígdala) y subcorticales (putamen, caudado y pálido) durante la ejecución de tareas de procesamiento emocional junto con menor activación del giro frontal inferior, del giro lingual y del putamen principalmente durante la ejecución de tareas cognitivas. Así mismo, mientras que los cambios en la actividad del giro frontal inferior se asociaban más específicamente con los episodios de manía y parecía haber una recuperación en su funcionamiento tras la remisión clínica, en eutimia se encontró evidencia convergente, en sentido de activación reducida, únicamente en la circunvolución lingual.

Dos meta-análisis enfocados exclusivamente en el procesamiento de estímulos emocionales en pacientes con trastorno bipolar en diferentes fases encontraron cambios tanto dependientes como independientes del estado (Hajek et al 2013, Houenou et al 2011). Houenou et al (2011) incluyeron 13 estudios que utilizaron tareas de procesamiento implícito y explicito (principalmente reconocimiento facial emocional) y/o de regulación emocional (versiones del Go/NoGo, Stroop y de la tarea Sternberg con componente emocional) y encontraron un aumento de activación en el hemisferio derecho del giro frontal medio y del tálamo en manía y en regiones límbicas (parahipocampo y amígdala) en eutimia, junto con una menor activación en el hemisferio izquierdo de la corteza dorsolateral prefrontal en manía y de regiones del precuneus, de la región posterior ventral del tálamo y del cerebelo en eutimia. Hajek et al (2013) incluyeron 30 estudios centrados en tareas de inhibición de respuesta, con y sin estímulos emocionales, y observaron cambios en la activación subcortical e hipoactivación frontal principalmente del giro frontal inferior, está última región igualmente afectada en manía y eutimia. En cuanto a los paradigmas cognitivos, una revisión de la tarea de memoria de trabajo n-back en 8 estudios en pacientes bipolares tipo I en eutimia mostró un patrón, aunque de forma heterogénea entre estudios, de alteraciones en regiones comúnmente implicadas en este paradigma: la corteza prefrontal dorsolateral y ventrolateral,

así como en regiones temporo-parietales (Cremaschi et al 2013). Los cambios en relación con esta tarea en las fases agudas del trastorno son, en cambio, muy limitados.

En los últimos años han surgido estudios que analizan muestras de pacientes en diferentes fases, y estudios longitudinales en menor medida, para poder diferenciar de una manera más directa los cambios dependientes del estado de ánimo de aquellos que son rasgo o inherentes al trastorno (Ver Anexo **Tabla 1**). No obstante, la mayoría de estos estudios tienen muestras pequeñas y utilizan aproximaciones basadas en análisis de regiones de interés (ROI, por sus siglas en inglés) definidas a priori y por tanto es difícil aún extraer conclusiones definitivas de ellos.

Dentro de los estudios que han utilizado paradigmas emocionales en muestras de bipolares con al menos 20 participantes en alguno de sus grupos destacan los siguientes estudios. Utilizando una tarea de emparejamiento de caras emocionales en una muestra de 30 bipolares en manía, 30 en depresión y 15 en eutimia y un grupo de 30 controles sanos, Hulvershorn et al (2012) encontraron un patrón de cambios independientes de la fase afectiva y en forma de hiperactivación subcortical en el putamen, ínsula y amígdala. De forma similar y utilizando un paradigma de procesamiento emocional implícito, Perlman et al (2012) encontraron un aumento de activación en la amígdala tanto en 21 pacientes bipolares en depresión como en 31 eutímicos, en comparación con 25 controles sanos. Liu et al (2012) utilizaron un paradigma similar con una muestra de 76 bipolares (18 bipolares en manía, 19 en depresión y 39 en eutimia) y 58 controles sanos y, mediante un análisis de ROI combinado con una análisis exploratorio de todo el cerebro, encontraron una disminución en la activación de la corteza orbitofrontal y del estriado ventral y sin diferencias significativas entre las diferentes fases. Utilizando también esta aproximación combinada, Hummer et al (2013) compararon 30 bipolares en manía, 30 en depresión y 14 eutímicos mediante una tarea de respuesta de inhibición con distractores emocionales (caras felices y tristes). Observaron que, en comparación con los controles, los pacientes mostraban una mayor activación en el giro frontal inferior izquierdo, la ínsula y la corteza orbitofrontal medial. Sin embargo, mientras que estas dos últimas regiones también mostraban diferencias entre los distintos grupos de pacientes, la hiperactivación del giro frontal inferior estaba presente independientemente de la fase afectiva.

Solo un estudio hasta la fecha ha utilizado la tarea de memoria de trabajo n-back para estudiar los cambios funcionales estado y/o rasgo en trastorno bipolar. Townsend et al (2010) utilizaron este paradigma en un estudio que incluyó 13 bipolares en manía, 14 en depresión, 15 en eutimia y 14 controles y centró los análisis en dos ROIs: la corteza dorsolateral prefrontal y la corteza inferior superior parietal. Se encontró una disminución de actividad en ambas áreas pero sin diferencias entre los distintos grupos de pacientes.

1.3.3. La red neuronal por defecto

La mayoría de los estudios de neuroimagen funcional se han centrado en el estudio de las activaciones cerebrales, mientras que las desactivaciones se han examinado con menor frecuencia. Sin embargo, en la última década ha surgido un interés creciente en la llamada red neuronal por defecto (DMN, por sus siglas en inglés), consistente en un conjunto de regiones de la línea media del cerebro, la corteza frontal medial y el cingulado posterior/precuneus, que se activan de forma conjunta durante tareas de reposo y se desactivan conjuntamente durante la realización de una amplia gama de tareas que requieren demandas atencionales externas (ver **Figura 3**) (Andrews-Hanna et al 2010, Buckner et al 2008, Raichle et al 2001). Otras regiones de la red incluyen la corteza parietal inferior, la corteza temporal lateral, y el complejo del hipocampo, incluyendo hipocampo y la corteza circundante (Buckner et al 2008).

Desde su descubrimiento mucho se ha investigado y especulado sobre el posible rol de la DMN en el funcionamiento cerebral (para una revisión ver Buckner et al (2008)). Dada su alta actividad en reposo, se ha relacionado con procesos de pensamiento internos no asociados directamente con el ambiente externo inmediato (Binder et al 1999, Mason et al 2007, McKiernan et al 2003), mientras que otros autores han postulado que tiene una función más general y amplia de monitorización externa, corporal y emocional o de atención pasiva de bajo nivel (Gilbert et al 2007, Hahn et al 2007, Shulman et al 1997). La visión de la DMN como participante en la mentalización interna ha sido reforzada con la evidencia proveniente de estudios que han encontrado activación de regiones similares a las de la DMN durante la realización de tareas como la memoria autobiográfica (Cabeza & St Jacques 2007, Maguire 2001); teoría de la mente (Amodio & Frith 2006, Saxe et al 2004); visualización futura (Addis et al 2007, Schacter et al 2007, Schacter et al 2008); o dilemas morales (Greene et al 2001).

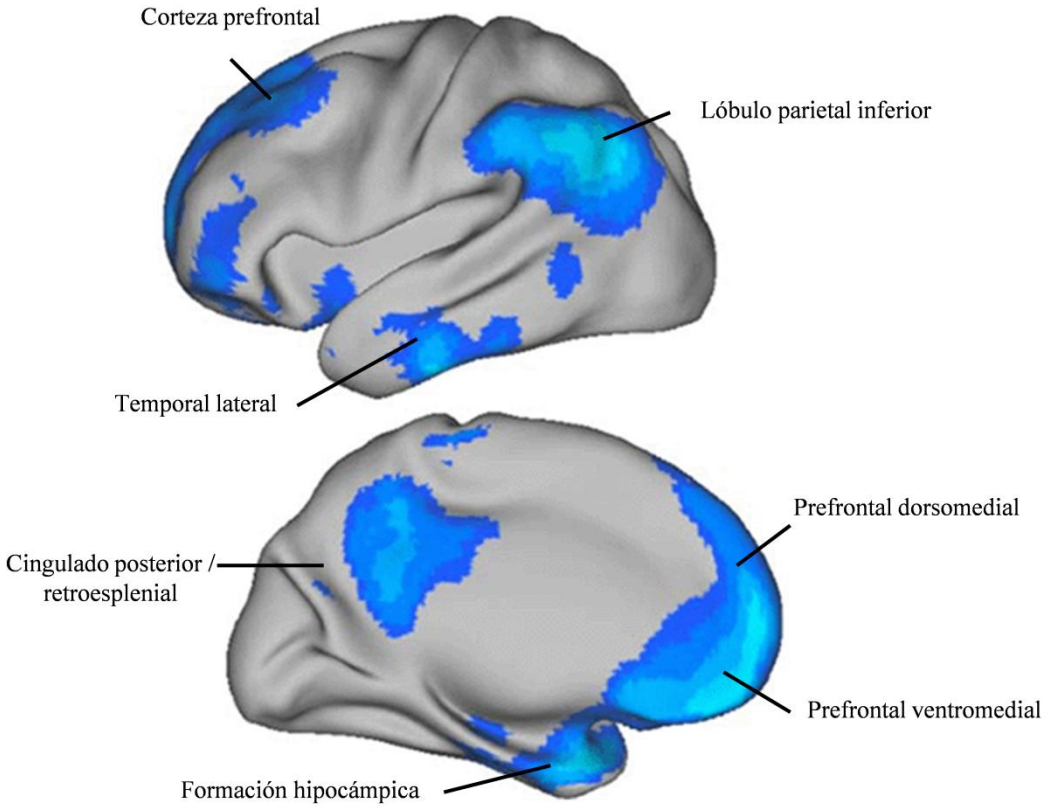

Figura 3. Superficie lateral y medial del hemisferio izquierdo y las regiones correspondientes a la DMN. Imagen adaptada de Buckner et al (2008).

Actualmente existe notable evidencia sobre alteraciones en esta red presentes en trastornos neurológicos y psiquiátricos, especialmente en esquizofrenia y en el trastorno depresivo mayor (para una revisión ver Broyd et al (2009) y Whitfield-Gabrieli & Ford (2012)). En cuanto a la esquizofrenia, los estudios de conectividad funcional en reposo han reportado aumento de conectividad funcional entre la DMN y redes que se activan durante la realización de tareas cognitivas atencionales (Jafri et al 2008, Zhou et al 2007), o ausencia de desactivación durante la realización de tareas cognitivas (Anticevic et al 2013, Dreher et al 2012, Milanovic et al 2011, Pomarol-Clotet et al 2008, Salgado-Pineda et al 2011, Schneider et al 2011, Whitfield-Gabrieli et al 2009). Estos resultados han sido investigados por su posible relación con síntomas clínicos del trastorno como las alucinaciones, delirios o ideas paranoides, y también han sido considerados como posibles mediadores del deterioro cognitivo característico de este trastorno (para una revisión ver Anticevic et al (2012) y Whitfield-Gabrieli & Ford (2012)). En cuanto al trastorno depresivo mayor, numerosos estudios han encontrado igualmente cambios en la activación y en la conectividad funcional de la DMN (Greicius et al 2007, Grimm et al 2009, Mulders et al 2015, Rodriguez-Cano et al

2014, Sheline et al 2009, Sheline et al 2010) y se han relacionado con algunos de los síntomas característicos de este trastorno, especialmente con la rumiación (Berman et al 2011, Hamilton et al 2011, Lemogne et al 2012). La evidencia de la alteración de la DMN en los trastornos del estado de ánimo, y en depresión concretamente, ha hecho que junto con las regiones clásicamente incluidas en los modelos neurobiológicos de estos trastornos (circuitos que engloban la corteza prefrontal y límbica principalmente), recientemente las regiones de la DMN hayan sido incorporadas en los nuevos modelos propuestos (Andrews-Hanna et al 2014, Malhi et al 2015, Pizzagalli 2011, Price & Drevets 2012).

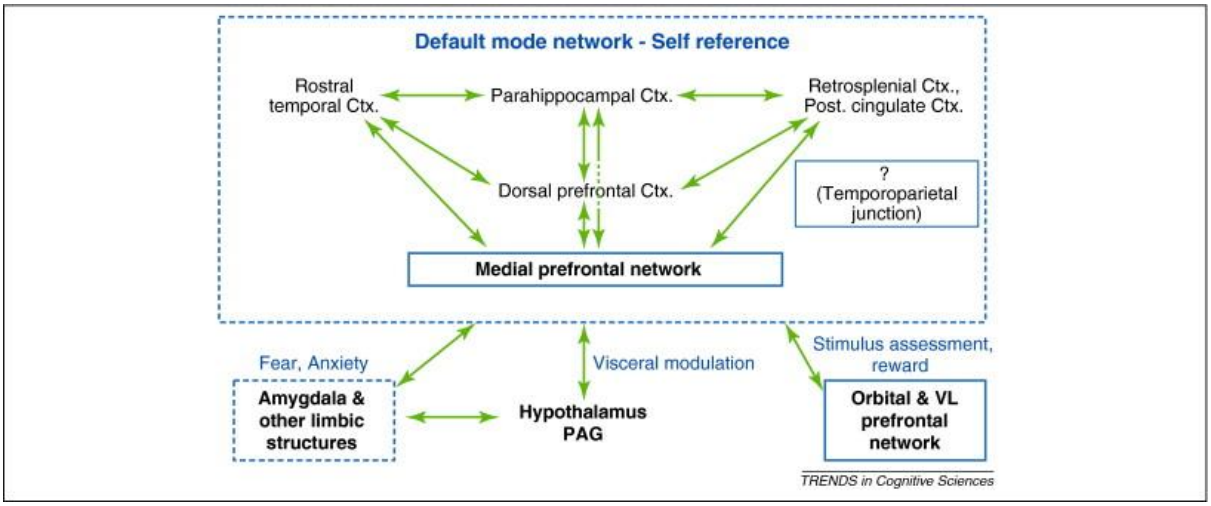

Figura 4. Diagrama de las conexiones entre la red prefrontal medial y otras áreas corticales como parte del sistema de la DMN; así como con la amígdala, el hipotálamo y la red prefrontal orbitofrontal, implicados en el procesamiento emocional, visceral y de refuerzo (Price & Drevets 2012).

Sin embargo, a día de hoy muy pocos estudios han explorado la integridad e implicación de esta red en el trastorno bipolar, aunque existe evidencia reciente que sugiere que el trastorno se puede caracterizar también por cambios en la desactivación que normalmente acompaña la ejecución de tareas cognitivas. Así, Pomarol-Clotet et al (2012) encontraron fracaso de la desactivación en la corteza frontal ventromedial durante la ejecución de una tarea de memoria de trabajo en pacientes maníacos en comparación con controles sanos, y Fernandez-Corcuera et al (2013) obtuvieron resultados similares cuando se exploró la fase depresiva del trastorno. Por el contrario, Strakowski et al (2008) encontraron una mayor desactivación en pacientes con un primer episodio maníaco en comparación con sujetos sanos en la corteza cingulada posterior bilateral, correspondiente al nodo posterior de la DMN, y en eutimia Allin et al (2010) y Costafreda et al (2011) observaron un fracaso de desactivación durante la ejecución de una tarea de fluidez verbal también en este nodo posterior.

1.3.4. Cambios cerebrales funcionales en familiares

Dado el componente genético del trastorno bipolar, surge la cuestión de si los cambios funcionales cerebrales observados en eutimia también se pueden detectar en los familiares de pacientes que no han desarrollado ningún trastorno mental.

En una revisión reciente realizada por Fusar-Poli et al (2012) en la que se incluyeron estudios de neuroimagen estructural y funcional en gemelos y familiares de primer o segundo grado de pacientes con trastorno bipolar, se observó que, a pesar de no haber diferencias significativas en el volumen de sustancia gris, los familiares mostraron un aumento en la activación frontal superior y medial, así como de la ínsula izquierda. Estos resultados indican que los cambios en el funcionamiento cerebral pueden ser mejores candidatos a la hora de identificar endofenotipos asociados al trastorno. Más recientemente, Piguet et al (2015) revisaron 25 estudios de fMRI con diversas tareas cognitivas y emocionales y encontraron que en conjunto, de los 12 estudios que examinaron diferencias en todo el cerebro, los cambios en los familiares se localizaban principalmente en regiones límbicas, especialmente en la amígdala, en la corteza prefrontal ventrolateral y medial y la corteza parietal, mostrando una cierta convergencia con los resultados obtenidos en los meta-análisis de neuroimagen funcional en trastorno bipolar (Chen et al 2011, Kupferschmidt & Zakzanis 2011).

En cuanto a los resultados en función de la tarea utilizada, los estudios que utilizan paradigmas de procesamiento emocional mostraron principalmente cambios a nivel de la amígdala y la corteza medial prefrontal. Por su parte, cuando se utilizan paradigmas cognitivos especialmente relacionados con funciones ejecutivas, las alteraciones funcionales se sitúan en regiones ventrolaterales prefrontales así como de la corteza cingulada posterior/precuneus y de los ganglios basales (Piguet et al 2015). Para un mayor detalle de los estudios realizados hasta la fecha, ver Anexo **Tabla 2**. En concreto, Drapier et al (2008) encontraron una mayor activación en la corteza orbitofrontal izquierda que se extendía hasta la corteza frontopolar y la corteza prefrontal ventrolateral en 20 familiares de primer grado de pacientes bipolares en comparación con 20 controles sanos durante la ejecución de la tarea n-back. Thermenos et al (2010) utilizando la misma tarea encontraron igualmente un aumento de la activación en la corteza frontopolar izquierda, esta vez junto con hiperactivación de la ínsula anterior y el lóbulo parietal derecho. Este aumento de activación en regiones parietales y de la ínsula también fue reportado utilizando una tarea de atención sostenida en un estudio

con una muestra de familiares ligeramente mayor (n=24) (Sepede et al 2012). Un patrón opuesto de resultados, es decir, disminución de la activación, también ha sido reportado. Así, Pompei et al (2011), utilizando la tarea Stroop, encontraron menor activación en la corteza parietal superior e inferior en 25 familiares en comparación con 48 controles. También se ha encontrado reducción en la activación frontotemporal y frontal medial utilizando una tarea de fluencia verbal (Allin et al 2010).

Sin embargo, cabe señalar que otros estudios no han encontrado cambios en activación en este tipo de muestras. El único estudio de fMRI realizado con gemelos monocigóticos de pacientes con trastorno bipolar no encontró diferencias de éstos con respecto a los controles, si bien la muestra era muy pequeña, 7 gemelos, y los análisis se restringieron a dos ROIs localizadas en regiones del giro frontal inferior bilateral (Costafreda et al 2009). Igualmente Whalley et al (2011) no encontraron diferencias en la activación cerebral durante la realización de una tarea de completamiento verbal, aunque sí se detectó un incremento de activación en la amígdala en relación con el incremento de la dificultad de la tarea en los familiares en comparación con los controles.

Por último, la reciente evidencia sobre la presencia de una posible disfunción en la DMN en el trastorno bipolar hace de estas regiones candidatas a la hora de explorar y determinar posibles biomarcadores o endofenotipos de la enfermedad. Sin embargo, actualmente no está claro si esta disfunción también caracteriza a los familiares de pacientes con trastorno bipolar. En el estudio anteriormente comentado, Allin et al (2010) encontraron un fracaso en la desactivación de la corteza cingulada posterior/precuneus no sólo en pacientes bipolares eutímicos sino también en 19 de sus familiares de primer grado no afectados. Por el contrario Sepede et al (2012) descubrieron un aumento en la desactivación de la corteza cingulada posterior en 22 familiares en comparación con 24 controles.

1.3.5. ¿Hay correlatos cerebrales del deterioro cognitivo en el trastorno bipolar?

Dadas las alteraciones tanto en la estructura como en el funcionamiento de determinadas regiones corticales y subcorticales, junto con la disminución del rendimiento cognitivo en al menos un porcentaje de los pacientes, es posible que estos dos fenómenos puedan estar asociados, es decir, que algunas de estas alteraciones cerebrales sean el correlato biológico del deterioro cognitivo presente en el trastorno bipolar.

Correlatos estructurales del deterioro cognitivo

Los primeros estudios de RM realizados en la década de los 90 fueron la primera evidencia sobre una posible relación entre los cambios volumétricos en regiones fronto-temporales y la presencia de hiperintensidades en la sustancia blanca con un peor rendimiento en pruebas cognitivas en pacientes con trastorno bipolar (para una revisión ver Bearden et al (2001)). Estudios posteriores realizados con muestras de mayor tamaño y con métodos de análisis más sofisticados de neuroimagen estructural encontraron diferencias en la relación entre el rendimiento en diversos test cognitivos y el volumen de sustancia gris de determinadas regiones cerebrales. Así, se han observado patrones de interacción diferenciales entre bipolares y controles en la correlación entre pruebas de funciones ejecutivas y la corteza cingulada anterior (Zimmerman et al 2006), la corteza parietal inferior y cuneus (Haldane et al 2008) o el volumen de los ventrículos laterales (Hartberg et al 2011b); junto con correlaciones específicas y positivas entre el volumen de la amígdala y el rendimiento en pruebas de memoria verbal inmediata y diferida (Killgore et al 2009) o entre la reducción en el cociente intelectual verbal y la pérdida de sustancia gris temporal en un estudio longitudinal de cuatro años de seguimiento (Moorhead et al 2007). Recientemente, Shepherd et al (2015), basándose en el rendimiento en un paradigma de memoria de trabajo, clasificaron una muestra de 70 sujetos con diagnóstico de esquizofrenia y trastorno bipolar tipo I en dos subgrupos (deteriorados y preservados). Mientras que ambos grupos mostraron disminución de sustancia gris en comparación con los controles en regiones fronto-temporales, cuando los pacientes deteriorados se compararon con aquellos preservados, el único cambio significativo entre ellos fue una mayor reducción de sustancia gris en el giro inferior frontal derecho y el giro precentral en el grupo de deteriorados.

Mediante el uso de técnicas de neuroimagen que evalúan el grosor cortical se han reportado correlaciones negativas específicas para el trastorno bipolar entre el grosor de la corteza cerebral del polo temporal derecho y el span de dígitos (Hartberg et al 2011a) y entre el grosor cortical del giro temporal superior izquierdo y del precuneus derecho con la capacidad de resolución de problemas (medida a través del tiempo invertido en el test de la Torre de Londres) y la velocidad psicomotora (medida a través del Trail Making Test) respectivamente (Oertel-Knochel et al 2015b). Por último, en otro estudio del mismo equipo en el que se utilizaron diferentes índices para evaluar la integridad de la sustancia blanca, se encontró una correlación significativa en los pacientes bipolares eutímicos entre el rendimiento en

resolución de problemas con medidas de difusión media y radial en el fórnix y en la radiación talámica derecha, mientras que no se observaron correlaciones significativas con el rendimiento en un test de aprendizaje verbal ni con medidas de FA (Oertel-Knochel et al 2014a).

Correlatos funcionales del deterioro cognitivo

Muy pocos estudios han tratado de determinar la relación entre el rendimiento en pruebas cognitivas en personas con trastorno bipolar con cambios en el funcionamiento cerebral (Oertel-Knochel et al 2013, Oertel-Knochel et al 2014b, Oertel-Knochel et al 2012, Oertel-Knochel et al 2015a). En uno de estos estudios realizados con una muestra de bipolares tipo I en remisión clínica, Oertel-Knochel et al (2013) utilizaron una tarea de memoria episódica y observaron tanto un menor rendimiento en la tarea como una menor activación cerebral en comparación con los controles. Las regiones afectadas incluían el giro frontal superior y medio durante la codificación, y el giro frontal inferior y medio más la región parahipocampal y otras regiones de la corteza medial posterior durante la recuperación, así como una asociación entre la activación de estas regiones parietales posteriores y del parahipocampo con el rendimiento en la tarea. Posteriormente, los mismos autores utilizaron una tarea de memoria episódica no verbal, a través de la cual reportaron una asociación específica entre la hipoactivación del giro lingual izquierdo y el rendimiento en la tarea y con la puntuación en aprendizaje verbal, que además se mostró inferior en comparación con la de los controles (Oertel-Knochel et al 2014b).

2 Objetivos e hipótesis

Los estudios llevados a cabo hasta la fecha han aportado una respuesta incompleta en relación a los cambios funcionales que caracterizan el trastorno bipolar, especialmente en cuanto a la determinación de los cambios dependientes del estado de ánimo frente a aquellos persistentes en eutimia. Además, estos estudios se han centrado principalmente en las activaciones, y poco se sabe acerca de los cambios en la desactivación.

Dado que los cambios funcionales cerebrales en eutimia no se relacionan directamente con los síntomas agudos de la enfermedad, es decir, la depresión o la manía, es posible que reflejen otros aspectos del trastorno. Una posibilidad es que representen un factor de riesgo, es decir, que reflejen la vulnerabilidad a la enfermedad. Puesto que uno de los principales factores que confieren vulnerabilidad al trastorno bipolar es la genética, se plantea la cuestión de si los cambios funcionales del cerebro, tal vez similares a los observados en eutimia, también se puedan detectar en los familiares de pacientes que no han desarrollado el trastorno.

Por otro lado, es posible que los cambios, tanto estructurales como funcionales, reflejen el deterioro cognitivo que se encuentra en pacientes en eutimia. Hasta la fecha pocos estudios se han centrado en el establecimiento de las bases neurobiológicas del deterioro cognitivo en eutimia y los resultados hasta el momento han sido inconsistentes.

El objetivo de este trabajo es, por tanto, 1) examinar los cambios en el funcionamiento cerebral durante la ejecución de una tarea cognitiva en cada una de las tres fases de trastorno bipolar; 2) examinar qué cambios en el funcionamiento cerebral están presentes en familiares sanos de primer grado de los pacientes; y 3) examinar si, y en qué medida, el deterioro cognitivo en pacientes eutímicos se asocia con cambios cerebrales funcionales y/o estructurales.

Estudio 1: Brain functional changes across the different phases of bipolar disorder

El objetivo de este estudio es identificar los patrones de activación y desactivación durante la ejecución de una tarea cognitiva en pacientes bipolares durante las diferentes fases del trastorno: manía, depresión y eutimia.

Hipótesis

1. Los pacientes bipolares mostrarán activación reducida en comparación con los controles sanos. Dados los hallazgos existentes, esta reducción afectará a la corteza prefrontal dorsolateral entre otras regiones y estará presente durante las dos fases agudas de la enfermedad y en eutimia.

2. Los pacientes bipolares mostrarán un fallo de desactivación en la región frontal medial y/o en el giro cingulado posterior/precuneus. Debido a la pequeña cantidad existente de estudios que evalúan las desactivaciones en el trastorno bipolar, no se plantean hipótesis en relación con las distintas fases de la enfermedad.

Estudio 2: Brain functional changes in first-degree relatives of patients with bipolar disorder

El objetivo de este estudio es determinar la presencia de cambios en el funcionamiento cerebral durante la ejecución de una tarea de memoria de trabajo en un grupo de hermanos sanos de estos pacientes, comparando su patrón de activación y desactivación con sus respectivos hermanos diagnosticados de trastorno bipolar y en eutimia, y con un grupo control de personas sin antecedentes de primer grado de enfermedad mental.

Hipótesis

1. Basado en el limitado número de estudios existentes, se plantea la hipótesis de que los hermanos sanos de los pacientes con trastorno bipolar mostrarán cambios de activación en comparación con los controles sanos. En la actualidad no es posible especificar las regiones afectadas, o si los cambios van a tomar la forma de activación relativamente reducida o aumentada.

2. Se plantea la hipótesis de que los hermanos de los pacientes con trastorno bipolar mostrarán un cambio en el patrón de desactivación en una o más áreas de la red neuronal por defecto. Teniendo en cuenta que existen actualmente escasos estudios en la literatura que examinan estas desactivaciones en los familiares, no hay hipótesis en relación a la dirección de los cambios.

3. El patrón de cambios de neuroimagen funcional en los hermanos de pacientes con trastorno bipolar mostrará similitudes con la observada en los pacientes en la fase de eutimia.

Estudio 3: Structural and functional brain correlates of cognitive impairment in euthymic patients with bipolar disorder

El objetivo de este último estudio es determinar los correlatos funcionales y/o estructurales del deterioro cognitivo en pacientes eutímicos con trastorno bipolar. Los cambios estructurales serán examinados mediante VBM para el volumen de sustancia gris y blanca, y los cambios funcionales serán evaluados mediante la ejecución de una tarea de memoria de trabajo.

Hipótesis

1. Los pacientes eutímicos con deterioro cognitivo mostrarán evidencia de disminución de volumen de sustancia gris y blanca en comparación con los pacientes preservados cognitivamente.

2. Los pacientes eutímicos con deterioro cognitivo mostrarán cambios funcionales en comparación con pacientes eutímicos sin deterioro cognitivo durante la realización de una tarea de memoria de trabajo. No se establecen hipótesis acerca de si estas diferencias afectan a la activación, desactivación o ambas.

3. Los pacientes eutímicos cognitivamente preservados mostrarán diferencias estructurales y funcionales en comparación con los controles sanos.

3 Métodos

La descripción detallada de las características de la muestra, las escalas clínicas y test neuropsicológicos, los procedimientos y los métodos estadísticos utilizados se encuentran en cada uno de los artículos correspondientes. A continuación se presentará un breve resumen de los métodos comunes a los tres estudios.

3.1. MUESTRA

La muestra de pacientes fue reclutada en tres hospitales: Hospital Benito Menni CASM, Hospital Clínic y el Hospital General de Granollers. Todos los pacientes cumplían los criterios del DSM-IV para el trastorno bipolar y fueron excluidos si: (a) eran zurdos (b) eran menores de 18 o mayores de 65 años, (c) tenían historia de traumatismo craneoencefálico o enfermedad neurológica, (d) presencia de abuso/dependencia de alcohol u otras sustancias tóxicas en los 12 meses previos a la participación, o (e) terapia electroconvulsiva en los 12 meses anteriores.

El grupo de controles sanos fue reclutado a través de carteles, publicidad y boca a boca en el hospital y la comunidad local por parte del personal de la unidad de investigación. Estos controles fueron entrevistados y excluidos si, además de los criterios de exclusión de los pacientes, también informaban de un historial de enfermedad mental y/o tratamiento con medicamentos psicotrópicos. También fueron excluidos si presentaban antecedentes de primer grado de enfermedad mental.

En el estudio que incluyó un grupo de hermanos no afectados de los pacientes reclutados, éstos cumplían los mismos criterios de exclusión presentados anteriormente y la ausencia de enfermedad mental se determinó mediante la evaluación a través de la entrevista diagnóstica computarizada para el DSM-IV (Robins et al 2000).

3.2. ESCALAS Y TEST ADMINISTRADOS

A continuación se detallan las escalas y los test administrados en los tres estudios:

- **Young Mania Rating Scale (YMRS)**: se trata de una escala de 11 ítems que permite evaluar y medir la intensidad de la sintomatología maníaca mediante una entrevista semi-estructurada (Young et al 1978) y adaptada para población española (Colom et

al 2002). Evalúa la presencia de euforia, hiperactividad, aumento del impulso sexual, cambios del sueño, presencia de irritabilidad, cambios en la expresión verbal, presencia de trastornos del pensamiento y lenguaje, agresividad, apariencia y conciencia de enfermedad (insight). La puntuación total va de 0 a 60 puntos y la puntuación requerida para determinar manía fue de > 18 y de <8 para la eutimia.

- **Hamilton Depression Rating Scale (HDRS):** se trata de una escala de 21 ítems que permite evaluar cuantitativamente la gravedad de los síntomas depresivos (Hamilton 1960) y está adaptada a la población española (Ramos-Brieva & Cordero Villafafila 1986). Las preguntas abarcan aspectos del estado de ánimo (humor depresivo, sentimiento de culpa); presencia de pensamiento suicida; insomnio precoz, in**t**ermedio y tardío; inhibición del pensamiento, lenguaje, concentración y de la actividad motora, agitación psicomotora; ansiedad psíquica y somática; síntomas somáticos gastrointestinales, genitales y generales, hipocondría; pérdida de peso; y disminución del insight. La puntuación para determinar depresión fue de >18 y de <8 para la eutimia.

- **Global Assessment of Functioning:** el funcionamiento psicosocial fue medido mediante esta escala que evalúa el funcionamiento psicológico, social y ocupacional a través de un continuo (Hall 1995).

- **Test de Acentuación de Palabras (TAP):** el cociente intelectual premórbido se estimó a través de este test que utiliza 30 palabras en español de baja frecuencia cuyos acentos se han eliminado (Del Ser et al 1997) y que ofrece una estimación fiable del cociente intelectual en sujetos normales y sensible a la diferencia de cociente intelectual premórbido-actual en pacientes con esquizofrenia (Gomar et al 2011).

- **Wechsler Adult Intelligence Scale – 3a versión (WAIS-III):** el cociente intelectual actual se evaluó mediante el prorrateo de cuatro pruebas del WAIS-III (Wechsler 2001): vocabulario, semejanzas, diseño de bloques y matrices.

3.3. PROCEDIMIENTOS DE NEUROIMAGEN

Los métodos de neuroimagen incluyen una variedad de técnicas que permiten obtener imágenes *in vivo* de la estructura o función del cerebro. La RM se hizo disponible en la década de 1980 y ofrece la ventaja de permitir un excelente contraste entre sustancia gris y blanca, tanto en regiones corticales como subcorticales. El posterior desarrollo de las técnicas de fMRI ha permitido medir la función cerebral a través de los cambios en la oxigenación local de la sangre, los cuales reflejan la cantidad de actividad cerebral local. Esta medición, conocida como señal dependiente del nivel de oxigeno en sangre (BOLD, por sus siglas en inglés) se ha convertido en el método más ampliamente utilizado para la investigación de los correlatos neurales de distintas funciones mentales. Su ventaja radica en su capacidad para obtener imágenes de forma segura y no invasiva con muy buena resolución espacial y relativamente buena resolución temporal en comparación con métodos anteriores.

3.3.1. Técnicas de de MRI y fMRI

Brevemente, la señal de la máquina de resonancia magnética se basa en los mismos principios del fenómeno de resonancia magnética que se da en la naturaleza al someter el núcleo del átomo de hidrógeno a un campo magnético (Huettel et al 2008). Nuestro cuerpo alberga grandes cantidades de hidrógeno ligado a los distintos tejidos y dado que esta vinculación en cada tejido tiene sus particularidades, su comportamiento dentro del campo magnético del escáner será sutilmente distinto. De ahí que las diferentes propiedades magnéticas que tienen los diferentes tipos de tejidos darán lugar a una señal distinta para cada uno de ellos. En un entorno no magnetizado, los núcleos de los átomos de hidrógenos rotan sobre sí mismos apuntando en dirección aleatoria, mientras que ante un campo magnético externo se alinean en dirección paralela o anti-paralela, provocando una magnetización del tejido proporcional a la intensidad del campo magnético. Sin embargo, para poder adquirir las imágenes falta añadir una perturbación mayor para que la magnetización sea completa. Cuando se introducen pulsos de radiofrecuencia, los protones son perturbados de tal modo que la dirección de magnetización se orienta perfectamente con la oscilación del pulso. En este momento de máxima excitación, los núcleos de los átomos de hidrogeno adquieren el máximo de energía, dando lugar al fenómeno de resonancia que se mantendrá mientras dure este pulso. Después de un corto periodo de tiempo, al eliminar el pulso, los átomos vuelven a su estado basal paralelo al campo magnético estático, y emiten

fotones de energía de radiofrecuencia que se liberan al medio, lo que se conoce como proceso de relajación. La frecuencia que emiten los distintos núcleos de hidrogeno durante la relajación, en determinados tiempos, nos indicarán la localización y el comportamiento de cada tejido (si alcanza pronto o más tarde el equilibrio). Sin embargo esta información está en un dominio frecuencial y para que la imagen pueda ser representada se debe traducir a un dominio espacial mediante la transformada de Fourier, dando lugar a la imagen de resonancia magnética capturada por las bobinas de detección de la señal del scanner.

La sensibilidad de la señal que podemos captar del escáner nos permite distinguir incluso la fluctuación de los niveles de oxigeno en sangre. Así, las técnicas de fMRI se basan en este fenómeno para medir la actividad del cerebro mediante la medición de los cambios en la oxigenación local de la sangre, que a su vez refleja la cantidad de actividad cerebral local (Forster et al 1998, Ramsey et al 2002). Una mayor concentración de oxígeno en una localización determinada del cerebro se asocia a una mayor actividad, ya que la cantidad de sangre que se envía a dicha zona es mayor de lo que sería necesario con tal de reponer el desgaste de oxígeno que se consume por la actividad de las células que trabajan a un mayor rendimiento. Por lo tanto, el aumento de la actividad en el flujo sanguíneo causado por la actividad neuronal conlleva un exceso relativo de oxígeno en la sangre local. La señal medida en fMRI depende de este cambio en el nivel de oxigenación y se conoce como señal BOLD. Para poder captar las diferencias entre los distintos niveles de señal BOLD, al contrario de lo que sucede cuando queremos obtener una imagen estructural, debemos adquirir un gran número de volúmenes cerebrales, con la intención de poder compararlos entre sí y determinar las fluctuaciones en el tiempo que han tenido lugar.

El auge de la neurociencia cognitiva en la década de 1980 se hizo servir de esta técnica para investigar numerosos procesos cognitivos y psicológicos (Huettel et al 2008). Para ello se diseñaron paradigmas que utilizan la sustracción de las activaciones cerebrales entre dos condiciones diferentes, cuya diferencia es el proceso psicológico de interés y, de esta forma, aislar su respuesta. En función de la hipótesis a estudiar, se pueden diseñar diferentes tipos de paradigmas de fMRI: diseño de bloques, diseño relacionado con eventos y diseños mixtos. El más utilizado dada su gran potencia estadística es el diseño de bloques, en el que dos o más condiciones se presentan de forma alterna en bloques de una determinada duración.

Pese a las ventajas que la fMRI presenta, sobre todo en relación a la posibilidad de estudiar *in vivo* el funcionamiento cerebral, siguen existiendo una serie de limitaciones y complejidades inherentes a la técnica (Liu 2016, Logothetis 2008). Su principal crítica se relaciona con el hecho de que la actividad neuronal se estudia de forma indirecta lo que limita la resolución espacial. Además, no tiene una gran resolución temporal ya que, aunque la activación neuronal es casi instantánea tras la presentación de un estímulo, el pico máximo de señal ocurre unos 4-6 segundos después. Así mismo, las imágenes son susceptibles a artefactos causados por el movimiento y aspectos fisiológicos y existe una gran variabilidad en los resultados debido a las diferencias entre individuos, diseños de paradigma o el uso de diferentes contrastes, entre otros.

3.3.2. Paradigma funcional

El paradigma utilizado fue una versión secuencial de letras de la tarea n-back (Gevins & Cutillo 1993) que evalúa memoria de trabajo, la capacidad para mantener elementos en la memoria mientras se atiende a un elemento actual (Lezak 2004). Para este estudio, se utilizó un diseño de bloques en el que se presentaron dos niveles de carga de memoria (1-back y 2-back). En la tarea 1-back, los participantes tuvieron que detectar y presionar un botón cuando una letra se repetía dos veces consecutivas, mientras que en la tarea 2-back los participantes hubieron de detectar cuándo una letra era igual a la presentada dos ítems antes. De forma intercalada a estos bloques, hubo otros bloques donde se presentaban asteriscos con la misma frecuencia que las letras y que constituían la línea basal.

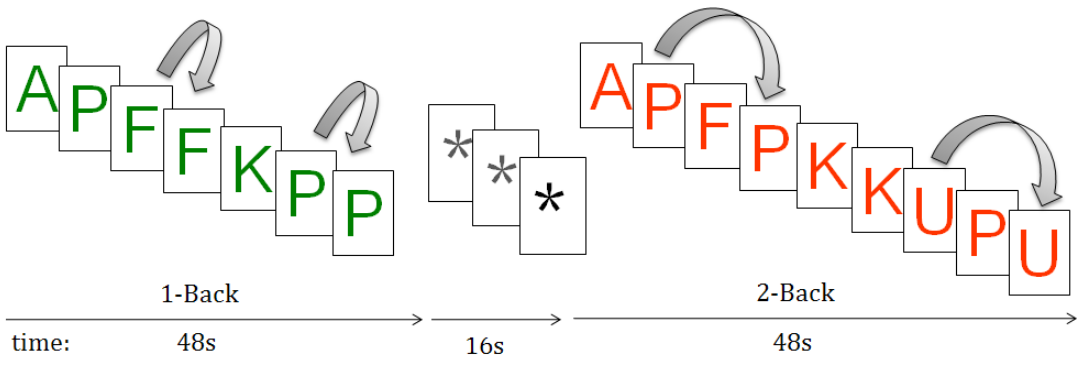

Figura 5. Versión de secuenciación de letras de la tarea n-back con dos niveles de carga de memoria: 1-back (verdes) y 2-back (rojas).

El rendimiento de los participantes se midió utilizando el índice de detección de señal de la teoría de la sensibilidad (d') que evalúa la capacidad de discriminar los ítems objetivo de los que no lo son (Green & Swets 1966). Los valores más altos de d' indican una mejor capacidad para discriminar entre objetivos y distractores.

3.3.3. Adquisición y análisis de las imágenes

Los datos de fMRI se adquirieron en un scanner 1.5T- General Electric Signa. Para cada sujeto, se adquirieron 266 volúmenes de imagen eco-planar gradiente que representa el contraste BOLD. Cada volumen contiene 16 planos axiales adquiridos con los siguientes parámetros: tiempo de repetición = 2000 ms, tiempo de eco = 20 ms, ángulo de rotación 70º, espesor: 7 mm, espacio inter-corte: 0.7 mm, resolución planar: 3x3 mm. Los primeros 10 volúmenes fueron descartados para evitar los efectos de saturación T1.

Los análisis se realizaron con el módulo de FEAT, incluido en el paquete de software FSL (Smith et al 2004) desarrollado por personal de la Universidad de Oxford en colaboración con otras instituciones. El proceso implica: a) corrección de movimiento (Jenkinson et al 2002); b) eliminación del tejido no cerebral (Smith 2002); c) suavizado Gaussiano isotrópico de amplitud máxima a media altura (FWHM, por sus siglas en inglés) de 5 mm; d) eliminación de bajas frecuencias mediante la aplicación de un filtro temporal de paso-alto (high-pass temporal filtering); e) análisis estadístico de la serie temporal con corrección de autocorrelación local (Woolrich et al 2001) y f) registro en el espacio estándar MNI 152 (Jenkinson et al 2002, Jenkinson & Smith 2001). Para minimizar los efectos no deseados relacionados con el movimiento, los parámetros de movimiento se utilizaron como covariable en el análisis individual y los participantes con un movimiento estimado máximo absoluto > 3,0 mm o un movimiento absoluto medio> 0,3 mm fueron excluidos del estudio.

Para generar los mapas de activación individuales se ajustó al modelo lineal general para tres contrastes diferentes: 1-back vs línea basal, 2-back vs línea basal, 2-back vs 1-back. Las diferencias en los mapas de activación entre pacientes y controles se analizaron mediante modelos lineales generales de efectos mixtos (Beckmann et al 2006). El modulo FEAT usa la teoría de campos aleatorios Gaussianos para determinar adecuadamente los patrones de distribución espacial cuando se realizan pruebas estadísticas. En concreto, los análisis se llevaron a cabo a través del FAME 1 utilizando un umbral z> 2.3 (Beckmann et al 2003,

Woolrich et al 2001) y un valor de p <0.05 corregido para comparaciones múltiples (Woolrich et al 2004, Worsley 2001).

3.4. ASPECTOS ÉTICOS

Los tres estudios fueron presentados ante el comité de ética de investigación clínica de las Germanes Hospitalàries y fueron debidamente aprobados. Todos los participantes fueron informados sobre la naturaleza del estudio y participaron de forma voluntaria, sin recibir compensación económica y firmando previamente el consentimiento informado aprobado por dicho comité. En el caso de los pacientes, el estudio no interfirió con el tratamiento prescrito por el psiquiatra de referencia.

Todos los participantes se sometieron a una sesión de RM tanto estructural como funcional, sin necesidad de administrar ningún tipo de contraste. La RM no emite radiación por lo que no tiene efectos nocivos para la salud; no obstante, antes de entrar en el escáner, los participantes fueron explorados para determinar posibles contraindicaciones y firmaron un cuestionario que exploraba posibles condiciones incompatibles con el escáner (por ejemplo, presencia de metales) para asegurarse de que no hubiera ningún riesgo potencial.

Todos los datos de identificación han recibido un tratamiento que garantiza la confidencialidad de los mismos. Cada participante tiene un código asignado y los datos de cada uno de ellos fueron introducidos en una base de datos a la que sólo el personal de investigación de FIDMAG tiene acceso a través de una contraseña individual. Los informes radiológicos y neuropsicológicos fueron incluidos en la historia clínica de los pacientes y todos los participantes fueron informados acerca de los resultados.

4 Resultados

Estudio 1

Brain functional changes across the different phases of bipolar disorder

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En este primer estudio de neuroimagen funcional en el que se compararon 38 bipolares en manía y 38 en depresión con 38 controles, se encontró que ambos grupos de pacientes presentaban un rendimiento significativamente menor durante la realización de la tarea n-back, tanto para la versión del 1-back como 2-back, y menor que un grupo de 38 pacientes eutímicos en el caso del grupo en manía. Las activaciones cerebrales medias fueron las esperadas e incluyeron principalmente regiones fronto-parietales así como desactivaciones de regiones de la DMN, mientras que en los grupos de pacientes, éstas siguieron un patrón similar al de los controles, pero fueron menos extensas e intensas.

La comparación de los grupos entre sí reveló que los pacientes en manía y depresión, en comparación con los controles, mostraban una reducción de la activación bilateral en la corteza prefrontal dorsolateral, parietal, precuneus, tálamo, ganglios basales y cerebelo junto con un fallo de desactivación de la corteza frontal medial. Así mismo, en comparación con los pacientes eutímicos, mostraron una activación reducida en la corteza parietal dorsal y precuneus bilateralmente en el caso de la manía, y únicamente en el hemisferio derecho en el caso de la depresión. Por último, los pacientes eutímicos, en comparación con los controles, únicamente mostraron un fallo de desactivación de la corteza medial frontal.

Incluyendo los cuatro grupos en un modelo de ANOVA se obtuvieron cuatro clústeres significativos. La corteza parietal dorsal bilateral mostró una activación reducida en manía y depresión en comparación con eutimia y el grupo control; en la corteza prefrontal dorsolateral los tres grupos mostraron una menor activación en comparación con el grupo control y además, el grupo de manía en comparación con el grupo eutímico; y los tres grupos de pacientes mostraron un fallo de desactivación en comparación con los controles en la corteza medial frontal.

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Background
Little is known about how functional imaging changes in bipolar disorder relate to different phases of the illness.

Aims
To compare cognitive task activation in participants with bipolar disorder examined in different phases of illness.

Method
Participants with bipolar disorder in mania ($n = 38$), depression ($n = 38$) and euthymia ($n = 38$), as well as healthy controls ($n = 38$), underwent functional magnetic resonance imaging during performance of the n-back working memory task. Activations and de-activations were compared between the bipolar subgroups and the controls, and among the bipolar subgroups. All participants were also entered into a linear mixed-effects model.

Results
Compared with the controls, the mania and depression subgroups, but not the euthymia subgroup, showed reduced activation in the dorsolateral prefrontal cortex, the parietal cortex and other areas. Compared with the euthymia subgroup, the mania and depression subgroups showed hypoactivation in the parietal cortex. All three bipolar subgroups showed failure of de-activation in the ventromedial frontal cortex. Linear mixed-effects modelling revealed a further cluster of reduced activation in the left dorsolateral prefrontal cortex in the patients; this was significantly more marked in the mania than in the euthymia subgroup.

Conclusions
Bipolar disorder is characterised by mood state-dependent hypoactivation in the parietal cortex. Reduced dorsolateral prefrontal activation is a further feature of mania and depression, which may improve partially in euthymia. Failure of de-activation in the medial frontal cortex shows trait-like characteristics.

Declaration of interest
None.

Functional imaging studies in bipolar disorder have had heterogeneous and at times confusing findings, although there is now a broad consensus that the disorder is characterised by overactivity in subcortical structures such as the amygdala, hippocampus and basal ganglia, coupled with reduced activity in prefrontal and some other cortical regions.[1–4] Recent meta-analyses suggest that this pattern is seen both at rest and in studies using task activation,[5] although the pattern differs to some extent depending on whether cognitive or emotional tasks (typically facial emotion processing) are used.[6] What remains less clear is the 'state' *v.* 'trait' characteristics of functional imaging abnormality in bipolar disorder, i.e. whether there are differences between patients in manic and depressed episodes and to what extent changes seen in both phases of illness persist into euthymia.

In Kupferschmidt & Zakzanis'[5] meta-analysis of 55 studies that pooled conventional effect-size data, resting and task-related changes were seen in episodes of illness and in euthymia but the differences between phases were complex. Cortical hypoactivity and limbic hyperactivity was found to be greater in patients in a manic phase than in euthymia, and patients in a depressed phase showed greater hypoactivation in frontal regions than in euthymia. However, patients in euthymia showed more evidence of limbic hyperactivity than those with depression. Abnormalities were also more pronounced in patients in a manic than in depressed phase. Rather differently, Chen *et al*'s[6] meta-analysis of voxel-based functional magnetic resonance imaging (fMRI) studies found that changes (reduced activation) were restricted to the lingual gyrus in 26 studies carried out on participants in a euthymic phase. There were only relatively few studies carried out exclusively on participants in manic and depressed phases (8 and 7 respectively), and so their findings – decreased activation in the inferior frontal gyrus in mania and no change in depression – may not have been reliable.

In what appears to be the only contemporary study to directly compare patients across phases, Townsend *et al*[7] examined 13 patients in a manic phase, 14 in a depressed phase and 15 in a euthymic phase, as well as 14 healthy controls, during performance of the n-back working memory task. Citing a lack of availability of methods for analysing differences among four groups at the whole-brain level, the authors only examined two predetermined regions of interest (ROIs), the left and right dorsolateral prefrontal cortex and the left and right posterior parietal cortex. They found reduced activation in both ROIs in mania, depression and euthymia, with no significant variation across phase.

Over the past decade the importance not only of task-related activations but also de-activations has become increasingly recognised. This follows the discovery of the so-called default mode network, an interconnected set of brain regions that are highly active at rest but de-activate during performance of a wide range of attention- demanding tasks.[8,9] Prominent among these regions are two midline cortical areas, the medial frontal cortex anteriorly and the posterior cingulate cortex/precuneus posteriorly. Recent evidence suggests that bipolar disorder may also be characterised by de-activation changes in the default mode network. Thus, Pomarol-Clotet *et al*[10] found failure of de-activation in the ventromedial frontal cortex during performance of the n-back task in participants in a manic episode compared with healthy controls, and Fernández-Corcuera *et al*[11] had similar findings in patients with bipolar depression.

Strakowski *et al*,[12] in contrast, found significantly greater de-activation in participants with first-episode mania compared with healthy controls in the bilateral posterior cingulate cortex. So far there has been only one study of patients in the euthymic phase: Allin *et al*[13] found no changes in the medial frontal or lateral parietal nodes of the default mode network during performance of a paced verbal fluency task, but failure of de-activation was seen in the retrosplenial cortex and adjacent precuneate cortex, an area conforming reasonably closely to the posterior midline node.

The aim in this study was to examine whether task-related activations differed in patients in manic, depressed and euthymic bipolar phases, and also to further clarify the pattern of de-activation changes associated with the disorder. We used a cognitive task, the n-back working memory task, which has been found to be associated with functional imaging changes in both illness phases of bipolar disorder[7,10,11] and in euthymia (for a review see Cremaschi *et al*[14]), and which we have found to reliably produce de-activation in the territory of the default mode network.[10,11,15,16] We used whole-brain voxel-based analysis and were able to take advantage of advances in fMRI methodology to carry out a conjoint analysis of the four groups of participants (i.e. the three bipolar disorder subgroups and the healthy control group).

Method

Participants

The patient sample was recruited from three hospitals in Barcelona, Benito Menni CASM, Hospital Clínic and Hospital General de Granollers. All patients met DSM-IV[17] criteria for bipolar disorder, made up of three subgroups, mania ($n = 38$, all type I), depression ($n = 38$, 32 type I and 6 type II) and euthymia ($n = 38$, all type I). The participants in the mania subgroup were required to have a Young Mania Rating Scale (YMRS)[18] score $\geqslant 18$ and those in the depression subgroup to have a score of $\geqslant 15$ on the Hamilton Rating Scale for Depression (21-items, HRSD).[19] Participants in the euthymia subgroup were required to have had no episodes of illness for at least 3 months and a score on the HRDS-21 of $\leqslant 8$ and YMRS of $\leqslant 8$ at the time of scanning. All patients were right handed.

Patients were excluded if: (a) they were younger than 18 or older than 65 years, (b) they had a history of brain trauma or neurological disease, or (c) there was alcohol/substance misuse in the 12 months prior to participation. Patients who had undergone electroconvulsive therapy in the previous 12 months were also excluded.

In the mania subgroup, patients were taking the following medications: mood stabilisers (lithium $n = 20$; other mood stabilisers $n = 5$); antidepressants ($n = 2$) and antipsychotics ($n = 28$, second generation 21; first generation 2; combination 5); all medication data were missing for 1 patient. In the depression subgroup, patients were taking mood stabilisers (lithium $n = 25$; other mood stabilisers $n = 9$) and/or antidepressants ($n = 22$) and antipsychotics ($n = 20$, all second generation). Most of the participants in the euthymia subgroup were on mood stabilisers (lithium $n = 28$; other mood stabilisers $n = 8$); some patients were taking antidepressants ($n = 8$) and some were also taking antipsychotics ($n = 21$, all second generation).

A healthy control group ($n = 38$) was recruited via poster and web-based advertisement in the hospital and local community, plus word-of-mouth requests from staff in the research unit. They met the same exclusion criteria as the bipolar group. They were interviewed and excluded if they reported a history of mental illness and/or treatment with psychotropic medication other than non-regular use of benzodiazepines or similar drugs for insomnia. They were also questioned about family history of mental illness and excluded if a first-degree relative had experienced symptoms consistent with major psychiatric disorder and/or had received any form of in- or out-patient psychiatric care. All were right handed.

All four groups were matched for age, gender and IQ, as estimated by the Word Accentuation Test (Test de Acentuación de Palabras, TAP),[20] a test requiring pronunciation of Spanish words whose accents have been removed. The TAP has been standardised against the Wechsler Adult Intelligence Scale (WAIS-III)[21] and scores can be converted into full-scale IQ estimates.[22] Both the bipolar and control groups were also required to have a current IQ in the normal range (i.e. $\geqslant 70$), as measured using four subtests of the WAIS-III: vocabulary, similarities, block design and matrix reasoning.

All participants gave written informed consent. The study was approved by the local research ethics committees.

Scanning procedure

While being scanned, individuals performed a sequential-letter version of the n-back task[23] in the scanner (Fig. 1). Two levels of memory load (1-back and 2-back) were presented in a blocked design manner. Each block consisted of 24 letters that were shown every 2 s (1 s on, 1 s off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within the blocks. Individuals had to indicate repetitions by pressing a button. 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 s. To identify which task had to be performed, characters were shown in green in 1-back blocks and in red in 2-back blocks. All participants first went through a training session outside the scanner.

Task performance was measured using the signal detection theory index of sensitivity (d') of ability to discriminate targets from non-targets.[24] Higher values of d' indicate better ability to discriminate between targets and distractors. Participants who had negative d' values in either or both of the 1-back and 2-back versions of the task, which suggests that they were not performing it, were *a priori* excluded from the study.

In each individual scanning session 266 volumes were acquired from a 1.5-T GE Signa scanner. A gradient-echo echo-planar imaging (EPI) sequence depicting the blood oxygenation level-dependent (BOLD) contrast was used. Each volume contained 16 axial planes acquired with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 20 ms, flip angle 70°, section thickness, 7 mm, section skip, 0.7 mm, in-plane resolution, 3 × 3 mm. The first 10 volumes were discarded to avoid T_1 saturation effects.

Individual fMRI analyses were performed with the FEAT module, included in FSL software (version 4.19 for Linux).[25] In the preprocessing phase, images were corrected for movement, co-registered and spatially filtered with a Gaussian filter (full-width at half maximum (FWHM) = 5 mm). To minimise 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. General linear models were fitted to generate individual activation maps for the contrast comparing blocks of baseline with blocks of the 2-back level of the task. To further reduce the potential effect of movement, values of movement parameters were included as nuisance covariates in the fitting of individual linear models.

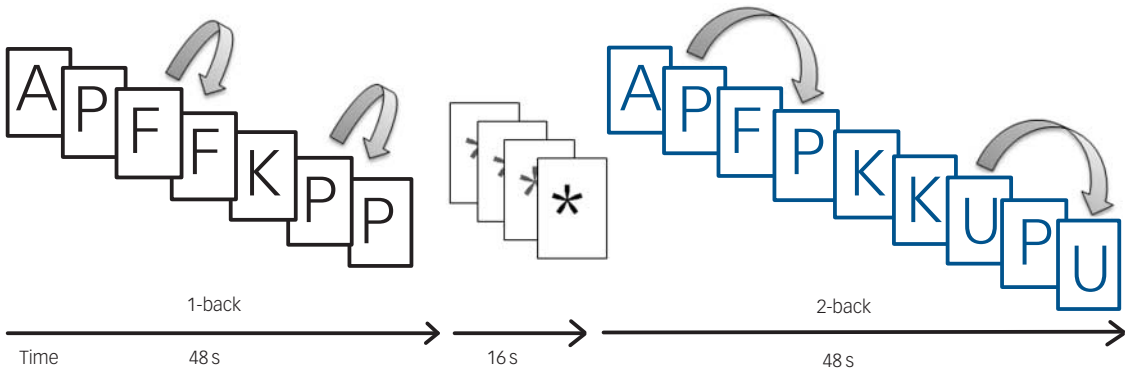

Fig. 1 Sequential-letter version of the n-back task with two levels of memory load, 1-back (black) and 2-back (blue).

Before the group analyses, images were normalised to a common stereotaxic space (Montreal Neurologic Institute (MNI) template).

Group comparisons

The same FEAT module was used to fit a linear mixed-effects model including the baseline *v.* 2-back activation images for the four independent groups. Using this model, each bipolar subgroup was individually compared with the healthy controls. The bipolar subgroups were also compared with each other, i.e. mania *v.* euthymia, depression *v.* euthymia and mania *v.* depression. Statistical tests on these contrasts were carried out at the cluster level with a family-wise 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.

Additionally, an ANOVA was run on all four groups together, using the same fitted linear mixed-effects model that defined clusters of difference between any of the four groups. Significant clusters were then taken as ROIs and were used to draw exploratory boxplots visualising the relative levels of activation/de-activation for the four groups in areas of functional abnormality.

Results

Demographic and clinical data on the bipolar and control groups are shown in Table 1. The groups were well-matched for age, gender and TAP-estimated IQ. However, the healthy control group had a higher mean current IQ than the bipolar subgroups, which was significant in the case of the mania and depression subgroups. The three bipolar subgroups did not differ significantly in duration of illness.

Performance on the n-back test

There were significant differences among the groups on both the 1-back version and the 2-back versions of the test ($F = 6.66$, $P < 0.001$ and $F = 12.74$, $P < 0.001$, respectively). In the 1-back version, *post hoc* testing (Tukey HSD) indicated that the mania subgroup performed significantly more poorly than the control group (mean d' 3.36 (s.d. = 1.10) *v.* 4.34 (s.d. = 0.76), < 0.001) as did the depression subgroup (mean d' 3.75 (s.d. = 1.17), $P = 0.04$); however, the euthymia subgroup did not perform significantly differently from the control group (mean d′ 3.91 (s.d. = 1.11), $P < 0.23$). Results were similar in the 2-back version, with the mania subgroup performing significantly worse than the control group (mean d' 2.02 (s.d. = 1.05) *v.* 3.22 (s.d. = 0.86), $P < 0.001$), and the depression subgroup performing worse than the control group (mean d′ 2.28 (s.d. = 1.13), $P < 0.001$); however, the performance of the euthymia subgroup did not differ from the control group (mean d′ 2.77 (s.d. = 0.90), $P < 0.15$). Within the bipolar subgroups the only significant difference was between the mania and the euthymia subgroups ($P = 0.006$).

Neuroimaging findings

As in previous studies by our group,[10,11,15] the 2-back *v.* baseline contrast delivered larger and more extensive activations and de-activations than the 1-back *v.* baseline contrast. Therefore, in what follows only the results for this contrast are reported.

Maps of mean activations for the three bipolar subgroups and the control group in the 2-back *v.* baseline contrast are shown in online Fig. DS1. Briefly, at $P < 0.05$ corrected, the healthy control group showed a pattern of bilateral activations in the anterior insula, the dorsolateral prefrontal cortex, and the precentral gyri, supplementary motor areas, cerebellum, thalamus, basal ganglia, and parts of the temporal and parietal cortex. They also showed de-activations: these were seen bilaterally in the medial frontal cortex, the amygdala, the hippocampus and adjacent cortical regions, the medial parietal cortex extending to primary visual areas, the posterior insula and the lateral parietal cortex.

Activations and de-activations in the mania, depression and euthymia subgroups followed a broadly similar pattern to that seen in the control group. However, the clusters were noticeably less extensive and less highly activated/de-activated, particularly in the mania and depression subgroups.

Comparisons between the individual subgroups and the healthy control group

Mania subgroup *v.* control group. As shown in Figure 2, at $P < 0.05$ corrected, the mania subgroup showed significant failure of activation in bilateral clusters involving the dorsolateral prefrontal cortex, the parietal cortex and the precuneus (left: 12272 voxels, peak activation in Brodmann area (BA) 6/8, MNI (−30, −2, 62), *z*-score = 5.06, $P = 7.13 \times 10^{-17}$; right: 1477 voxels, peak activation in BA 6/8, MNI (24, 6, 58), *z*-score = 5.29, $P = 0.002$). Clusters of reduced activation were also seen in the basal ganglia and thalamus bilaterally (right: 1409 voxels, peak activation in MNI (18, 8, 16), *z*-score = 4.1, $P = 0.002$); left: 1208 voxels, peak activation in MNI (−18, −10, 18), *z*-score = 3.87, $P = 0.006$) and the cerebellum (right: 1654 voxels, peak activation in MNI (30, −44, −32), *z*-score = 4.21, $P = 0.0008$; left: 1259 voxels, peak activation in MNI (−44, −70, −10), *z*-score = 3.87, $P = 0.005$).

The mania subgroup also showed failure of de-activation in the ventromedial prefrontal cortex relative to the control group (2605 voxels, peak activation in MNI (−2, 46, −28), *z*-score = 4.73, $P = 1.87 \times 10^{-5}$).

Table 1 Demographic and clinical characteristics of bipolar subgroups and control group

	Mania subgroup ($n=38$)	Depression subgroup ($n=38$)	Euthymia subgroup ($n=38$)	Control group ($n=38$)	F	χ^2	KW	P	*Post hoc*
Age, years: mean (s.d.)	39.74 (11.36)	39.89 (10.39)	40.00 (8.78)	39.68 (8.88)	0.01			0.99	
Gender, men/women: *n*	18/20	17/21	17/21	18/20		0.11		0.99	
TAP, mean (s.d.)	22.75 (4.52)	22.47 (4.85)	23.67 (3.15)	22.71 (3.28)	0.62			0.60	
TAP_FISQ, mean (s.d.)	101.81 (8.65)	101.33 (9.39)	103.50 (6.02)	101.66 (6.21)	0.57			0.63	
WAIS-III, mean (s.d.)	95.15 (14.28)	93.17 (15.05)	97.47 (13.87)	105.61 (14.59)	5.06			0.002	M, D<C
Duration of illness, years: mean (s.d.)	11.59 (11.67)	14.51 (10.17)	13.03 (7.28)	N/A	0.81			0.45	
YMRS score, mean (s.d.)	21.84 (3.67)	1.29 (2.24)	1.41 (1.88)	N/A	717.81			<0.001	D, E<M
HRSD score, mean (s.d.)	4.14 (3.65)	22.13 (4.03)	2.73 (2.18)	N/A	383.07			<0.001	M, E<D
CGI score mean (s.d.)	4.66 (0.72)	4.51 (0.65)	2.06 (1.03)	N/A			60.39	<0.001	M, D>E
GAF score, mean (s.d.)	45.81 (11.05)	44.77 (11.90)	76.78 (11.17)	N/A	84.43			<0.001	M, D<E
History of psychosis, yes/no: *n*	30/8	24/10*	30/8	N/A		1.31		0.52	

M, mania subgroup; D, depression subgroup; C, control group; E, euthymia subgroup; KW, Kruskal–Wallis; TAP, Word Accentuation Test (Test de Acentuación de Palabras); TAP_FISQ, TAP–estimated Full-Scale IQ; WAIS-III, Wechsler Adult Intelligence Scale III; YMRS, Young Mania Rating Scale; HRSD, Hamilton Rating Scale for Depression; CGI, Clinical Global Impressions;[26] GAF, Global Assessment of Functioning.[27] *Data missing for 4 participants.

Depression subgroup *v.* control group. Once again the patients showed a pattern of hypo-activation in the bilateral dorsolateral prefrontal cortex extending to the basal ganglia and thalamus (4415 voxels, peak activation in MNI (−32, −2, 50), *z*-score = 4.71, $P = 1.9 \times 10^{-14}$); in the bilateral parietal cortex and precuneus (2687 voxels, peak activation in MNI (8, −64, 62), *z*-score = 4.86, $P = 1.3 \times 10^{-5}$); and in the cerebellum (2707 voxels, peak activation in MNI (−32, −54, −30), *z*-score = 4.89, $P = 1.2 \times 10^{-5}$). Like the mania subgroup, the depression subgroup also showed failure of de-activation in the ventromedial prefrontal cortex, (4415 voxels, peak activation in MNI (0, 46, −20), *z*-score = 4.68, $P = 5.9 \times 10^{-8}$) (Fig. 2).

Euthymic subgroup *v.* control group. In contrast to the other two groups, the euthymia subgroup did not show any clusters of reduced activation compared with the control group. However,

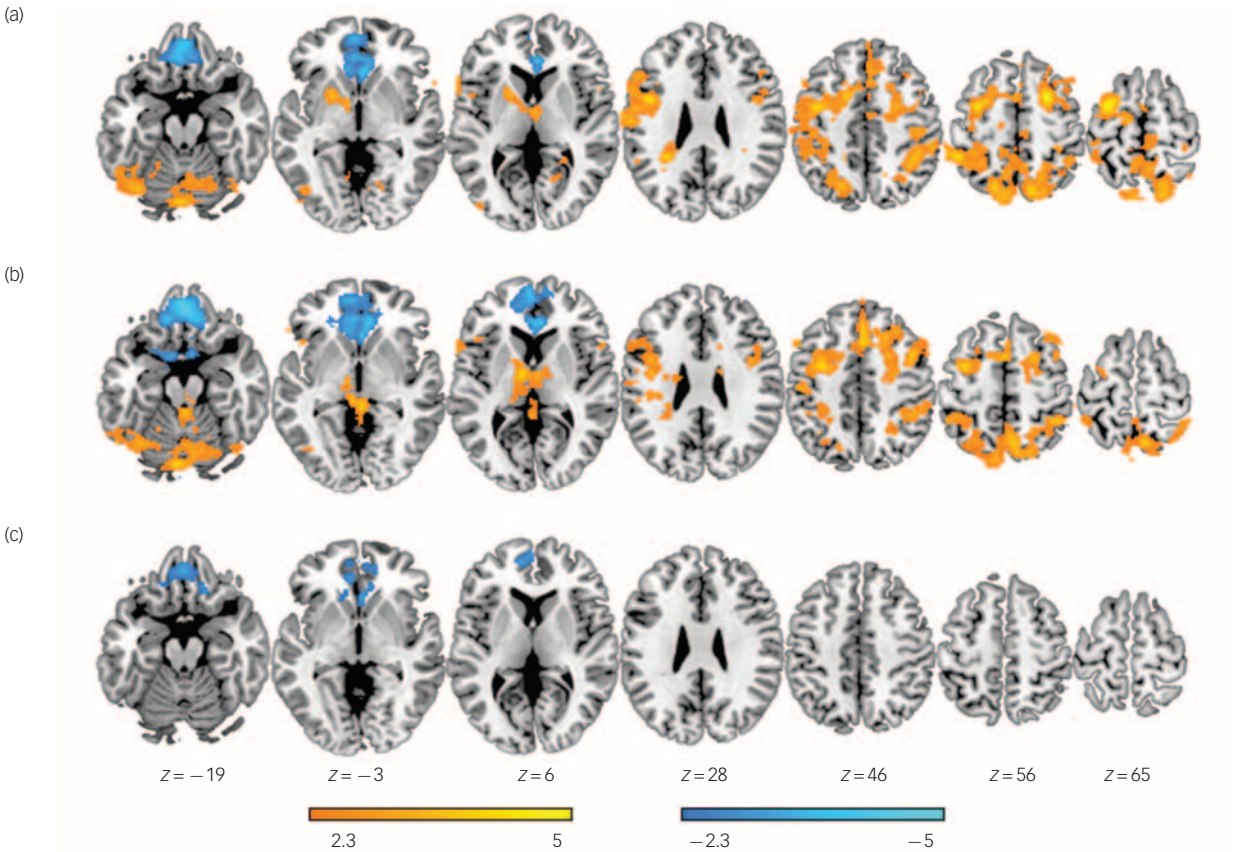

Fig. 2 Brain clusters showing statistically significant differences in the 2-back *v.* baseline contrast (at $P<0.05$ corrected) among the three bipolar subgroups compared with the controls.

(a) Mania subgroup *v.* control group; (b) depression subgroup *v.* control group; and (c) euthymia subgroup *v.* control group. The right side of the image is the right side of the brain.

failure of de-activation was again seen in the ventromedial frontal cortex (3511 voxels, with peak activation in BA 25, MNI (−6, 16, −10), *z*-score = 4.12, $P = 1.31 \times 10^{-6}$) (Fig. 2).

Since the mania and depression subgroups showed significantly worse n-back task performance than the healthy control group, we repeated these comparisons including performance as a covariate. Although there was a reduction in the area of some of the clusters found, for the most part they were still evident in the same locations. The findings are shown in online Fig. DS2.

Comparisons within the bipolar subgroups

Mania *v.* euthymia subgroup. The mania subgroup showed two clusters of significantly reduced activation compared with the euthymia subgroup. These were symmetrically located in the left and right dorsal parietal cortex and precuneus. The cluster on the left had a larger extension (2229 voxels, peak activation in BA 40, MNI (−46, −42, 56), *z*-score = 3.93, $P = 7.83\ 10^{-5}$), than that on the right (1368 voxels, peak activation in BA 7, MNI (26, −50, 56), *z*-score = 3.9, $P = 2.97 \times 10^{-3}$). The findings are shown in Fig. 3.

Depression *v.* euthymia subgroup. Results for this comparison were similar to those for the mania *v.* euthymia contrast. Once again the depression subgroup showed significantly reduced activation in the dorsal parietal cortex and precuneus. This time, however, the reduction was unilateral, being seen only on the right (982 voxels, peak activation in BA 40, MNI (40, −44, 56), *z*-score = 3.95, $P = 0.02$). The findings are also shown in Fig. 3.

Mania *v.* depression subgroup. No significant differences in levels of activation or de-activation were found between these two phases of illness. For the comparison between the mania and euthymia subgroups, the only pair-wise comparison where the two groups differed significantly in n-back performance, the analysis was repeated adding d' as a covariate. The results remained similar. The findings are shown in online Fig. DS2.

Four-group ANOVA and ROI analysis

Results from the ANOVA including the three bipolar subgroups and the control group are shown in Fig. 4. Four clusters of significant difference between at least one group and the others were found. Two of the clusters were symmetrically located in the left and right dorsal parietal cortex, similar to the significant clusters found in the mania *v.* euthymia and in the depression *v.* euthymia contrasts (right: 1582 voxels, peak activation in MNI (40, −46, 56), *z*-score = 4.05, $P = 0.001$; left 1118 voxels, peak activation in MNI (−58, −40, 54), *z*-score = 4.17, $P = 0.009$). Boxplots of mean activations in ROIs based on these two clusters indicated significantly reduced levels of activation in both phases of illness compared with euthymia and the control group. However, the euthymia subgroup did not differ significantly from the control group in either of the clusters (see online Table DS1 for details of the means, standard deviations and significance levels).

A third cluster, also found in the individual analyses, was located in the ventromedial frontal cortex (1943 voxels, peak activation in MNI (−2, 46, −28), *z*-score = 5.06, $P = 0.0002$). The accompanying boxplots indicate significantly lower for the mania, depression and euthymia subgroups than the de-activation control group.

This analysis also produced a new cluster. This was located in the left dorsolateral prefrontal cortex (1256 voxels, peak activation in BA 6, MNI (−34, −2, 54), *z*-score = 4.32, $P = 0.005$). As can be seen from the boxplots, there was significantly reduced activation in the mania, depression and euthymia subgroups compared with the control group. The mania subgroup also showed significantly reduced activation compared with the euthymia subgroup.

Discussion

Main findings

The analyses carried out in this study provide evidence that bipolar disorder is characterised by both mood-state-dependent and mood-state-independent functional imaging abnormalities.

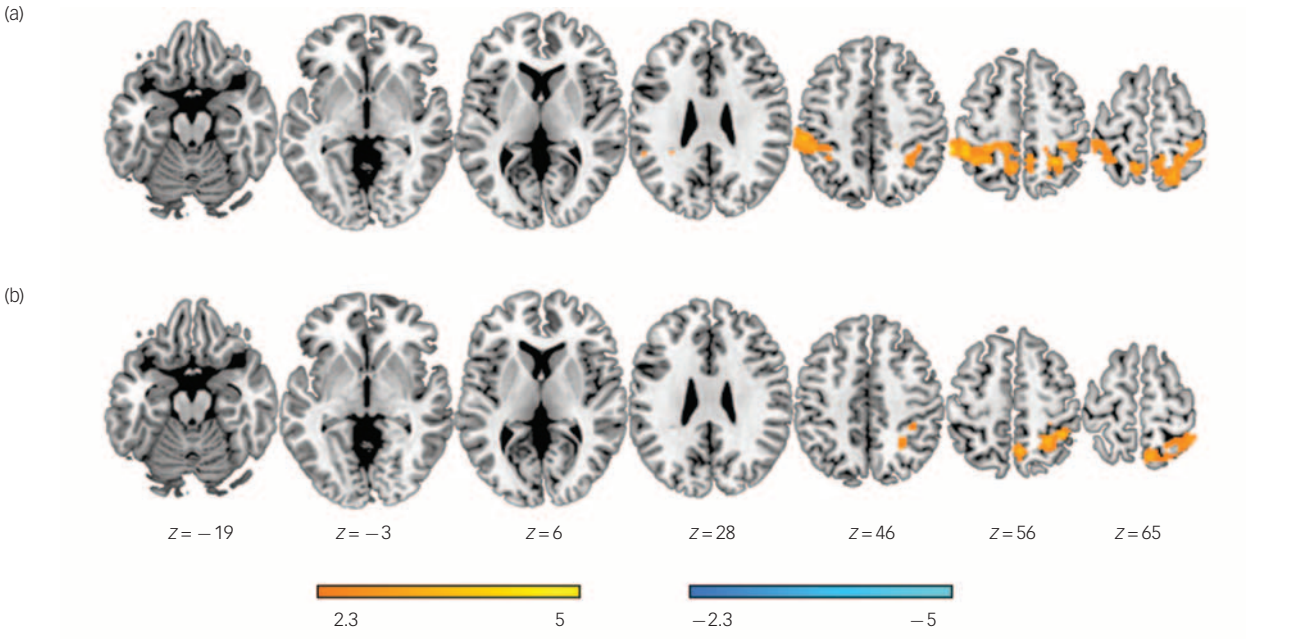

Fig. 3 Brain clusters showing statistically significant differences in the 2-back ***v.*** **baseline contrast (at $P<0.05$ corrected) in the mania and depression subgroups compared with the euthymia subgroup.**

(a) Mania *v.* euthymia subgroup and (b) depression *v.* euthymia subgroup. No differences were found when the mania subgroup were compared with the depression subgroup. The right side of the image is the right side of the brain.

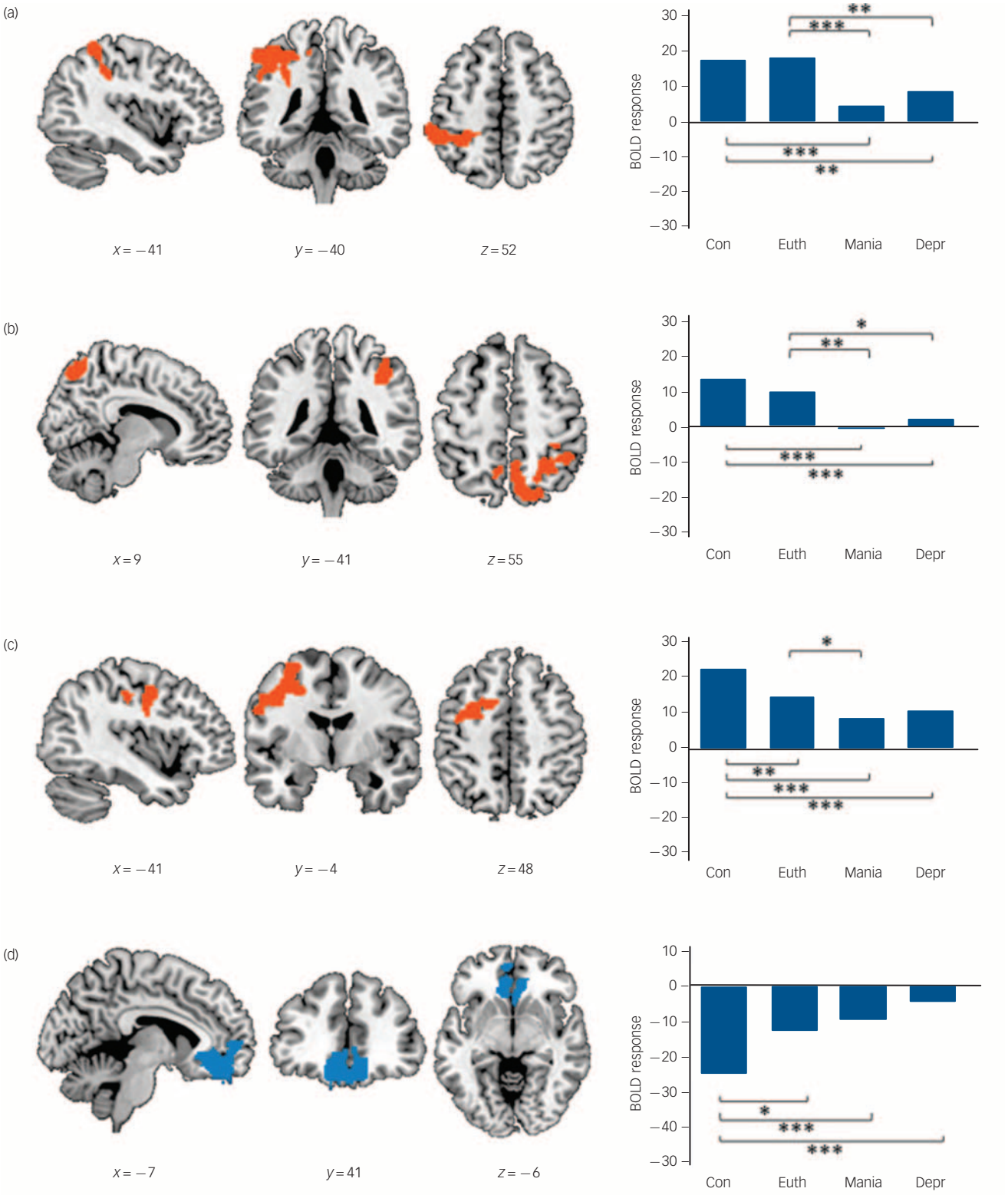

Fig. 4 The four clusters of significant difference found comparing all three bipolar subgroups and the control group.

The first three clusters, left parietal (a), right parietal (b) and left dorsolateral frontal (c) were regions of activation in the control group; the fourth in the ventromedial and orbitofrontal cortex (d) was a region where the control group showed de-activation. Boxplots are based on mean activation values from regions of interest (ROIs) extracted from the four significant clusters. BOLD, blood oxygen level-dependent; Con, control group; Euth, euthymia subgroup; Mania, mania subgroup; Depr, depression subgroup. ***significant at $P<0.001$, **significant at $P<0.01$, *all results significant at $P<0.05$ based on the *post hoc* Tukey's HSD test. The right side of the image is the right side of the brain.

Reduced activation in the dorsal parietal cortex was seen in both mania and depression but not in euthymia. Reduced activation was also seen in the dorsolateral prefrontal cortex, but here the changes showed a more complicated relationship with phase of illness – activation was reduced across all three phases of illness, although with greater reductions in mania (but not depression) than in euthymia. On the other hand, failure of de-activation in the medial frontal cortex was seen in all three illness phases and so seems to represent a trait-like abnormality.

Changes in the dorsal parietal and dorsolateral prefrontal cortex

Our finding of mood-state dependent changes in the dorsal parietal cortex is unexpected – this region was not identified in either Kupferschmidt & Zakzanis's[5] or Chen *et al*'s[6] meta-analyses, including in their subanalyses directed to mood state. One possible explanation for this relates to the fact that the parietal cortex forms part of the 'working memory network' activated the n-back task,[28] and, although both meta-analyses pooled data from studies using a range of different cognitive tasks, relatively few of them employed the n-back or other working memory tasks (10/32 and 7/29 respectively). Among studies that did use the n-back task, Pomarol-Clotet *et al*[10] found reduced activation in the parietal cortex along with other parts of the working memory network in patients in a manic phase, and Fernández-Corcuera *et al*[11] had similar results in bipolar depression (it should be noted that both these studies were carried out on samples that overlapped with the present study). With respect to euthymia, Cremaschi *et al*[14] reviewed eight studies using the n-back task in this phase of illness and found reduced parietal activation only in one of them (Townsend *et al*[7] – discussed further below); there no differences between patients and controls in three of the studies and three found increased activation. Accordingly, the literature to date provides some support for mood state-related differences in this region during performance of this cognitive task.

If this explanation is correct, it might be expected that a different pattern of mood-state dependent changes would be found if other tasks were used. Some support for this view comes from a study by Chen *et al*.[29] They scanned 12 patients with bipolar disorder during performance of a facial emotion identification task, first when they were in a manic episode and then again when they had become euthymic. Twelve healthy controls were also scanned twice. A significant group × time interaction was found in the right amygdala and hippocampus, which was the result of increased activation in the patients when they were euthymic. (It should be noted that the authors used a mask restricting the analysis to brain regions involved in emotional processing and so the possibility of changes in other regions cannot be ruled out.)

We also found reduced activation in the dorsolateral prefrontal cortex, which showed ambiguous evidence of state-like characteristics. It did not appear in any of the contrasts between pairs of bipolar subgroups, but emerged in the ANOVA comparing all three bipolar subgroups and the controls. Reduced prefrontal cortex activation has been a regular finding in bipolar disorder, although it has mainly been documented in the orbitofrontal cortex,[30–32] the ventrolateral prefrontal cortex[33] and the frontal pole[34,35] perhaps reflecting the nature of the tasks used in these studies – the go/no-go task, the Stroop task and a gambling task. Consistent with such an interpretation, all of a small number of studies that have used working memory tasks have found reduced activation in or close to the dorsolateral prefrontal cortex in mania,[10] depression[11] and euthymia.[36–38]

The study of Townsend *et al*,[7] described in the introduction, is the only other study to date that has examined patients in all three illness phases during performance of the n-back task. Their findings were quite different to ours in that they failed to find significant variation across phase in either the parietal cortex or the dorsolateral prefrontal cortex, although activation was reduced in all three patient groups compared with controls. There are two potential reasons why these authors may have failed to detect differences across phase, however. First, at 13–15 per group, the sample sizes may have been too small to detect differences, particularly when it is considered that between-patient differences are likely to be more subtle than those between patients and healthy controls. Second, group comparisons were carried out at the ROI rather than the whole brain level. Here it is noteworthy that, rather than using anatomically defined ROIs, the authors employed a 5 mm sphere around the maximally activated voxels in each bilateral region. It seems possible that this might have resulted in ROIs that favoured finding differences between patients and controls, but were not optimally located to detect differences between phases.

The activation changes between illness and euthymia we found in the dorsal parietal cortex, and more equivocally between mania and euthymia in the dorsolateral prefrontal cortex, could have reflected either the obvious symptomatic differences between the two states, or alternatively improvement in cognitive function taking place with recovery. Of the two, the latter seems intuitively more likely, given that we used a cognitive as opposed to an emotional task. A cautionary note needs to be sounded here, however, because the view that cognitive impairment in depression and mania normalises with clinical recovery[39] is almost certainly an oversimplification. On the one hand, it is now accepted that cognitive impairment is also seen in a proportion of patients in euthymia (see, for example, Robinson & Ferrier[40]). On the other, the few studies that have directly compared the degree of impairment in different phases of illness have not found evidence that it is substantially less marked in euthymia (for example see Martinez-Aran *et al*[41]).

Failure of de-activation in the medial frontal cortex

The final finding of this study was that failure of de-activation in the medial frontal cortex distinguished the patients from the controls but was present to a similar degree in all three phases of illness. This finding is in line with those of our previous studies in mania[10] and bipolar depression,[11] although not with that of Strakowski *et al*[12] in patients in a first-episode of mania. Calhoun *et al*[42] additionally found failure of de-activation that affected particularly the medial frontal cortex in a mixed group of patients with bipolar disorder. Potentially also relevant here is a finding from Chen *et al*'s[6] meta-analysis of whole-brain voxel-based studies. This found the medial frontal cortex to be a site of increased activation compared with controls, and this continued to be seen in the subanalysis of the euthymia group. It is quite possible that this finding could actually represent failure of de-activation in the patients, since hyperactivation and failure of de-activation can give similar findings when conventional subtractive analysis is carried out (see Gusnard & Raichle[43] for a detailed explanation).

Implications and limitations

This study found that brain functional changes in bipolar disorder can be divided into those that are state-related and those that have more enduring, trait-like characteristics. The parietal cortex, an area that is implicated in working memory performance, showed evidence of belonging to the former category. Failure of de-activation in the medial frontal cortex, and so by implication default mode network dysfunction, appeared to fall into the latter. The dorsolateral prefrontal cortex showed a combination of both characteristics, exhibiting reduced activation in both phases of active illness but without fully normalising between episodes.

Our study has some limitations that should be acknowledged. Most notably, the patients were taking medication, which differed in dosage and type in the different phases of illness. We studied unselected patients with bipolar disorder: most but not all had type I illness, but we did not preselect patients with non-psychotic

forms of illness. Additionally, the cross-sectional nature of the study means it may be susceptible to unknown, but potentially relevant, sampling biases.

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EXTRA CONTENT ONLINE

reflection

On *Memoirs of My Nervous Illness*, by Daniel Paul Schreber

Louis Sass

Daniel Paul Schreber's *Memoirs of my Nervous Illness* profoundly influenced many key figures of modern psychiatry, including Bleuler and Jaspers, Freud and Jung. Author Elias Canetti described it as the 'most important document in psychiatric literature'. To read this work – typically considered a paradigmatic expression of paranoid schizophrenia – is to risk a shaking of one's complacency, especially concerning the key symptom of delusion. For me personally, it was a revelation.

Schreber was an appeals court judge and German citizen who wrote his memoir during an 8-year stay at the Sonnenstein hospital near Dresden. This dense, often convoluted work was published in 1903, together with documents from Schreber's successful suit for release from involuntary confinement. Against the asylum director's claim that the patient took his delusions and hallucinations for 'factual and real', with 'unshakeable certainty and [as] adequate motive for action', Schreber replied with 'the strongest possible ''no'' ': 'My Kingdom is not of this world', he wrote; those who think otherwise have 'not really entered into my inner spiritual life'.

Many of Schreber's reports are certainly bizarre: a foreign soul 'joined in looking out of my eyes'; 'the weather [was] dependent on *my* actions and thoughts'. He often claimed absolute certitude, and spoke of 'divine revelation . . . founded on truth'. Yet it turns out to be difficult to assess the kind or quality of reality that Schreber either experienced or attributed to what he himself termed his 'so-called delusional system'. How, for example, should we understand his claim that people around him would temporarily exchange heads, or that his own internal organs were 'torn or vanished repeatedly', only to reappear 'without any permanent effect'? Was this simple irrationality and poor 'reality-testing', or does it suggest a less literal-minded sort of world – one Schreber himself experienced as being more like a dream than a shared world of real consequences?

Many of Schreber's (so-called) delusional experiences and claims do not, in fact, suggest the literalness and error so often assumed. He speaks, for example, of seeing 'rays' and other delusional entities '*only* with my mind's eye'. Nor are the experiences well captured by the popular notion of an 'externalisation' bias. What Schreber describes often seems, in fact, less an objectifying of something inner or imaginary than a subjectivising, derealising, or internalising of something external and real. Thus, he often experienced the actual people or other creatures in the asylum as *unreal*: 'miracled up' or 'fleetingly improvised', and as existing only within range of his own gaze.

It is, perhaps, a certain *solipsistic* stance that is the most distinctive as well as 'psychotic' feature of the *Memoirs*. Indeed, Schreber sometimes suggests that he himself was the true centre of the world, not only because 'everything that happens is in reference to me', but in the deeper, metaphysical sense that things only existed within his own point of view. 'Seeing' itself, says Schreber, is 'confined to my person and immediate surroundings'.

All this is exceptionally hard to sort out in terms of any standard notions of knowledge, belief, and error – Schreber himself speaks of 'a tangle of contradictions that cannot be unraveled'. The abnormality seems to involve not mere error or cognitive bias, but an entirely different constitution of the world itself. Grasping the *possibility* of such overall, ontological alterations would seem crucial for any psychotherapist concerned about the patient's viewpoint; but also for neurobiologists and cognitive scientists: both the experience and underlying 'mechanisms' of at least *some* delusions can, it seems, be vastly different from what we typically imagine. Schreber's memoir is a book to be sampled, savoured, and pondered, especially for the challenges it poses to standard assumptions, whether from common sense, philosophy, or psychiatric theory.

Daniel Paul Schreber. *Memoirs of my Nervous Illness*. Transl & ed Ida Macalpine, Richard A. Hunter. Cambridge MA: Harvard University Press, 1988 (Orig: *Denkwürdigkeiten eines Nervenkranken*. Leipzig 1903). Quotations, listed in the order of appearance, on pp. 320, 301f, 157, 47, 41, 207, 301, 134, 99, 227, 101–107, 197, 232, 152.

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Pomarol-Clotet et al. Brain functional changes across the different phases of bipolar disorder. *Br J Psychiatry* doi: 10.1192/bjp.bp.114.152033

Table DS1 Mean activation values (SD) in the four clusters of significant difference found between the four groups and p values with Tukey HSD test.

Cluster of activation	Controls (n=38)	Euthymia (n=38)	Mania (n=38)	Depression (n=38)	P value
Cluster 1 (left parietal)	17.45 (10.53)	17.87 (13.61)	4.65 (12.13)	8.55 (9.20)	C vs E; p= 0.99 C vs M; p= 0.00001 C vs D; p= 0.005 E vs M; p= 0.000008 E vs D; p=0.003 M vs D; p=0.45
Cluster 2 (right parietal)	13.10 (11.27)	9.54 (13.55)	-1.00 (13.32)	1.80 (12.53)	C vs E; p= 0.61 C vs M; p= 0.00002 C vs D; p= 0.0009 E vs M; p=0.002 E vs D; p=0.04 M vs D; p=0.77
Cluster 3 (left frontal-dorsal)	22.41 (9.45)	14.75 (8.28)	8.45 (9.34)	10.68 (10.44)	C vs E; p= 0.003 C vs M; p= 0.000 C vs D; p= 0.000001 E vs M; p= 0.02 E vs D; p=0.24 M vs D; p=0.73
Cluster 4 (medial orbito-frontal)	-25.06 (18.92)	-12.72 (15.11)	-9.58 (18.70)	-4.47 (16.68)	C vs E; p= 0.01 C vs M; p=0.0009 C vs D; p=0.000005 E vs M; p=0.86 E vs D; p=0.17 M vs D; p=0.58

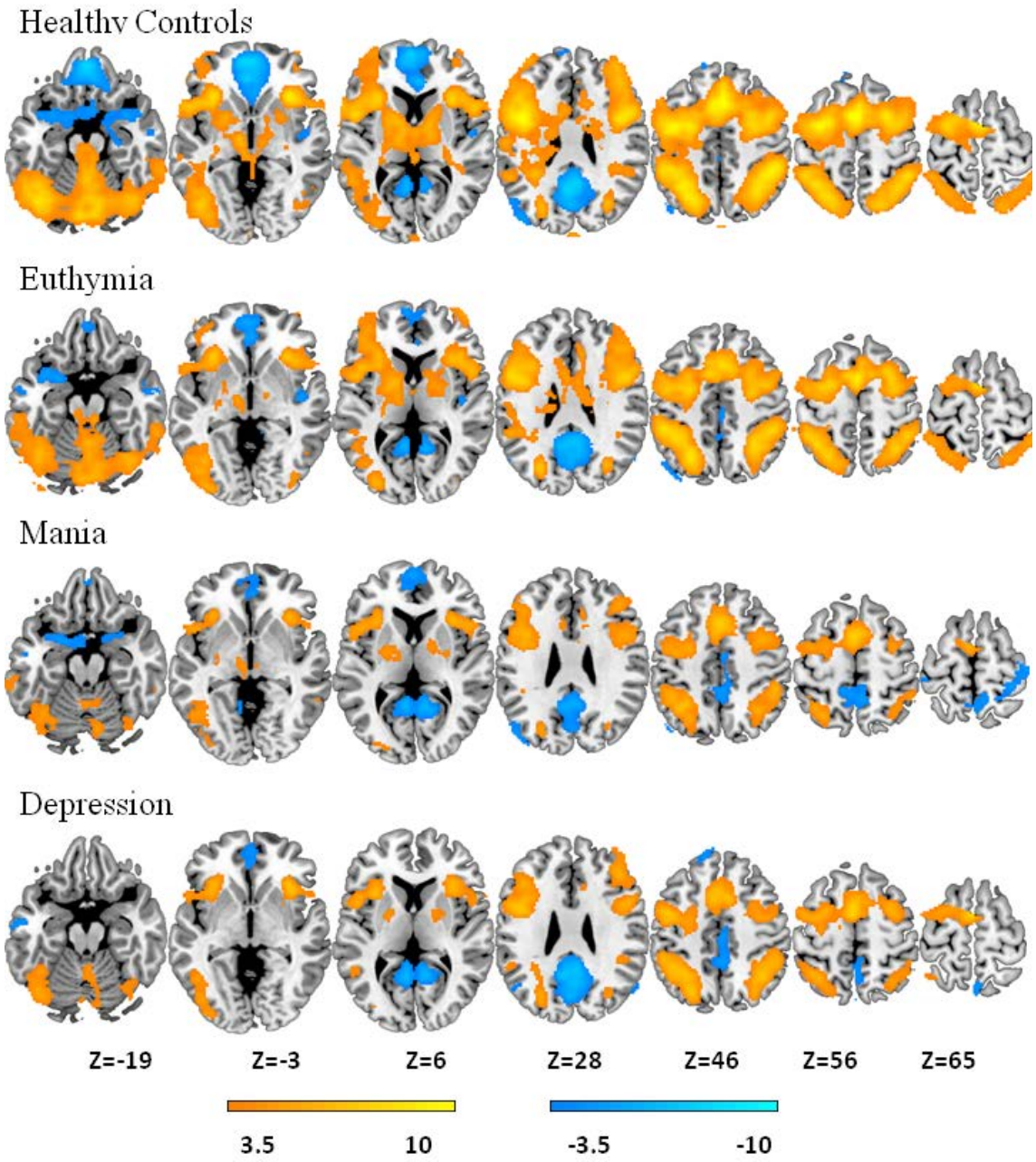

Fig. DS1 Areas of significant activations (red- yellow) and deactivations (blue) from the 2-back vs baseline contrast in the four groups of subjects. The right side of the image is right side of the brain. MNI coordinates for each one of the axial slices are shown in the last row. Colors depict scores from statistical z maps (negative values in the deactivations).

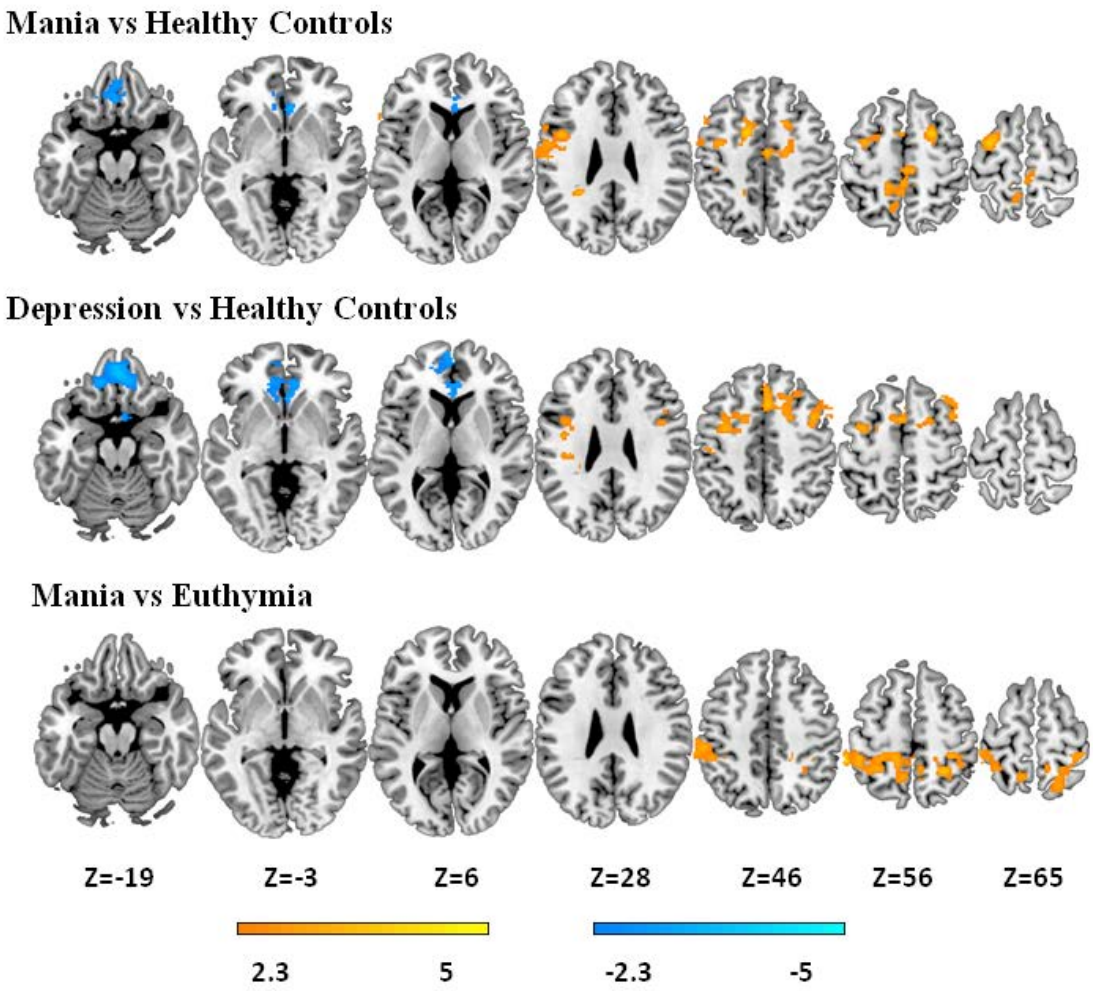

Fig. DS2 Brain clusters showing statistically significant differences in the 2-back vs baseline contrast (at $p < 0.05$ corrected) in the mania vs controls, depression vs controls and mania vs euthymic patients comparisons, adding task performance (d') as a covariate. The right side of the image is the right side of the brain

Brain functional changes across the different phases of bipolar disorder

Edith Pomarol-Clotet, Silvia Alonso-Lana, Noemi Moro, Salvador Sarró, Mar C. Bonnin, José M. Goikolea, Paloma Fernández-Corcuera, Benedikt L. Amann, Anna Romaguera, Eduard Vieta, Josep Blanch, Peter J. McKenna and Raymond Salvador

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Estudio 2

Brain functional changes in first-degree relatives of patients with bipolar disorder: evidence for default mode network dysfunction

Psychological Medicine

JCR-2015: IF= 5.491, Posición en Psiquiatría=17/140, Cuartil=1, Decil=1

En este segundo estudio de neuroimagen funcional, 20 pacientes bipolares en eutimia, 20 de sus respectivos hermanos sanos y un grupo de 40 controles sanos no mostraron diferencias en el rendimiento en la versión 1-back, mientras que en el 2-back, la única diferencia significativa fue observada entre los pacientes bipolares eutímicos en comparación con los controles. Las activaciones medias fueron las esperadas e incluyeron principalmente regiones bilaterales dorsolaterales, precentrales, del área motora suplementaria e ínsula anterior, junto con otras regiones subcorticales (tálamo y ganglios basales), la corteza parietal y temporal y el cerebelo así como desactivaciones de corteza medial frontal, corteza medial y lateral parietal, la amígdala, el hipocampo y la ínsula posterior. En los grupos de pacientes y hermanos éstas siguieron un patrón similar, pero fueron menos extensas e intensas.

La comparación entre los tres grupos mediante un ANOVA mostró un único clúster de diferencia significativa localizado en la corteza frontal medial bilateral, en el que los bipolares y sus hermanos mostraron una menor desactivación en comparación con los controles; y los bipolares también una menor desactivación en comparación con sus hermanos. No se observó aumento o reducción de la activación entre ninguno de los grupos.

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ORIGINAL ARTICLE

Brain functional changes in first-degree relatives of patients with bipolar disorder: evidence for default mode network dysfunction

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Background. Relatively few studies have investigated whether relatives of patients with bipolar disorder show brain functional changes, and these have focused on activation changes. Failure of de-activation during cognitive task performance is also seen in the disorder and may have trait-like characteristics since it has been found in euthymia.

Method. A total of 20 euthymic patients with bipolar disorder, 20 of their unaffected siblings and 40 healthy controls underwent functional magnetic resonance imaging during performance of the n-back working memory task. An analysis of variance (ANOVA) was fitted to individual whole-brain maps from each set of patient–relative–matched pair of controls. Clusters of significant difference among the groups were used as regions of interest to compare mean activations/de-activations between them.

Results. A single cluster of significant difference among the three groups was found in the whole-brain ANOVA. This was located in the medial prefrontal cortex, a region of task-related de-activation in the healthy controls. Both the patients and their siblings showed significantly reduced de-activation compared with the healthy controls in this region, but the failure was less marked in the relatives.

Conclusions. Failure to de-activate the medial prefrontal cortex in both euthymic bipolar patients and their unaffected siblings adds to evidence for default mode network dysfunction in the disorder, and suggests that it may act as a trait marker.

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Key words: Bipolar disorder, default mode network, euthymia, first-degree relatives, functional magnetic resonance imaging.

Introduction

Brain functional changes are well documented in bipolar disorder, and while the findings have been heterogeneous, there is an emerging consensus that the overall pattern is one of reduced activity in prefrontal and some other cortical regions coupled with overactivity in subcortical structures such as the amygdala, hippocampus and basal ganglia (Strakowski *et al.* 2005, 2012; Bellack *et al.* 2007; Savitz & Drevets, 2009). Most studies have examined patients in the manic or depressed phase, but changes have also been found in euthymia. Thus, a meta-analysis of positron emission tomography, single-photon emission computed tomography and functional magnetic resonance (fMRI) studies (Kupferschmidt & Zakzanis, 2011) found support for cognitive task-related hypoactivations affecting the inferior and middle lateral frontal cortex in euthymic patients, plus hyperactivations in the superior temporal gyrus and ventrolateral prefrontal cortex. On the other hand, in another meta-analysis (Chen *et al.* 2011), this time restricted to voxel-based fMRI studies, changes in euthymia were seen only in the lingual gyrus.

Since bipolar disorder has a hereditary component (McGuffin *et al.* 2003; Craddock & Sklar, 2013), the question arises of whether brain functional changes,

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perhaps similar to those seen in euthymic patients, might also be seen in their first-degree relatives. Studies to date, however, have been relatively few and have mixed findings. Drapier *et al.* (2008) found increased activation in the left orbitofrontal cortex extending to the frontopolar and ventrolateral prefrontal cortex in 20 unaffected first-degree relatives of bipolar patients compared with 20 healthy controls during performance of the n-back working memory task. Thermenos *et al.* (2010) also used the n-back task and found a pattern of increased activation in the left frontopolar cortex, the anterior insula and the right parietal lobe in 18 first-degree relatives compared with 19 controls. Pompei *et al.* (2011) examined 25 relatives and 48 controls using the Stroop task and found reduced activation affecting the superior and inferior parietal cortex. In contrast, four studies failed to find any cortical activation differences between relatives and controls (Allin *et al.* 2010; Whalley *et al.* 2011; Sepede *et al.* 2012; Roberts *et al.* 2013), although one of them (Whalley *et al.* 2011) found greater activation in a subcortical structure, the left amygdala, in a secondary analysis taking into account task difficulty (Whalley *et al.* 2011). Findings in studies using emotional tasks (typically facial expression recognition) rather than cognitive tasks have been similarly heterogeneous (Surguladze *et al.* 2010; Linke *et al.* 2012; Kanske *et al.* 2013; Roberts *et al.* 2013).

Since 2001, the existence has been recognized of brain regions which, rather than activating, de-activate in response to performance of a wide range of attention-demanding tasks (Gusnard & Raichle, 2001; Raichle *et al.* 2001). These regions are jointly referred to as the default mode network, and include the medial prefrontal cortex, the posterior cingulate cortex/precuneus, parts of the parietal and temporal lobe cortex, and also the hippocampus (Buckner *et al.* 2008). Failure of de-activation in parts of this network has been found in a range of psychiatric disorders, including schizophrenia, autism and attention-deficit/hyperactivity disorder (see Broyd *et al.* 2009). It is also increasingly well documented in major depression (e.g. Frodl *et al.* 2009; Grimm *et al.* 2009; Sheline *et al.* 2009) and bipolar disorder (Allin *et al.* 2010; Fernandez-Corcuera *et al.* 2013; Pomarol-Clotet *et al.* 2015), where it has been found to affect particularly the anterior midline 'node' in the medial frontal cortex. Pomarol-Clotet *et al.* (2015) found medial frontal failure of de-activation in euthymic bipolar patients, whereas two other studies (Allin *et al.* 2010; Costafreda *et al.* 2011) found that the region affected was the posterior cingulate gyrus/precuneus, corresponding to the posterior midline node of the network.

Currently, findings concerning default mode network function in relatives of patients with bipolar disorder are few. Allin *et al.* (2010) found failure of de-activation in the posterior cingulate cortex/precuneus in 18 euthymic bipolar patients and in 19 of their unaffected first-degree relatives, in a study using a verbal fluency task. In contrast, Sepede *et al.* (2012), using the Continuous Performance Test, found increased de-activation in the posterior cingulate cortex in 22 relatives compared with 24 controls.

The aim of this study was to further examine the pattern of brain functional changes, including both activations and de-activations, in the unaffected siblings of bipolar patients. We used a cognitive task, the n-back task, which has regularly been found to produce activation changes in bipolar disorder (Townsend *et al.* 2010; Fernandez-Corcuera *et al.* 2013), including in euthymia (Cremaschi *et al.* 2013), and which, as an attention-demanding cognitive task, should also induce de-activation in the default mode network.

Method

Subjects

The patient samples consisted of 20 right-handed individuals with bipolar disorder ($n = 16$ type I, $n = 4$ type II) and 20 of their unaffected siblings. A total of 40 healthy controls, two for each patient–relative pair, were also recruited. This strategy was adopted in order to be able to match properly in those cases where the patient–relative pair consisted of a male and a female, and to allow for better age and premorbid intelligence quotient (IQ) matching.

The patients all met Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for bipolar disorder, based on interview and review of case notes, and were euthymic at the time of scanning. Euthymia was defined on the basis of having experienced no episodes of illness for at least 3 months and having a score of $\leqslant 8$ on the 21-item Hamilton Rating Scale for Depression (Hamilton, 1960), and $\leqslant 8$ on the Young Mania Rating Scale (Young *et al.* 1978). Patients were excluded: (*a*) if they were younger than 18 or older than 65 years; (*b*) if they had a history of brain trauma or neurological disease; (*c*) if they had shown alcohol/substance abuse within 12 months prior to participation; and (*d*) if they had undergone electroconvulsive therapy in the previous 12 months.

The unaffected siblings met the same exclusion criteria as the patients. They were also excluded if they reported a history of mental illness and/or treatment with psychotropic medication as assessed using the Computerized Diagnostic Interview Schedule for the DSM-IV (C DIS-IV; Robins *et al.* 2000).

Healthy subjects were recruited via poster and web-based advertisement in the hospital and local

community, plus word-of-mouth requests from staff in the research unit. They met the same exclusion criteria as the patients and, like the unaffected siblings, were excluded if they reported a history of mental illness and/or treatment with psychotropic medication, on interview with the C DIS-IV. They were also excluded if they had a first-degree relative with a major psychiatric disorder.

The three groups were matched for age, sex and premorbid IQ. This latter variable was estimated using the Word Accentuation Test (Test de Acentuación de Palabras; TAP) (Del Ser *et al.* 1997; Gomar *et al.* 2011), a test that is conceptually similar to the National Adult Reading Test used in the UK (Nelson & Willison, 1991) and the Wide Range of Achievement Test in the USA (Jastak & Wilkinson, 1984). Subjects have to pronounce low-frequency Spanish words whose accents have been removed.

All participants gave written informed consent and the study was approved by the hospital research ethics committee. All procedures were carried out according to the Declaration of Helsinki.

Procedure

While being scanned, participants performed a sequential-letter version of the n-back task (Gevins & Cutillo, 1993). Two levels of memory load (1-back and 2-back) were presented in a blocked design manner. Each block consisted of 24 letters that were shown every 2 s (1 s on, 1 s off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within the blocks. Individuals had to indicate repetitions by pressing a button. 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 s. To identify which task had to be performed, characters were shown in green in 1-back blocks and in red in the 2-back blocks. All participants first went through a training session outside the scanner.

The behavioural measure used was the signal detection theory index of sensitivity, d' (Green & Swets, 1966). Higher values of d' indicate better ability to discriminate between targets and distractors. If subjects showed negative d' values in either or both of the 1-back and 2-back versions of the task, which suggests that they were not performing it, they were not included in the study.

In each individual scanning session 266 volumes were acquired from a 1.5-T GE Signa scanner. A gradient echo echo-planar imaging (EPI) sequence depicting the blood oxygenation level-dependent (BOLD) contrast was used. Each volume contained 16 axial planes acquired with the following parameters: repetition time = 2000 ms, echo time = 20 ms, flip angle = 70°, section thickness = 7 mm, section skip = 0.7 mm, in-plane resolution = 3r3 mm. The first 10 volumes are discarded to avoid T1 saturation effects.

fMRI image analyses were performed with the FEAT module included in FSL software (Smith *et al.* 2004). At a first level, images were corrected for movement and then co-registered to a common stereotaxic space [Montreal Neurological Institute (MNI) template]. Before the group analyses, normalized images were spatially filtered with a Gaussian filter [full-width at half maximum (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. General linear models were fitted to generate individual activation maps for the 1-back *v.* baseline and 2-back *v.* baseline contrasts. Values for movement parameters were included as nuisance covariates in the fitting of individual linear models.

Data analysis

The FEAT module was used to fit a linear mixed-effects model including the baseline *v.* 1-back and the baseline *v.* 2-back activation images for the three groups. The groups were then compared using a whole-brain (voxel-level) analysis of variance (ANOVA). We did not do this simply by carrying out a one-way between-group ANOVA with three levels, because such an analysis assumes the complete independence of individuals (apart from the shared group effect). This was not the case in our study, where each bipolar patient was sampled together with his/her sibling, thus creating covariation between pairs. Therefore, a block design was employed to take into account the within-family covariability (in a block design, related individuals are included in the same block). Specifically, each set of patient–sibling–matched pair of controls was considered as a block, and a one-way blocked ANOVA was performed to detect statistical differences between groups. Statistical tests on these contrasts were carried out at the cluster level with a family-wise 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.

Any clusters showing significant differences among the groups in the ANOVA were examined further in a region of interest (ROI) analysis. Specifically, for each individual, the mean value of each ROI was calculated. Then, these mean values were compared between pairs of groups by means of paired t tests. For

Table 1. *Demographic and clinical characteristics of the sample*

	Euthymic bipolar patients ($n = 20$)	Unaffected siblings ($n = 20$)	Healthy controls ($n = 40$)	Statistical test
Mean age, years (S.D.)	41.02 (10.83)	43.77 (11.09)	42.38 (10.70)	$F = 0.32$, $p = 0.73$
Sex, *n*				$\chi^2 = 0.12$, $p = 0.94$
Male	5	6	11	
Female	15	14	29	
Mean TAP score (S.D.)	102.11 (7.67)[a]	102.21 (9.70)[a]	103.41 (7.90)[b]	$F = 0.20$, $p = 0.82$
Mean duration of illness, years (S.D.)	15.45 (11.29)[c]			
Mean YMRS score (S.D.)	0.79 (1.32)[a]			
Mean HAMD score (S.D.)	2.53 (2.32)[a]			
Mean GAF score (S.D.)	76.00 (10.55)[d]			

S.D., Standard deviation; TAP, Word Accentuation Test (Test de Acentuación de Palabras); YMRS, Young Mania Rating Scale; HAMD, Hamilton Rating Scale for Depression; GAF, Global Assessment of Functioning.

[a] Data missing for one participant.

[b] Data missing for six participants.

[c] Data missing for two participants.

[d] Data missing for five participants.

the bipolar *v.* relative comparison, the 20 patients were compared with their 20 relatives. For the bipolar *v.* control comparison we compared the 20 patients with the 20 controls that had been matched for sex, age and pre-morbid IQ with the patients. For the relative *v.* control comparison we used the remaining 20 controls (who had been specifically matched with the group of relatives).

Results

Demographic and behavioural findings

As shown in Table 1, the three groups were matched for age, sex and TAP-estimated IQ. None of the participants was excluded due to excessive head movement or because of lack of compliance with the task (i.e. negative *d′* scores).

All patients were taking mood stabilizers (lithium 11; other mood stabilizer 2; combinations 7). Six patients were taking antidepressants and 14 were also taking antipsychotics (second generation 13 and combined first and second generation 1). The mean daily dose (in chlorpromazine equivalents) in these patients was 268.37 (S.D. = 276.88) mg/day.

There were no differences on 1-back performance between the unaffected siblings and the healthy controls [*d′* 4.39 (S.D. = 0.76) *v.* 4.24 (S.D. = 0.68); $t = 0.58$, $p = 0.57$], between the bipolar patients and the healthy controls [*d′* 4.18 (S.D. = 0.81) *v.* 4.41 (S.D. = 0.63); $t = -1.32$, $p = 0.20$], and between the bipolar patients and their unaffected siblings [*d′* 4.18 (S.D. = 0.81) *v.* 4.39 (S.D. = 0.76); $t = -0.83$, $p = 0.42$]. In the 2-back task, the bipolar patients performed more poorly than the healthy controls [*d′* 2.68 (S.D. = 0.82) *v.* 3.58 (S.D. = 0.75); $t = -3.54$, $p = 0.002$]. There were no significant differences between the unaffected siblings and the healthy controls [*d′* 2.91 (S.D. = 0.81) *v.* 3.40 (S.D. = 0.93); $t = -1.76$, $p = 0.09$] or between the bipolar patients and their unaffected siblings [mean *d′* 2.68 (S.D. = 0.82) *v.* 2.91 (S.D. = 0.81); $t = -0.86$, $p = 0.40$].

Mean activations and de-activations in the three groups

Mean activations in the 1-back *v.* baseline contrast were generally similar to but less marked than in the 2-back *v.* baseline contrast. Therefore, only the findings for the 2-back *v.* baseline contrast are described here. Clusters of activation for the three groups are shown in Fig. 1. At $p < 0.05$ corrected, the healthy controls showed bilateral clusters of activation in the anterior insula, the dorsolateral prefrontal cortex, the precentral gyrus, the supplementary motor area, the cerebellum, the thalamus, the basal ganglia, and parts of the temporal and parietal cortex. De-activations were seen bilaterally in the medial frontal cortex, the amygdala, the hippocampus and adjacent cortical regions, the medial parietal cortex extending to primary visual areas, the posterior insula and the lateral parietal cortex.

Activations and de-activations in the euthymic bipolar patients and their unaffected siblings followed a broadly similar pattern to those in the controls. Both the clusters of activation and de-activation appeared less extensive in the unaffected siblings and the euthymic bipolar patients, but it should be borne in mind

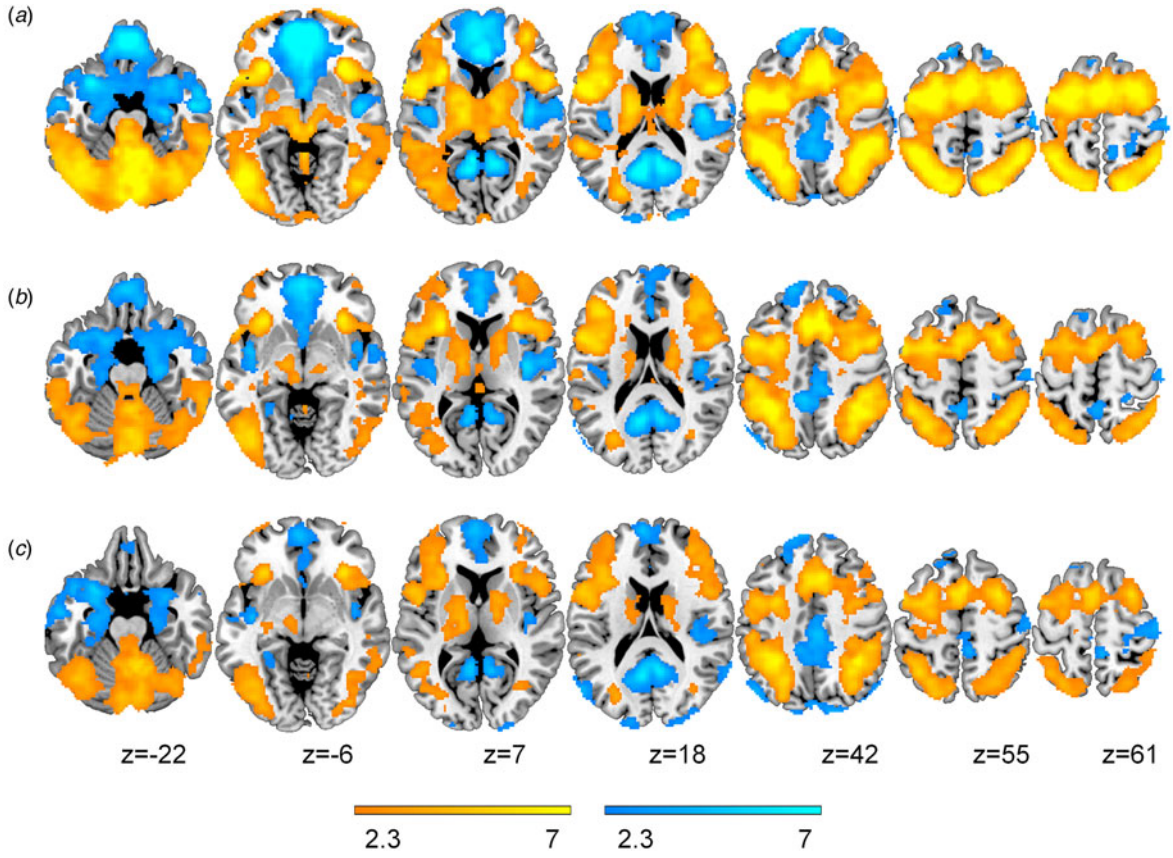

Fig. 1. Brain regions showing a significant effect in the 2-back *v.* baseline contrast in healthy controls (*a*), unaffected siblings (*b*) and euthymic bipolar patients (*c*). Colour bars indicate *z* scores; red to yellow colours indicate significant activation and blue to cyan colours indicate regions with significant deactivation. Numbers refer to Montreal Neurological Institute (MNI) *z* coordinates of the slice shown. The right side of the image is the right side of the brain.

that this may have reflected the fact that there were only half the number of subjects in these groups than in the healthy controls.

ANOVA comparing the three groups

No clusters of significant difference emerged in the 1-back *v.* baseline contrast. In the 2-back *v.* baseline contrast there was a single cluster of significant difference in the medial and inferior frontal cortex bilaterally, also including portions of the orbitofrontal cortex [cluster size 1167 voxels, peak activation in MNI coordinates (2, 52, −14), *z* max = 3.66, $p = 0.006$] (see Fig. 2*a*).

Mean activation values for this cluster in the three groups are shown in Fig. 2*b*. It can be seen that the euthymic bipolar patients showed significantly less de-activation than healthy controls ($p = 0.009$) and their unaffected siblings ($p = 0.03$). The unaffected siblings also showed significant failure of de-activation compared with healthy controls ($p = 0.03$).

No correlations were found between individual mean activation values and the behavioural performance (d') for any of the groups: euthymic bipolar patients ($r = -0.13$, $p = 0.59$); unaffected siblings ($r = 0.19$, $p = 0.43$); and healthy controls ($r = 0.03$, $p = 0.87$).

Discussion

This study found that euthymic bipolar patients showed failure of de-activation in the medial frontal cortex, an area which constitutes the anterior midline node of the default mode network. This was not accompanied by any activation changes. A similar, though less marked failure of de-activation, again with no activation changes, was also seen in the unaffected siblings of patients with the disorder.

At first sight our failure to find activation changes in euthymic bipolar patients seems surprising, since the disorder is widely recognized as being associated with a pattern of task-related hypoactivations and hyperactivations (Strakowski *et al.* 2012). However, it should be noted that these changes have mostly been documented in patients in the manic or depressed phase. In fact, in Chen *et al.* (2011)'s meta-analysis of voxel-based fMRI studies the only area of

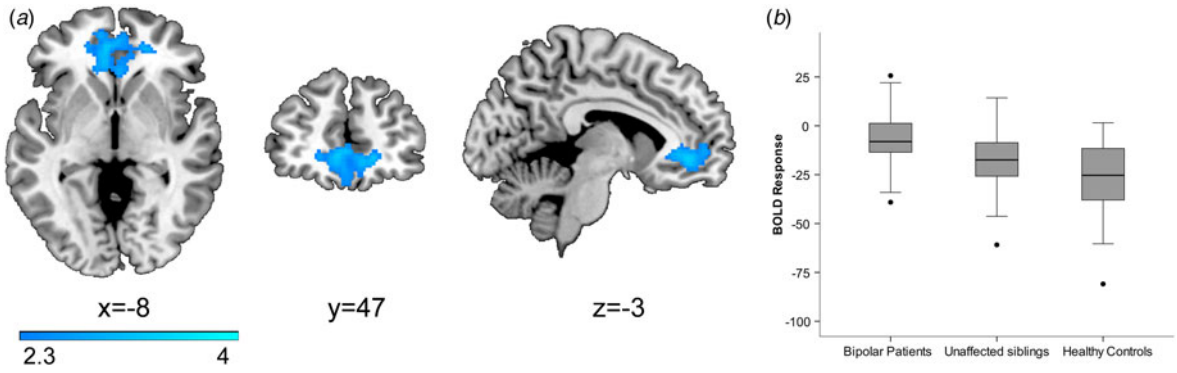

Fig. 2. (*a*) Cluster of significant difference in the medial prefrontal cortex found comparing bipolar patients, unaffected siblings and healthy controls in the 2-back *v.* baseline contrast. Numbers refer to Montreal Neurological Institute (MNI) coordinates of the slice shown. Colour bar indicates *z* scores from the group-level analysis. The right side of the image is the right side of the brain. (*b*) Boxplot based on individual mean activation values from the region of interest extracted from this significant cluster. Centre lines show the medians; box limits indicate the 25th and 75th percentiles; whiskers extend 1.5 times the interquartile range from the 25th and 75th percentiles; and outliers are represented by dots. BOLD, Blood oxygen level dependent.

hypoactivation found in euthymic patients was the lingual gyrus. This meta-analysis did find evidence of task-related hyperactivations in euthymia; here, however, the areas affected included the medial frontal cortex, the superior temporal gyrus, the parahippocampal gyrus and the cingulate cortex, and so it seems possible that at least some of the changes actually represented failure of de-activation rather than true hyperactivation (hyperactivation and failure of de-activation give the same appearance in functional imaging studies using subtraction analysis; for discussions, see Gusnard & Raichle, 2001; Pomarol-Clotet *et al.* 2008).

Similarly, the relatives of the bipolar patients did not show activation changes. This finding goes against those of a number of studies that have found hypoactivations, and more consistently hyperactivations, in such individuals (Drapier *et al.* 2008; Thermenos *et al.* 2010; Pompei *et al.* 2011). However, as noted in the Introduction, other studies have failed to find any evidence of activation differences (Allin *et al.* 2010; Sepede *et al.* 2012; Roberts *et al.* 2013), or have found evidence of subcortical changes only (Whalley *et al.* 2011).

As noted in the Introduction, failure of de-activation is now a relatively robust finding in bipolar disorder. It has been documented in both manic (Fernandez-Corcuera *et al.* 2013) and depressed (Fernandez-Corcuera *et al.* 2013) patients, and also in patients unselected for phase of illness (Calhoun *et al.* 2008), where it affects particularly the medial frontal cortex. We (Pomarol-Clotet *et al.* 2015) also found failure of de-activation in the same location in euthymic patients, and two other studies (Allin *et al.* 2010; Costafreda *et al.* 2011) found that the region affected was the posterior cingulate gyrus/precuneus. The present study found that the relatives of bipolar patients also showed failure of de-activation, which was located in the medial frontal cortex and was less marked than that seen in the patients. Previous studies have also found de-activation changes in relatives: Allin *et al.* (2010) found failure of de-activation, although this was in the posterior cingulate cortex/precuneus rather than in the medial prefrontal cortex as in our study. In contrast, Sepede *et al.* (2012) found exaggerated de-activation in the same area. Also relevant here is the study of Thermenos *et al.* (2010) which found four areas of what the authors considered to be increased activation in relatives of bipolar patients; however, in two of these regions, the left orbitofrontal cortex and the parietal cortex, plots of mean activations revealed that this actually represented failure of de-activation.

The question arises of what medial frontal failure of de-activation in relatives of bipolar patients might mean. The fact that it was also present in euthymic patients suggests that one is dealing with a trait abnormality. Beyond this, evidence from studies using a small number of tasks that have been found to activate parts of the default mode network rather than de-activate it suggests that it has roles as diverse as autobiographical recall, thinking about the future, theory of mind, moral decision-making and making judgements about characteristics that apply to oneself *v.* others (Buckner *et al.* 2008; Whitfield-Gabrieli *et al.* 2011). The medial frontal cortex, in particular, may also have a role in emotion: Price & Drevets (2012) have pointed out that this region has close connections with the amygdala and both structures form part of a wider network that includes the ventral striatum, the medial thalamus, the hypothalamus and the brainstem. Data from animals suggest that this system is

involved in forebrain modulation of visceral function in response to sensory or emotive stimuli.

In conclusion, this study provides evidence that bipolar disorder in euthymia is characterized by a failure to de-activate the medial prefrontal cortex, and that this change is present to a lesser extent in the unaffected first-degree relatives of patients. Taken together these findings suggest that default mode network dysfunction might represent a trait abnormality and possibly even an endophenotype for the disorder. Limitations of the study include the relatively small sample sizes for the patients and their relatives, and it is possible that a larger sample would have revealed changes in activation as well as in de-activation. As in most studies, the bipolar patients were on medication; however, current evidence suggests that the confounding effects of this are relatively limited (Hafeman *et al.* 2012). Finally, the finding that the relatives showed an intermediate level of medial frontal de-activation between the bipolar patients and the controls depended on ROI analysis. When reported clusters are large (which was not the case in our study) they may contain functionally and anatomically heterogeneous ensembles of voxels, which therefore may not be well characterized by a single ROI (Poldrack, 2007).

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Declaration of Interest

None.

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Estudio 3

Structural and functional brain correlates of cognitive impairment in euthymic patients with bipolar disorder

Plos One

JCR-2015: IF= 3.057, Posición en Ciencias Multidiscplinarias=11/63, Cuartil=1, Decil=2

En este último estudio en el que se compararon 33 bipolares eutímicos preservados cognitivamente, 28 deteriorados cognitivamente y 28 controles, se encontró que los pacientes cognitivamente preservados, en comparación con el grupo control, mostraban una reducción significativa del volumen de sustancia gris en un pequeño clúster situado en la circunvolución precentral derecha y una reducción significativa del volumen de sustancia blanca en regiones bilaterales del genu del cuerpo calloso. No hubo diferencias en el volumen de sustancia gris o blanca entre los grupos de pacientes cognitivamente preservados o deteriorados.

De la muestra total, se compararon 27 bipolares cognitivamente preservados, 23 deteriorados cognitivamente y los 28 controles durante la realización de la tarea n-back. A pesar de que no hubo diferencias significativas en el rendimiento de la tarea, los pacientes cognitivamente preservados mostraron un fallo en la desactivación de la corteza medial frontal en comparación con los controles en el 2-back vs línea basal y en el 2-back vs 1back. Cuando se compararon los grupos de pacientes entre sí, el contraste 2-back vs 1-back reveló un clúster de activación reducida en el grupo de deterioro cognitivo y situado en la corteza frontal lateral derecha, extendiéndose desde el opérculo frontal inferior a regiones laterales frontales superiores e incluyendo partes de la corteza prefrontal dorsolateral.

PLOS ONE

RESEARCH ARTICLE

Structural and Functional Brain Correlates of Cognitive Impairment in Euthymic Patients with Bipolar Disorder

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Abstract

Introduction

Cognitive impairment in the euthymic phase is a well-established finding in bipolar disorder. However, its brain structural and/or functional correlates are uncertain.

Methods

Thirty-three euthymic bipolar patients with preserved memory and executive function and 28 euthymic bipolar patients with significant memory and/or executive impairment, as defined using two test batteries, the Rivermead Behavioural Memory Test (RBMT) and the Behavioural Assessment of the Dysexecutive Syndrome (BADS), plus 28 healthy controls underwent structural MRI using voxel-based morphometry (VBM). Twenty-seven of the cognitively preserved patients, 23 of the cognitively impaired patients and 28 controls also underwent fMRI during performance of the n-back working memory task.

Results

No clusters of grey or white matter volume difference were found between the two patient groups. During n-back performance, the cognitively impaired patients showed hypoactivation compared to the cognitively preserved patients in a circumscribed region in the right dorsolateral prefrontal cortex. Both patient groups showed failure of de-activation in the medial frontal cortex compared to the healthy controls.

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Conclusions

Cognitive impairment in euthymic bipolar patients appears from this study to be unrelated to structural brain abnormality, but there was some evidence for an association with altered prefrontal function.

Introduction

Studies over the last two decades have demonstrated that a proportion of patients with bipolar disorder show cognitive impairment that persists beyond episodes of illness into euthymia [1]. The deficits are wide ranging [2], but may involve executive function and long-term memory particularly [1], and they are associated with impaired functioning in daily life [3, 4]. Presence of residual mood disturbance does not appear to fully account for the impairment seen [5], nor, according to a meta-analysis, does treatment with antipsychotic drugs [6]. Lithium [7] and anticonvulsants [8] have been found to impair only some areas of cognitive function in bipolar patients and so also appear to be unlikely to be the whole explanation.

Since patients with bipolar disorder do not show evidence of premorbid intellectual disadvantage [9–11], some form of brain dysfunction presumably underlies this form of persistent cognitive impairment. One possibility is that it is a consequence of structural brain pathology. Bipolar disorder is known to be associated with lateral ventricular enlargement [12–14], and there is evidence for a small reduction in brain size, although this reached significance in only one of two meta-analyses [13, 14]. Studies using whole-brain techniques such as voxel-based morphometry (VBM) have additionally found evidence for volume reductions in the anterior cingulate cortex, the insula and the inferior frontal cortex, among other regions [15–18]. White matter changes are also well documented in bipolar disorder, both in the form of subcortical signal hyperintensities [19] and reduced fractional anisotropy on diffusion tensor imaging (DTI); the latter changes have been found most consistently in the right temporo-parietal and the left anterior and mid-cingulate regions [20].

Relatively few studies have examined whether structural changes in bipolar patients are related to presence of cognitive impairment. Early studies reviewed by Bearden et al [21] found some evidence of associations with increased lateral ventricular volume and volume reductions in the prefrontal cortex, and more robustly with presence of white matter signal intensities. However, more recent studies examining multiple grey and white matter regions have generally found few significant correlations with executive, memory or other cognitive deficits [22–26].

Findings from many functional imaging studies in bipolar disorder have led to a consensus that it is characterized by reduced resting and task-related activity in the prefrontal cortex and some other cortical regions, coupled with overactivity in the amygdala, hippocampus and parahippocampal gyrus and the basal ganglia [27]. Not all of these abnormalities are seen in euthymia, however. Thus, in a meta-analysis pooling effect size data from PET, SPECT and fMRI studies, Kupferschmidt et al [28] found that euthymic patients showed evidence of task-related hypoactivations in the inferior and middle frontal cortex and the dorsolateral prefrontal cortex (DLPFC), as well as hyperactivity in the superior temporal gyrus and ventrolateral prefrontal cortex. On the other hand, in a meta-analysis of voxel-based studies, Chen et al [29] found evidence only for reduced activation in the lingual gyrus in euthymic patients.

To date, very few studies have investigated brain activations in relation to cognitive impairment in bipolar disorder [30–32]. In one study that examined patients in the euthymic phase, Oertel-Knöchel et al [33] found that 26 euthymic bipolar patients were impaired on a

verbal learning and recognition task, and also showed a pattern of reduced activation compared to healthy controls when they performed the same task while being scanned. The areas affected included the left middle and superior frontal gyrus during encoding, and the bilateral middle and inferior frontal gyrus, plus the parahippocampal and other posterior medial cortical areas during retrieval.

The aim of this study was to determine whether and to what extent cognitive impairment in euthymic bipolar patients has brain structural and/or functional correlates. To do this, we recruited groups of demographically well-matched patients who either showed or did not show executive and/or memory impairment, defined according to predetermined criteria, in the euthymic phase. Healthy controls were also employed. Both whole-brain structural imaging (VBM) and functional imaging (cognitive task-related fMRI) were carried out.

Materials and Methods

Participants

The patient sample consisted of two groups of adults with bipolar disorder, who were prospectively recruited on the basis of showing (N = 28) or not showing (N = 33) cognitive impairment (as defined below) in the euthymic phase. Patients were from the outpatient departments of two psychiatric hospitals in Barcelona: Benito Menni CASM and the University of Barcelona Hospital Clínic. They all met DSM-IV criteria for bipolar I disorder and were required to have had at least two episodes of illness. Patients were excluded if a) they were younger than 18 or older than 55; b) they had a history of brain trauma or neurological disease, c) they had shown alcohol/substance abuse within 12 months prior to participation; d) they had undergone electroconvulsive therapy in the previous 12 months; and e) they showed evidence of general intellectual impairment/handicap, as indexed by a current IQ outside the normal range (i.e. below 70) as measured using four subtests of the Wechsler Adult Intelligence Scale III (WAIS-III) (vocabulary, similarities, block design, and matrix reasoning). All patients were right-handed.

Patients were considered to be euthymic if they had had no episodes of illness for at least three months and if they had a score on Hamilton Rating Scale for Depression (HDRS-21) of ≤ 8 and Young Mania Rating Scale (YMRS) of ≤ 8 at the time of testing. These quite strict requirements were used in order to avoid the potentially confounding effects of subthreshold depressive and manic symptoms on cognitive function [34]. The upper age limit of 55 was chosen in order to exclude late-onset affective disorder which has an association with vascular and neurodegenerative disease and so might be independently associated with cognitive impairment [35].

Patients in the cognitively preserved group were on treatment with mood stabilizers (lithium alone n = 13, other mood stabilizers alone n = 6; lithium in combination with other mood stabilizers n = 9), antidepressants (n = 8) and antipsychotics (n = 21; second generation n = 21, first generation n = 2; mean chlorpromazine equivalent dose 284.65 ±337.31 mg/day). The cognitively impaired patients were also on treatment with mood stabilizers (lithium alone n = 13, other mood stabilizers alone n = 4; lithium in combination with other stabilizers n = 7), antidepressants (n = 7); 17 were taking antipsychotics (second generation n = 15, first generation n = 1, both n = 1; mean chlorpromazine equivalent dose 245.20± 209.77 mg/day).

A group of 28 right-handed healthy controls were recruited via poster and web-based advertisement in the hospital and local community, plus word-of-mouth requests from staff in the research unit. The controls met the same exclusion criteria as the patients. They were also excluded if they reported a history of mental illness or treatment with psychotropic medication, and/or had a first-degree relative with a psychiatric illness.

The three groups were selected to be matched for age, sex and estimated IQ (premorbid IQ in the patients). IQ was estimated using the Word Accentuation Test (Test de Acentuación de Palabras, TAP) [36] a pronunciation test that is conceptually similar to the National Adult Reading Test (NART) used in the UK [37] and the Wide Range of Achievement Test (WRAT) in the USA [38]. Subjects have to pronounce low-frequency Spanish words whose accents have been removed. Scores can be converted into IQ estimates [39].

Cognitive assessment

This was based on Spanish versions of two well-validated memory and executive test batteries, the Rivermead Behavioural Memory Test (RBMT) [40] and the Behavioural Assessment of the Dysexecutive Syndrome (BADS) [41]. These two tests provide a wide ranging assessment of different aspects of memory and executive function, respectively, and are designed to be 'ecologically valid', that is to capture the broad range of executive and memory functions required in real-life settings. Both have been subjected to extensive validation in healthy adults and normative data for healthy adults are available.

The RBMT consists of 12 subtests examining verbal recall, recognition, orientation, remembering a route and three measures of prospective memory, the ability to remember to do things. Pass/fail scores are summed to give a 'screening' score. The BADS consists of 6 subtests covering cognitive estimation, rule shifting, planning, problem solving and decision making under multiple task demands (the Modified Six Elements Test). Scores from 0 to 4 on each subtest are summed to give an overall 'profile' score.

The patients were classified as cognitively preserved or impaired using 5th percentile cutoffs based on normative data for adults. Thresholding for impairment at the 5th percentile for the normal population is an established method in neuropsychology [42]. Specifically, patients were considered cognitively impaired if they scored below the 5th percentile on the RBMT and/or the BADS (screening score of $\leq$7 on the RBMT and profile score of $\leq$11 on the BADS), and were considered cognitively preserved if they scored at or above the 5th percentile on both tests ($\geq$8 or more on the RBMT and $\geq$12 on the BADS).

Scanning procedure

All subjects underwent structural and functional MRI scanning using a 1.5 Tesla GE Signa scanner (General Electric Medical Systems, Milwaukee, Wis) located at the Sant Joan de Déu Hospital in Barcelona (Spain).

Structural neuroimaging. High resolution structural T1-weighted MRI data were acquired with the following acquisition parameters: matrix size 512x512; 180 contiguous axial slices; slice thickness of 1 mm, no slice gap; voxel resolution 0.47x0.47x1 mm^3; echo time (TE) = 3.93 ms, repetition time (TR) = 2000 ms and inversion time (TI) = 710 ms; flip angle 15°.

Brain structure (grey matter) was examined using FSL-VBM, an optimized VBM style analysis [43, 44] carried out with FSL tools; this yields a measure of difference in local grey matter volume. First, structural images were brain-extracted [45]. Next, tissue-type segmentation was carried out. The resulting grey matter partial volume images were then linearly aligned to MNI 152 standard space [46, 47], followed by nonlinear registration. The resulting images were averaged to create a study-specific template, to which the native grey matter images were then nonlinearly re-registered. The registered partial volume images were then modulated by dividing by the Jacobian of the warp field. The modulated gray matter segments were then smoothed with an isotropic Gaussian kernel using a sigma of 4mm (equivalent to Full Width at Half Maximum (FWHM) of 9.4 mm) (technical details are available at www.fmrib.ox.ac.uk/fsl/fslvbm/). Voxel-size after VBM processing was 2x2x2mm.

Group comparisons were performed using permutation-based non-parametric tests. The TFCE (Threshold-Free Cluster Enhancement) method, also implemented in FSL, was used for this purpose. TFCE finds clusters in the data without having to define the initial cluster-forming threshold [48]. Cluster-like structures are enhanced but the image remains fundamentally voxel-wise. In the resulting maps, obtained with 5000 permutations, family-wise error (FWE) rate was used to control for multiple comparisons and only FWE-corrected cluster p-values <0.05 were considered.

We also examined white matter volume. Since the VBM analysis in FSL has only been validated for grey matter, this was carried out with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The following standard pre-processing steps were carried out: (1) tissue-type segmentation, (2) normalization to standard space of the obtained white matter images and (3) modulation. The resulting images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm. In order to make the results comparable to those reported for grey matter using FSL-VBM, statistical analysis were conducted with the same correction method. That is, all comparisons were carried out with the TFCE method included in FSL, using 5000 permutations and a FWE-corrected threshold of $p < 0.05$.

Functional neuroimaging. For this we used the n-back task [49], which has been widely employed as a probe for executive function, specifically working memory, in fMRI studies in healthy subjects [50] and psychiatric disorders including schizophrenia [51] and bipolar disorder [52]. Two levels of memory load (1-back and 2-back) were presented in a blocked design manner; in the 1-back task, participants had to respond with a key press when a letter was the same as the one that was presented immediately previously, whereas in the 2-back task they had to respond when the letter was the same as that presented two letters previously (Fig 1). Each block consisted of 24 letters which were shown every two seconds (1 second on, one second off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within block. Individuals had to detect these repetitions and respond by pressing a button. In order to identify which task had to be performed, characters 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. All individuals went through a training session before entering the scanner.

Performance was measured using the signal detection theory index of sensitivity (d') of ability to discriminate targets from non-targets [53]. Higher values of d' indicate better ability to discriminate between targets and distractors. Subjects who had negative d' values in either the 1-back and 2-back versions of the task, which suggests that they were not performing it, were excluded from the analysis.

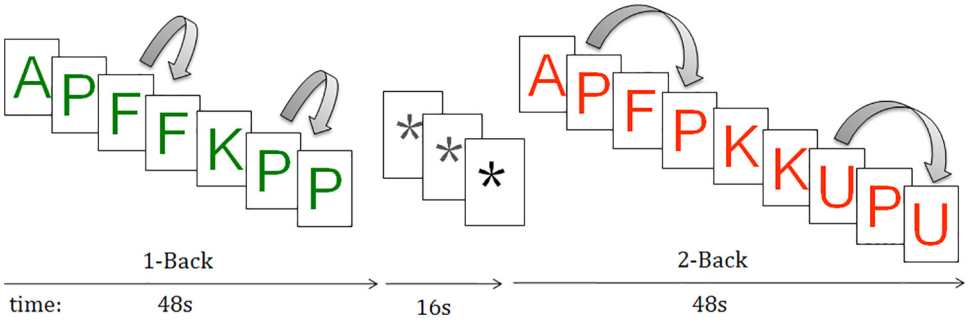

Fig 1. Sequential-letter version of the n-back task with two levels of memory load, 1-back (green) and 2-back (red).

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In each individual scanning session 266 volumes were acquired. A gradient echo echo-planar sequence depicting the BOLD contrast was used. Each volume contained 16 axial planes acquired with the following parameters: TR = 2000 ms, TE = 20 ms, flip angle = 70 degrees, section thickness = 7 mm, section skip = 0.7 mm, in-plane resolution = 3x3 mm. The first 10 volumes were discarded to avoid T1 saturation effects.

fMRI image analyses were performed with the FEAT module, included in FSL software [54]. Pre-processing with FSL-FEAT included: a) motion correction [47]; b) non-brain removal [45]; c) isotropic 5mm-FWHM Gaussian smoothing; d) high-pass temporal filtering; e) time-series statistical analysis with local autocorrelation correction [55]; and f) registration to the MNI 152 standard space [46, 47]. To minimize unwanted movement-related effects, participants with an estimated maximum absolute movement >3.0 mm or an average absolute movement >0.3 mm were excluded from the study.

General linear models (GLMs) were fitted to generate the individual activation maps for the 1-back vs. baseline, 2-back vs. baseline and 2-back vs. 1-back comparisons. Differences in fMRI activation maps between patients and controls were generated within the FEAT module, using mixed effects GLM models [56]. FEAT uses Gaussian random field theory to properly account for the spatially distributed patterns when performing statistical tests. Specifically, the analyses were performed with the FLAME stage 1 with default height threshold ($z > 2.3$) [55, 57] and a p-value < 0.05 corrected for multiple comparisons [58, 59].

Ethics statement

All subjects gave written informed consent prior to participation in accordance to the Declaration of Helsinki. Only individuals judged to have decision-making capacity were included. The subjects in the cognitively impaired group were included on the basis that they showed memory and/or executive function as detected during the course of the neuropsychological testing carried out for the purpose of the study, not because they had been found to show clinically significant cognitive impairment by their treating clinicians. The research protocol was approved by the Clinical Research Ethics Committee of the Sisters Hospitallers (Comité de Ética de Investigación Clínica de las Hermanas Hospitalarias), which also approved this method of obtaining informed consent for the study.

Data analysis

Demographic, clinical and cognitive variables were compared among the groups using SPSS version 17. Normality of continuous variables was examined for and parametric (t-test or ANOVA) or non-parametric tests (Mann-Whitney or Kruskal-Wallis test) were applied as appropriate.

In order to examine the relationship between presence of cognitive impairment and brain structure and function, we carried out two comparisons using a strategy we have employed previously for schizophrenia [60]. First, we contrasted the cognitively preserved group with the control group; this gives a measure of changes in brain structure and/or function that are attributable to bipolar disorder uncontaminated by presence of cognitive impairment. Secondly, to detect changes attributable to the presence of cognitive impairment, we contrasted the cognitively preserved and cognitively impaired patient groups.

Results

Demographic characteristics of the patients and controls are shown in Table 1. The groups were matched for age, sex and TAP-estimated IQ. There were no differences in psychopathological measures (YMRS and HRSD scores), duration of the illness, functioning (GAF score)

Table 1. Demographic, neurocognitive and psychopathological characteristics of the groups.

	Controls (n = 28)	Cognitively preserved (n = 33)	Cognitively impaired (n = 28)	Statistics	Post hoc testing
Age	44.01 (6.03)	44.13 (6.63)	46.17 (7.40)	F = 0.94 p = 0.40	
Sex (male/female)	12/16	18/15	17/11	χ^2 = 1.85 p = 0.40	
Estimated premorbid IQ (TAP)	105.93 (7.25)	106.03 (6.32)	102.71 (8.81)	H = 3.08 p = 0.21	
BADS profile score	19.18 (2.40)	17.12 (2.25)	13.89 (3.54)	F = 26.09 p<0.001	CI < CP (p<0.001)
					CI < CON (p<0.001)
					CP < CON (p = 0.01)
RBMT screening score	10.61 (1.64)	9.76 (1.41)	6.11 (1.29)	H = 55.43 p<0.001	CI < CP (p<0.001)
					CI < CON (p<0.001)
					CP < CON (p = 0.02)
Duration of illness (years)	-	16.76 (7.44)	19.13 (8.16)	t = 1.17 p = 0.25	
YMRS score	-	1.18 (1.81)	1.77 (2.10)	U = 360.50 p = 0.25	
HRSD score	-	2.55 (2.02)	2.19 (2.35)	U = 367.00 p = 0.33	
GAF score	-	79.07 (11.35)	75.75 (12.72)	t = -0.99 p = 0.33	

Values are given as mean (SD). IQ, intelligence quotient; TAP, Word Accentuation Test; BADS, Behavioural Assessment of the Dysexecutive Syndrome; RBMT, Rivermead Behavioural Memory Test; YMRS, Young Mania Rating Scale; HRSD, Hamilton Rating Scale for Depression; GAF, Global Assessment of Functioning; F, one-way ANOVA test; χ^2, Chi-square test; H, one-way Kruskal-Wallis test; U, Mann-Whitney test; CON, controls; CP, cognitively preserved; CI, cognitively impaired.

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and antipsychotic dosage between the cognitively preserved and the cognitively impaired patients (Table 1).

As expected, the two patient groups differed in their performance on the BADS and RBMT (Table 1). The cognitively preserved group was also found to show significant differences from the healthy controls. A scatter plot of scores for all three subject groups is shown in Fig 2 and indicates that this latter finding was due to more cognitively preserved patients falling into low average ranges than the healthy controls.

VBM findings

Controls vs. cognitively preserved patients. At $p < 0.05$ corrected, the cognitively preserved patients showed significantly reduced grey matter volume in a single small cluster located in the right precentral gyrus [173 voxels, p = 0.03; peak in BA6, MNI (38,-10,38)] (Fig 3).

The cognitively preserved patients also showed bilaterally symmetrical clusters of significantly reduced white matter volume compared to the controls. On the left side, a cluster extended from the inferior occipito-frontal and uncinate fasciculus to the genu of corpus callosum [2966 voxels, p = 0.01, peak in MNI (-30, 46.5, 1.5)]. A second smaller cluster on the same side was located in the white matter adjacent to the inferior frontal cortex [337 voxels, p = 0.03, peak in MNI (-36, 21, 22.5)]. On the right side, there was only one cluster [4294 voxels, p = 0.02, peak in MNI (27, 46.5, 3)] (Fig 3).

Cognitively preserved vs. cognitively impaired patients. There were no areas of significant grey matter volume difference between the cognitively preserved patients and the cognitively impaired patients at $P<0.05$, corrected. Lowering the threshold to $p<0.005$ uncorrected

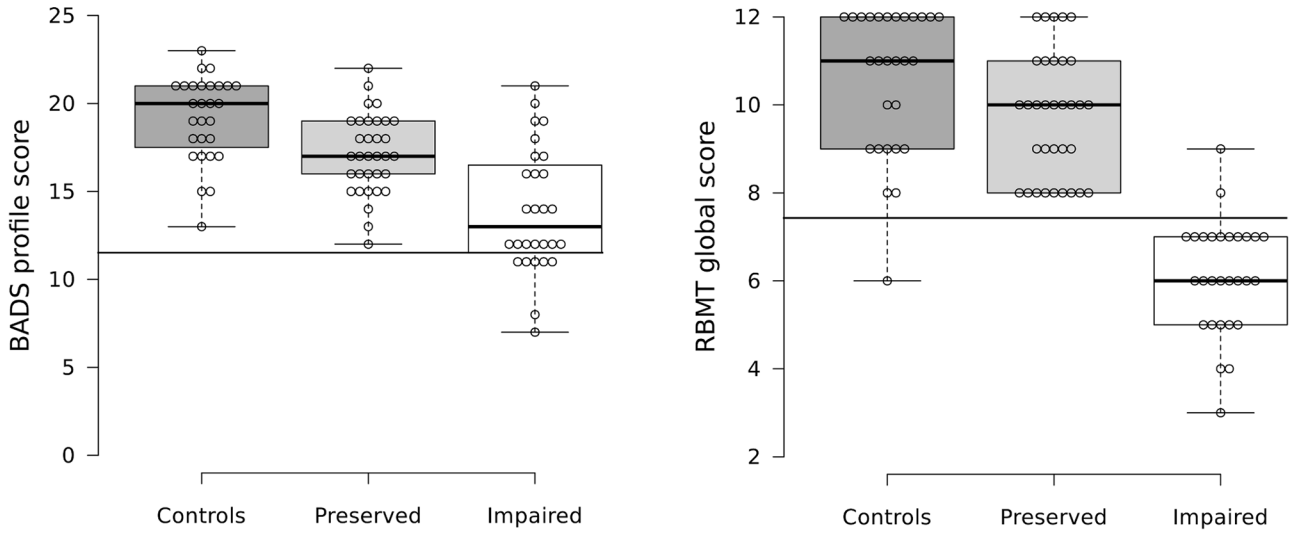

Fig 2. Scatter plots for the controls, cognitively preserved and cognitively impaired groups. Scatter plot of scores on (A) the RBMT and (B) the BADS. The horizontal lines show 5th percentile cutoffs for impairment.

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did not result in the appearance of any clusters. Substituting non-modulated images in the analysis also failed to reveal any clusters of significant difference.

Functional imaging findings

Twenty-eight of the healthy controls, 27 of the cognitively preserved patients and 23 of the cognitively impaired patients participated in this part of the study (5 cognitively preserved patients and 5 cognitively impaired patients could not be included because of technical problems with the acquisition and processing of the images; 1 cognitively preserved patient was excluded because of excessive movement). There continued to be no significant differences between the three groups in demographic characteristics, and between the two patient groups in clinical ratings (S1 Table).

Behavioural performance. The mean level of performance (d') on the 1-back and 2-back versions of the n-back task was lower in the cognitively preserved patients than in the healthy controls, and lower in the cognitively impaired patients than in the cognitively preserved patients [1-back: 4.40 (0.57) vs. 4.17 (0.63) vs. 3.67 (1.09); $H = 7.56$; $p = 0.02$; 2-back: 3.33 (0.83) vs. 3.00 (0.69) vs. 2.52 (0.73); $F = 7.32$, $p<0.001$]. However, only the differences between the controls and the cognitively impaired patients reached significance (S1 Table).

Within-group activations and de-activations. In the 2-back vs. baseline comparison the healthy controls showed bilateral activations in the DLFPC, precentral gyri, supplementary motor area, anterior insula, cerebellum, thalamus, basal ganglia, and parts of the temporal and parietal cortex. In the 1-back vs. baseline, activations followed a broadly similar pattern but the clusters were less extensive, the basal ganglia were activated only in the left side and no activations were seen in cerebellum and thalamus (S2 Table, S1 and S2 Figs).

Task-related de-activations in the 2-back vs. baseline contrast were seen bilaterally in the medial frontal cortex, amygdala, hippocampus, the medial parietal cortex, the posterior insula and the lateral parietal cortex. In the 1-back vs. baseline contrast, only the medial frontal cortex showed de-activation (S1 and S2 Figs).

Activations and de-activations in the two groups of euthymic bipolar patients followed a broadly similar pattern to that seen in the controls. However, both the activation and

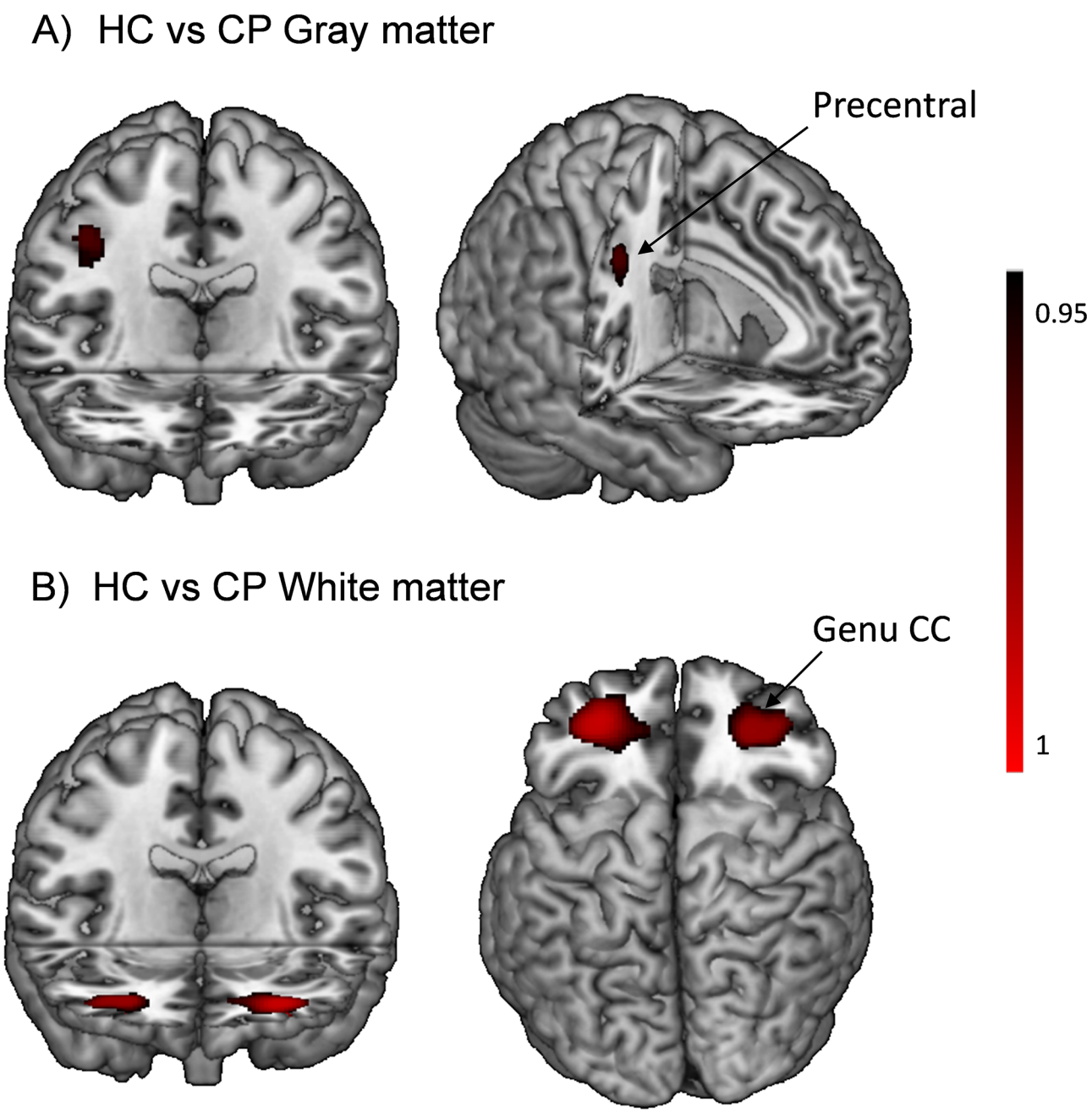

Fig 3. Brain regions showing significant gray and white matter volume reduction in the cognitively preserved patients with bipolar disorder compared with controls.

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de-activation clusters were noticeably less extensive. The cognitively impaired patients in particular showed less extensive prefrontal activation in 2-back vs. baseline contrast and no de-activation in the medial prefrontal, amygdala, hippocampus and posterior insula in both the 1-back vs. baseline and 2-back vs. baseline contrasts (S1 and S2 Figs).

Controls vs. cognitively preserved patients. There were no activation differences between the healthy controls and the cognitively preserved patients in the 1-back vs. baseline or the 2-back vs. baseline contrasts, or in the 2-back vs. 1-back contrast. The cognitively preserved

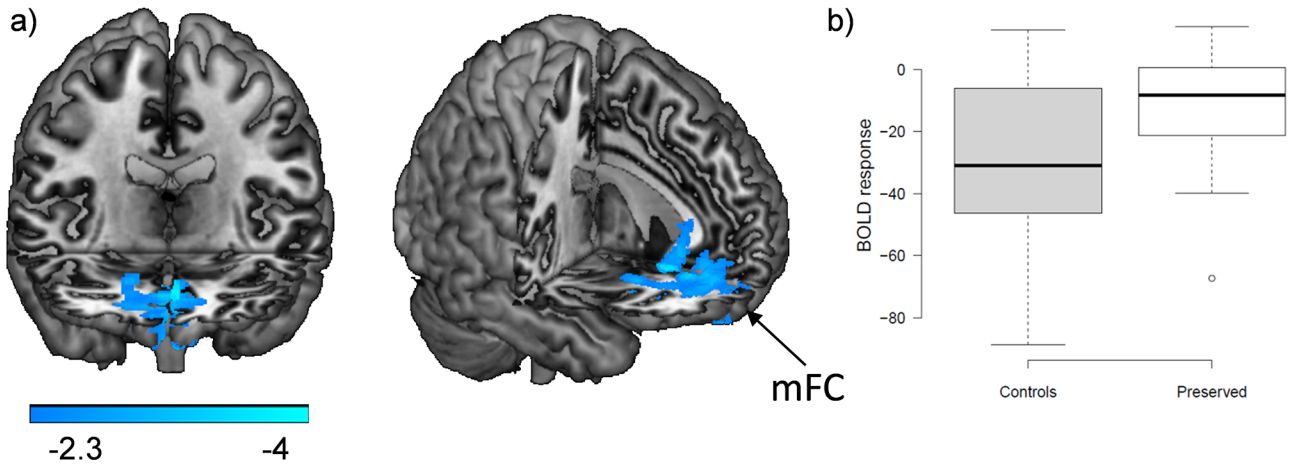

Fig 4. Brain functional changes between controls and cognitively preserved patients. (A) Brain regions where the cognitively preserved patients showed significant failure of de-activation compared with the controls in the 2-back vs. 1-back contrast. MFC: medial frontal cortex. (B) Boxplots of mean de-activations within this ROI.

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patients did, however, show a cluster of failure of de-activation in comparison to the healthy controls in both contrasts. In the 2-back vs. baseline contrast this cluster was located in the medial prefrontal cortex affecting the gyrus rectus and extended to the medial orbitofrontal and anterior cingulate cortex [4743 voxels, $p = 2.18 \times 10^{-9}$; peak activation in BA11, MNI (4, 34,-8), z score = 4.5]. In the 2-back vs. 1-back contrast the cluster occupied a similar but smaller area in the medial prefrontal cortex [1718 voxels, $p = 2.04 \times 10^{-4}$; peak activation in BA25, MNI (2,36,6), z score = 4.16]. The findings for the 2-back vs. 1-back contrast are shown in Fig 4A. Boxplots of the averaged values in the medial prefrontal region-of-interest (ROI) for the controls and the cognitively preserved patients for this contrast confirm that the differences represented failure of de-activation: the controls showed de-activation whereas in the patients the mean value was close to zero (Fig 4B).

Cognitively preserved vs. cognitively impaired patients. There were no differences between the two patient groups in the 1-back vs. baseline and the 2-back vs. baseline contrasts. The 2-back vs. 1-back contrast, however, revealed a cluster of reduced activation in the cognitively impaired group in the right lateral frontal cortex, extending from the inferior frontal operculum to lateral superior frontal regions and including parts of the DLPFC [905 voxels, $p = 0.008$; peak activation in BA8, right superior frontal, MNI (24, 20, 46), z score = 4.12]. The findings are shown in Fig 5. The two patient groups did not show differences in de-activation.

Discussion

Cognitive impairment in the euthymic phase—i.e. that is persistent and unrelated to mood disturbance—is now a well-established finding in bipolar disorder. Our study suggests that its basis does not lie in brain structural change. However, there was a positive signal in relation to brain function, with the cognitively impaired patients showing reduced activation in the right DLPFC compared to the cognitively preserved patients.

Given that in neurological disease structural brain damage is commonly associated with neuropsychological deficits, our failure to find differences in grey or white matter volume between bipolar patients with and without cognitive impairment might be considered surprising. One possible reason for this might be that, with sample sizes of 33 and 28 patients, the study might simply have lacked sufficient power to detect differences. Against this, however, is

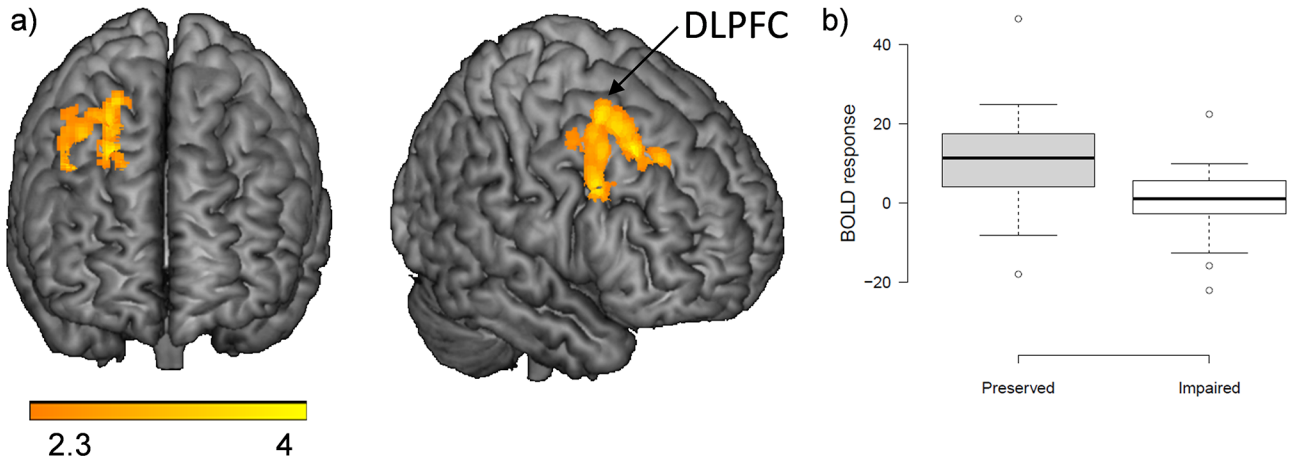

Fig 5. Brain functional changes between cognitively impaired and preserved patients. (A) Brain regions where the cognitively impaired patients showed significantly reduced activation compared with the preserved patients in the 2-back v. 1-back contrast. (B) Boxplots of mean activations within this ROI.

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the fact that grey matter changes were still not seen when a more liberal threshold of $p<0.005$ uncorrected was used in the VBM analysis, or when the modulation step was omitted, which also increases sensitivity [61].

Our negative structural imaging findings might also be considered inconsistent with the current widely held view that the occurrence of persistent cognitive impairment in some patients with bipolar disorder reflects a neurodegenerative process [62]. Of course, being cross-sectional in nature, the study does not speak directly to this issue. Nevertheless, it is interesting to note that the evidence that progressive brain structural change takes place at all in bipolar disorder is actually quite weak. Thus, reviewing the small number of longitudinal studies carried out to date, Lim et al [63] found no evidence for change in whole brain volume over time. Progressive volume reductions were found in the frontal lobe cortex in two small studies (N = 8 and N = 10) but not in a third, larger study (N = 58) which also employed healthy controls. Findings were likewise conflicting for the anterior cingulate cortex, amygdala and hippocampus.

On the other hand, we found evidence that cognitive impairment in euthymic bipolar patients was associated with brain functional changes, specifically reduced activation in a region that conformed reasonably closely to the right DLPFC, although this was only seen in the 2-back vs. 1-back contrast. Our findings here show a notable similarity to those of Oertel-Knöchel et al [33] described in the Introduction—they found reduced activation in the left middle superior frontal gyrus in 26 euthymic bipolar patients, who as a group showed poor memory test performance, during the encoding phase of a memory task (reduced activation was seen in other lateral frontal regions during retrieval). The DLPFC is implicated in both the cognitive, i.e. executive, aspects of frontal lobe function [64] and in long-term memory [65], and so is a plausible location for brain functional changes associated with performance of both types of task in bipolar disorder.

A factor complicating the interpretation of this finding concerns the 'chicken and egg' nature of the relationship between cognition and brain activity. Does reduced activation in cognitively impaired euthymic bipolar patients point to underlying regional cerebral dysfunction? Or does it merely index the fact that the patients performed the task more poorly than the cognitively preserved patients and so activated their frontal lobes to a correspondingly lesser degree? To put it another way, would healthy subjects who were below the 5th percentile on a memory or executive test (as some will inevitably be) show less DLPFC activation during n-

back performance than those who are above this threshold? This problem has been considered in some depth in the schizophrenia literature e.g. [66–70], where the main conclusion reached has been that there is no simple linear relationship between cognitive performance and regional cortical activation. However, to our knowledge the same issue has not so far been addressed with respect to the cognitive impairment that sometimes accompanies bipolar disorder.

The other functional imaging finding in our study was failure of de-activation in the medial frontal cortex, which was seen in both groups of bipolar patients. This abnormality has been found in several other studies of bipolar disorder [71–73], with one additional study [74] finding failure of de-activation in the posterior cingulate cortex/precuneus. Both the medial frontal cortex and the posterior cingulate cortex/precuneus are components of the default mode network, a series of interconnected brain regions that are active at rest but which de-activate during performance of attention-demanding tasks [75]. Resting state connectivity studies have also implicated the default mode network in bipolar disorder [76]. The function or functions of the default mode network are currently uncertain, although a role in a range of high-level, self-related cognitive operations seems likely [75]. It has also been suggested that the network exerts a general influence on cognitive function—thus, in healthy subjects lower default mode network activity has been found to be associated with more successful task performance, and lapses of attention are associated with reduced de-activation (for a review see [77]). The fact that we found that medial frontal failure of de-activation did not distinguish cognitively preserved from cognitively impaired euthymic patients, suggests that this general modulatory function carried out by the default mode network dysfunction does not play a role in the cognitive impairment seen in euthymic patients with bipolar disorder.

Conclusions and Limitations

Our findings do not suggest that brain structural alterations are related to the persistent cognitive impairment that is seen in a proportion of patients with bipolar disorder. However, we find evidence that it might be related to functional changes in the prefrontal cortex. Limitations of the study include that our strategy for recruiting patients meant that the cognitively preserved patients were not explicitly matched with the healthy controls for cognitive function, and in fact they were significantly impaired compared to them. Accordingly, this group should be considered to have been only relatively cognitively preserved. Also, the sample sizes in the structural imaging comparison may have been too small to detect subtle volume differences between the two patient groups. Finally, we scanned at 1.5 Tesla, and our examination of white matter was limited to volume measurement only. Use of 3 Tesla scanning and/or examining white matter integrity using DTI might lead to changes related to cognitive impairment in bipolar disorder being found.

Supporting Information

S1 Dataset. Individual demographic, behavioral and fMRI data.
(XLSX)

S1 Fig. Mean activations and de-activations in the two patient groups and the controls from the 1-back vs. baseline contrast. Areas of significant activations (red- yellow) and deactivations (blue) in the three groups of subjects. The right side of the image is right side of the brain. MNI coordinates for each one of the axial slices are shown in the last row. Colors depict scores from statistical z maps (negative values in the deactivations). A: Healthy controls; B: Cognitively preserved patients; C: Cognitively impaired patients.
(TIFF)

S2 Fig. Mean activations and de-activations in the two patient groups and the controls from the 2-back vs. baseline contrast. Areas of significant activations (red- yellow) and deactivations (blue) in the three groups of subjects. The right side of the image is right side of the brain. MNI coordinates for each one of the axial slices are shown in the last row. Colors depict scores from statistical z maps (negative values in the deactivations). A: Healthy controls; B: Cognitively preserved patients; C: Cognitively impaired patients.
(TIFF)

S1 Table. Demographic and psychopathological characteristics in the fMRI sample (SDs in brackets).
(DOCX)

S2 Table. Clusters of significant activation/de-activation in the comparison between the 1-back vs. baseline, 2-back vs. baseline and between the 1-back vs. 2-back contrasts.
(DOCX)

Author Contributions

Conceived and designed the experiments: EP-C PM. Performed the experiments: SA-L JMG CMB SS BS BLA NM PFC. Analyzed the data: SA-L GCM RS EP-C. Contributed reagents/materials/analysis tools: TM. Wrote the paper: SA-L JMG EV EP-C PM.

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5 Discusión y conclusiones

Esta tesis ha abordado principalmente los cambios en el nivel de activación y desactivación en el trastorno bipolar durante la ejecución de una tarea de memoria de trabajo. Los análisis realizados indican que el trastorno bipolar se caracteriza por alteraciones funcionales tanto dependientes como independientes del estado de ánimo. Así, se observó una reducción de la activación en la corteza parietal dorsal tanto en manía como en depresión, pero no en eutimia; una activación reducida en la corteza prefrontal dorsolateral en las tres fases de la enfermedad, aunque con una mayor reducción en manía en comparación con la eutimia; y un fallo en la desactivación de la corteza frontal medial similar en las tres fases que parece indicar una alteración en la DMN como marcador rasgo del trastorno.

Además, este fallo en la desactivación medial frontal también se observó en los hermanos no afectados de pacientes con el trastorno, aunque de una manera menos marcada que los pacientes bipolares. Por lo tanto, la disfunción de la DMN podría ser reflejo del riesgo genético que confiere vulnerabilidad para el trastorno y por lo tanto, podría ser un endofenotipo potencial.

Por último, se objetivó que la disfunción de la DMN no parece mediar el deterioro cognitivo presente en el trastorno bipolar, sino que éste se relaciona con cambios en la activación cerebral, en concreto con una activación reducida en la corteza prefrontal dorsolateral derecha.

A continuación, estos resultados se discutirán con más detalle y se sugerirán posibles implicaciones y líneas de investigación futuras.

5.1. Alteraciones funcionales dependientes del estado

La reducción de la activación en la corteza parietal dorsal se observó en relación a los episodios de manía y depresión, pero no en eutimia. Este hallazgo de cambios dependientes del estado de ánimo en la corteza parietal dorsal es inesperado ya que esta región no fue identificada en ninguno de los dos meta-análisis realizados hasta la fecha y que incluyen subanálisis en relación a las diferentes fases del trastorno (Chen et al 2011, Kupferschmidt & Zakzanis 2011). Una posible explicación reside en el hecho de que esta región forma parte de la "red de la memoria de trabajo' que activa la tarea n-back (Owen et al 2005) y, aunque ambos meta-análisis incluyeron diferentes tareas cognitivas, relativamente pocos estudios

emplearon el n-back o tareas similares de memoria de trabajo (7/29 y 10/32, respectivamente).

Entre los estudios que han hecho uso de esta tarea, Pomarol-Clotet et al (2012) encontraron reducción de la activación en la corteza parietal, junto con otra regiones de la red de memoria de trabajo en pacientes en fase maníaca, y Fernandez-Corcuera et al (2013) obtuvieron resultados similares cuando incluyeron pacientes bipolares durante un episodio de depresión, si bien cabe señalar que estos dos estudios se llevaron a cabo sobre muestras que se superponen con el presente estudio. Con respecto a la eutimia, Cremaschi et al (2013) revisaron ocho estudios que utilizaron la tarea n-back en esta fase de la enfermedad y encontraron activación parietal reducida sólo en uno de ellos (Townsend et al 2010), mientras que en el resto no hubo diferencias entre pacientes y controles o se encontró un patrón opuesto de aumento de activación. El estudio de Townsend et al (2010) era de hecho el único estudio hasta la fecha que había examinado pacientes en las tres fases de la enfermedad durante la ejecución de la tarea n-back. Sus resultados fueron muy diferentes a los nuestros en cuanto a que no pudieron encontrar variaciones significativas entre fases, ya sea en la corteza parietal o la corteza prefrontal dorsolateral, ya que la activación se redujo indiferenciadamente en los tres grupos de pacientes en comparación con los controles. Hay dos posibles razones por las que estos autores pueden no haber detectado diferencias entre fases. En primer lugar, el tamaño de la muestra puede haber sido demasiado pequeño para detectar diferencias (de 13 a 15 por grupo), en particular considerando que entre pacientes las diferencias son probablemente más sutiles que las que hay entre pacientes y controles sanos. En segundo lugar, las comparaciones de grupo se llevaron a cabo en ROIs empleando una esfera de 5 mm alrededor de los vóxeles de máxima activación en cada región, en lugar de utilizar ROIs definidas anatómicamente. Es posible que esto pudiera haber dado lugar a regiones de interés que favorecen la búsqueda de diferencias entre pacientes y controles, pero que no sean óptimas para detectar diferencias entre los grupos de pacientes.

Por otro lado, también encontramos activación reducida en la corteza prefrontal dorsolateral, que mostró evidencia ambigua sobre sus posibles características rasgo o estado en relación a las diferentes fases del trastorno. A pesar de que en un primer lugar no apareció en ninguno de los contrastes entre los subgrupos de pacientes, surgió en el ANOVA cuando se compararon los tres subgrupos de pacientes y los controles. Los valores individuales medios de este clúster mostraron una reducción significativa entre los tres grupos de bipolares en

comparación con los controles, así como una menor activación en manía en comparación con la eutimia. La reducción de activación de la corteza prefrontal ha sido un hallazgo regular en el trastorno bipolar, aunque principalmente se ha documentado en regiones de la corteza orbitofrontal o ventrolateral prefrontal, quizás reflejando la naturaleza de las tareas que se utilizan en estos estudios como el Go/NoGo o la tarea de Stroop (Hajek et al 2013). En consonancia con esta interpretación, el pequeño número de estudios que han utilizado tareas de memoria de trabajo sí que han encontrado reducción de la activación en o cerca de la corteza prefrontal dorsolateral en manía (Pomarol-Clotet et al 2012), depresión (Fernandez-Corcuera et al 2013) y eutimia (Lagopoulos et al 2007, Monks et al 2004, Townsend et al 2010).

5.2. Alteraciones funcionales rasgo

En este primer estudio se encontró además evidencia de un cambio funcional independiente de la fase y consistente en un fallo en la desactivación en la corteza frontal medial entre los pacientes y los controles que puede interpretarse como una disfunción en el nodo anterior de la DMN. Este cambio estaba presente en un grado similar en las tres fases de la enfermedad y fue el único resultado cuando los pacientes eutímicos se compararon con los controles, lo cual fue replicado en los tres estudios realizados.

No evidenciamos cambios de activación en pacientes bipolares eutímicos, lo que parece contrastar con la literatura previa en la que este trastorno se ha asociado con un patrón de hipoactivaciones corticales e hiperactivaciones límbicas relacionadas con la ejecución de diversas tareas (Strakowski et al 2012). Sin embargo, hay que señalar que la mayoría de estos cambios se han documentado en los pacientes en la fase de manía o depresión. De hecho, en el meta-análisis de Chen et al (2011) en el que sólo se incluyeron estudios de fMRI, la única área en la que se encontró una hipoactivación en pacientes eutímicos fue la circunvolución lingual.

Por otro lado, el fallo en la desactivación de la corteza frontal medial en el trastorno bipolar está en línea con los resultados de nuestros estudios anteriores con muestras de bipolares en manía (Pomarol-Clotet et al 2012), depresión (Fernandez-Corcuera et al 2013) y Calhoun et al (2008) encontraron, además, un fracaso de la desactivación que afectó particularmente la corteza frontal medial en un grupo mixto de pacientes con trastorno bipolar. Sin embargo,

Strakowski et al (2008) encontraron una mayor desactivación en participantes con un primer episodio maníaco en comparación con controles en la corteza cingulada posterior. En cuanto a la presencia de esta alteración en eutimia, dos estudios anteriores (Allin et al 2010, Costafreda et al 2011) encontraron que la región afectada fue la circunvolución del cíngulo posterior/precuneus. Así mismo, los estudios de conectividad funcional en reposo también han implicado esta red en el trastorno bipolar (Vargas et al 2013). Por último, cabe señalar también que el meta-análisis de Chen et al (2011) encontró evidencia de hiperactivaciones relacionadas con la tarea en zonas de la corteza medial frontal, el giro temporal superior, la circunvolución del hipocampo y la corteza cingulada, por lo que parece posible que al menos algunos de los cambios realmente representen un fracaso de desactivación en lugar de la verdadera hiperactivación (la hiperactivación y el fracaso en la desactivación tienen el mismo resultado en los estudios de neuroimagen funcional utilizando el análisis de sustracción (Gusnard et al 2001, Pomarol-Clotet et al 2008).

5.3. Alteraciones funcionales en hermanos sanos

El fallo en la desactivación de la corteza frontal medial observada en el primer estudio también se encontró en el segundo estudio, cuando se comparó un grupo de 20 bipolares eutímicos con controles, pero no sólo eso, sino que se encontró además que los hermanos sanos de los pacientes también mostraban este fracaso de desactivación, aunque de forma menos marcada que la observada en los pacientes.

Estudios anteriores también han encontrado cambios en la desactivación en familiares. Allin et al (2010) encontraron fracaso en la desactivación, si bien en este caso éste tuvo lugar en la corteza cingulada posterior/precuneus. Por el contrario, Sepede et al (2012) encontraron una mayor desactivación en esta misma zona. Por último, en el estudio de Thermenos et al (2010) se encontraron cuatro regiones que los autores interpretaron como una mayor activación en los familiares pero que, sin embargo, en dos de estas regiones, la corteza orbitofrontal izquierda y la corteza parietal, los diagramas de cajas de las activaciones medias revelan que este resultado podría en realidad representar un fallo en la desactivación de estas regiones.

Por lo tanto, el hecho de la presencia de una disfunción en la DMN en pacientes bipolares eutímicos así como en familiares sanos de los mismos indica que esta alteración puede considerarse un marcador rasgo y potencialmente un endofenotipo para el trastorno.

5.4. Correlatos neuronales del deterioro cognitivo

Varios hallazgos pueden ser candidatos a ser los correlatos neuronales del deterioro cognitivo presente en el trastorno bipolar. Los cambios de activación entre los episodios agudos del trastorno y la eutimia que encontramos en el primer estudio en la corteza parietal dorsal, y entre la manía y eutimia en la corteza prefrontal dorsolateral, podrían reflejar diferencias sintomáticas entre las dos fases o, alternativamente, la cierta mejora en la función cognitiva que tiene lugar con la remisión clínica. De estas dos opciones, esta última parece intuitivamente más probable, teniendo en cuenta que se utilizó una tarea cognitiva en lugar de una emocional. Sin embargo, el deterioro cognitivo también se observa en una proporción de pacientes en eutimia (véase, por ejemplo, Kurtz and Gerraty (2009)) y los pocos estudios que han comparado directamente el grado de deterioro en diferentes fases de la enfermedad no han encontrado evidencia de que esté sustancialmente menos marcado en eutimia (Martinez-Aran et al 2004). Por otro lado, el primer y el segundo estudio encontraron evidencia, incluso en eutimia, de un fallo en la desactivación del nodo anterior de la DMN, la cual también parece ejercer una influencia general sobre la función cognitiva tal y como se comentó en la introducción (Anticevic et al 2012).

Para determinar qué alteraciones pueden por tanto estar relacionadas con el deterioro cognitivo presente en eutimia llevamos a cabo el tercer estudio de esta tesis. En este estudio encontramos que el deterioro cognitivo en pacientes bipolares eutímicos se asoció con cambios funcionales cerebrales, específicamente con la activación reducida en una región cercana a la corteza prefrontal dorsolateral derecha, aunque esto sólo se observó en el contraste 2-back vs 1-back.

A nivel estructural, sin embargo, no se encontró ninguna alteración subyacente a este deterioro. Teniendo en cuenta que el daño cerebral estructural se asocia comúnmente con déficits neuropsicológicos, nuestro fracaso en encontrar diferencias en el volumen de materia gris o blanca entre los pacientes bipolares con y sin deterioro cognitivo podría considerarse sorprendente. Una posible razón de esto podría ser que, con tamaños de muestra de 33 y 28 pacientes, el estudio podría simplemente no haber tenido el poder estadístico suficiente para detectar diferencias. Sin embargo, no se observaron cambios cuando se utilizó un umbral más liberal de $p < 0{,}005$ sin corregir por comparaciones múltiples o cuando se omitió la etapa de modulación, que también aumenta la sensibilidad para detectar cambios (Radua et al 2014).

Estos resultados negativos en cuanto a cambios estructurales asociados con el deterioro cognitivo también podrían considerarse incompatibles con la corriente de opinión generalizada de que la aparición de deterioro cognitivo persistente en algunos pacientes con trastorno bipolar refleja un proceso neurodegenerativo (Goodwin et al 2008b). Dada la naturaleza transversal de este estudio, es obviamente difícil abordar esta cuestión, sin embargo, es interesante observar que la evidencia de cambios progresivos estructurales en el trastorno bipolar es bastante débil. En una reciente revisión del pequeño número de estudios longitudinales realizados hasta la fecha, Lim et al (2013) no encontraron ninguna evidencia de cambio longitudinal en el volumen total del cerebro. Sólo se encontraron reducciones progresivas de volumen en la corteza del lóbulo frontal en dos estudios pequeños (n = 8 y N = 10), pero no en un tercer estudio más grande (N = 58) que también empleó controles sanos. Los resultados fueron igualmente contradictorios para la corteza cingulada anterior, la amígdala y el hipocampo.

En cambio, sí que encontramos evidencia de que el deterioro cognitivo en pacientes bipolares eutímicos se asociaba con cambios funcionales del cerebro, específicamente con una activación reducida en una región cercana a la corteza prefrontal dorsolateral derecha. Estos resultados guardan una notable similitud con los de Oertel-Knochel et al (2013) que encontraron una activación reducida en la circunvolución frontal superior media izquierda en 26 pacientes bipolares eutímicos durante la fase de codificación de una tarea de memoria episódica en la que mostraron un rendimiento disminuido (una activación reducida se observó también en otras regiones frontales laterales durante la fase de recuperación). De hecho, la corteza prefrontal dorsolateral está implicada en los aspectos cognitivos ejecutivos de la función del lóbulo frontal (Elliott 2003) y en la memoria a largo plazo (Blumenfeld & Ranganath 2007), y por lo tanto es un lugar plausible para los cambios funcionales del cerebro asociadas con el rendimiento de este tipo de tarea en el trastorno bipolar.

Un factor que complica la interpretación de este hallazgo se refiere a la naturaleza de la relación entre la cognición y la actividad cerebral. Es posible que la activación reducida en los pacientes bipolares eutímicos con deterioro cognitivo refleje una disfunción cerebral regional subyacente, o puede ser que el hecho de que los pacientes realizaran la tarea peor que los pacientes cognitivamente conservados explique que activaran estas regiones frontales en un grado correspondientemente menor. Este problema ha sido considerado con cierta profundidad en la literatura sobre la esquizofrenia (Callicott et al 2003, Fletcher et al 1998,

Karlsgodt et al 2009, Tan et al 2007, Weinberger et al 2001), donde la principal conclusión ha sido que no existe una simple relación lineal entre el rendimiento cognitivo y la activación cortical regional. Sin embargo, esta cuestión no ha sido abordada hasta ahora con respecto al deterioro cognitivo que a veces acompaña el trastorno bipolar.

Por último, el hecho de que se encontrara que el fracaso de la desactivación en la corteza frontal medial no distinguiera a los pacientes eutímicos cognitivamente preservados de aquellos con deterioro cognitivo, sugiere que esta función moduladora en general llevada a cabo por la DMN no juega un papel en el deterioro cognitivo presente en el trastorno bipolar.

5.5. Conclusiones

Los cambios funcionales cerebrales en el trastorno bipolar se pueden dividir en aquellos que están relacionados con el estado y los que son marcadores de rasgo. La corteza parietal mostró evidencia de pertenecer a la primera categoría. La corteza prefrontal dorsolateral mostró una combinación de ambas características, exhibe una activación reducida en ambas fases agudas de la enfermedad, pero sin normalizarse completamente en eutimia. El fallo en la desactivación en la corteza frontal medial, y por lo tanto, una disfunción en la DMN, muestra una clara evidencia de ser un marcador rasgo para el trastorno. Esta alteración, se observó igualmente, pero en menor medida, en los familiares sanos de primer grado de los pacientes. Estos resultados sugieren que la disfunción de la DMN podría representar una anormalidad rasgo y, potencialmente, un endofenotipo para el trastorno. Por último, el deterioro cognitivo presente en eutimia parece estar relacionado con cambios funcionales en la corteza prefrontal dorsolateral y no guardar relación con alteraciones en el funcionamiento cerebral de regiones de la DMN.

En conclusión, estos resultados tomados en conjunto ponen de relieve la implicación de la DMN en el trastorno bipolar. Sin embargo, la naturaleza de esta disfunción y su relación con la sintomatología del trastorno bipolar es aún desconocida y, por lo tanto, son necesarios estudios futuros para determinar su rol en este trastorno.

5.6. Limitaciones

Nuestros estudios tienen algunas limitaciones que deben ser señaladas. En primer lugar, el tamaño de las muestras puede haber influido en los resultados obtenidos. Es posible que una muestra más grande en el caso de las comparaciones entre bipolares eutímicos y controles (n=38vs38 en el primer estudio, n=20vs20 en el segundo estudio y n=27vs28 en el tercer estudio) hubiera revelado también cambios en la activación de diferentes regiones además de los cambios en la desactivación que obtuvimos. Igualmente, en el caso del análisis estructural del último estudio (n=33vs28), esta muestra puede haber sido demasiado pequeña para detectar diferencias sutiles de volumen entre los dos grupos de pacientes. Dado que las diferencias estructurales y/o funcionales entre los pacientes o entre los pacientes y sus hermanos sanos son menores que con respecto a un grupo control, son necesarias muestras más grandes que las utilizadas convencionalmente para demostrar los cambios de una manera más robusta. Sin embargo, hay que señalar que esta limitación se ha tratado de contrarrestar con un buen apareamiento entre grupos en variables relevantes (edad, sexo y cociente intelectual premórbido) para así incrementar el poder estadístico.

En segundo lugar, la naturaleza transversal de estos tres estudios hace que los análisis puedan ser susceptibles a sesgos muestrales desconocidos pero potencialmente relevantes. En particular, los pacientes en las diferentes fases del trastorno estaban tomando medicación que difería en la dosis y en el tipo. Sin embargo, la evidencia actual sugiere que los efectos de confusión de los fármacos son relativamente limitados (Hafeman et al 2012). De la misma forma, la mayoría de los pacientes estaban diagnosticados de trastorno bipolar tipo I, pero no todos puesto que 6/38 bipolares en depresión en el primer estudio y 4/20 pacientes en el segundo estudio tenían diagnostico de trastorno bipolar tipo II; y la historia de presencia de síntomas psicóticos no se tuvo en cuenta a la hora de incluir los pacientes en las muestras y por lo tanto no se controló de forma directa. Igualmente, en el caso del estudio en el que se dividió la muestra en función de la presencia o ausencia de deterioro cognitivo asociado, los pacientes cognitivamente preservados no fueron apareados de forma explícita con los controles sanos en función de su rendimiento cognitivo y, de hecho, como grupo mostraron un rendimiento menor en comparación con ellos. En consecuencia, se ha de considerar que este grupo sólo se mostró relativamente conservado cognitivamente.

En cuanto a los resultados estructurales, el análisis de la sustancia gris y blanca se limitó únicamente al estudio del volumen, por lo que es posible que el uso de otras medidas como el grosor cortical o la difusión pudiera reflejar cambios relacionados con el deterioro cognitivo no encontrados con los métodos empleados en este estudio. En esta línea cabe también señalar el uso de un scanner de 1.5 Tesla, lo cual puede haber limitado también los resultados obtenidos.

Finalmente, algunos de los hallazgos reportados provienen de análisis basados en ROI. Por ejemplo, el resultado obtenido de un nivel intermedio en la desactivación frontal medial en la muestra de familiares, situado entre los pacientes bipolares y los controles, dependía de este tipo de análisis. Cuando los clústeres reportados son grandes pueden contener conjuntos de vóxeles anatómica y funcionalmente heterogéneos, y por lo tanto pueden no ser bien caracterizados por un solo ROI (Poldrack 2007), aunque este no era el caso de nuestro estudio.

5.7. Perspectivas futuras

Si bien estos estudios son importantes de cara a destacar la relevancia de la DMN en la neurobiología subyacente al trastorno bipolar, los resultados son exploratorios y limitados en cuanto a determinar explicaciones causales y comprender los mecanismos implicados en esta alteración. Por lo tanto, se necesita de más estudios para avanzar en la comprensión a este respecto.

En concreto, esperamos replicar estos resultados a través de estudios longitudinales, los cuales permiten evitar los posibles sesgos muestrales presentes cuando se incorporan grupos independientes de pacientes en diferentes fases del trastorno. Para ello analizaremos los cambios funcionales longitudinales partiendo de grupos de pacientes durante un episodio de manía o de depresión y posteriormente una vez alcanzada la eutimia. De esta forma, los resultados del primer estudio podrán o no ser corroborados de una forma más robusta.

Así mismo, se prevé analizar esta alteración en grupos de pacientes tras un primer episodio afectivo, lo cual, junto con la evidencia de esta alteración en pacientes eutímicos y en familiares de primer grado sanos serviría para arrojar luz sobre la relación de esta alteración con factores genéticos, del neurodesarrollo y neurodegenerativos. De la misma forma, la

inclusión de este tipo de muestras ofrece la ventaja de evitar variables confusoras como es el uso continuado de tratamientos farmacológicos y la variabilidad existente en el curso de la enfermedad y las alteraciones asociadas (deterioro cognitivo, deterioro psicosocial o comorbilidades médicas).

De cara a entender el rol de la DMN en el trastorno bipolar, es necesario estudiar su integridad no solo en relación a este trastorno, sino también en comparación con otros trastornos psiquiátricos y neurológicos en los que existe evidencia de alteraciones a este nivel. Por ello, completaremos estos resultados con estudios que comparen pacientes diagnosticados de esquizofrenia, trastorno depresivo mayor y trastorno bipolar. De esta forma se podrá arrojar luz sobre la implicación de esta red en síntomas concretos de cada una de estas patologías, si su alteración implica cambios en procesos más generales y comunes a cualquier patología, si las diferencias entre los diferentes trastornos radica en la gravedad de estas alteraciones, o una combinación de estas posibilidades. Esta búsqueda de especificidad entre diferentes entidades diagnósticas es necesaria, ya que el verdadero desafío consiste en determinar biomarcadores que permitan distinguir entre patologías cuando a menudo los síntomas observables pueden ser similares y compartidos, así como biomarcadores que permitan pronosticar diferentes cursos y respuestas a tratamientos.

Junto con esto, la función de esta red ha de ser estudiada igualmente con paradigmas funcionales que busquen activarla, y no solo a través de las desactivaciones presentes durante la ejecución de tareas cognitivas. Por ello se prevé estudiar los cambios funcionales mediante tareas como la memoria autobiográfica y de auto-reflexión para completar la visión sobre los las alteraciones de la DMN en el trastorno bipolar.

Por último, cabe señalar también la necesidad de estudios que integren distintas modalidades de neuroimagen para entender no sólo qué regiones presentan cambios con respecto a un grupo control, sino también para poder estudiar con más detalle las características concretas de estas alteraciones y los procesos biológicos implicados. Esperamos llevar a cabo estudios que evalúen distintos parámetros de la sustancia gris y blanca, como podrían ser los estudios de grosor cortical y difusión, junto con técnicas de conectividad funcional y estudios que combinen información genética y de neuroimagen. Sin la integración de todas estas técnicas, los modelos explicativos carecerán de la riqueza necesaria para entender la etiología de trastornos tan complejos y multicausales como es el trastorno bipolar.

6 Resumen

Los estudios de neuroimagen funcional en el trastorno bipolar han descrito un patrón de activación reducida de regiones prefrontales junto con hiperactivación en estructuras subcorticales. Una cuestión que está sin resolver es la determinación de los cambios dependientes del "estado" vs "rasgo", es decir, si existen diferencias entre los episodios maníacos y depresivos, y hasta qué punto los cambios observados persisten en eutimia. Además, los estudios hasta la fecha se han centrado principalmente en el estudio de las activaciones, y poco se sabe acerca de los cambios en la desactivación. Dado que los cambios funcionales cerebrales en eutimia no están directamente relacionados con los síntomas agudos de la manía o depresión, parece probable que reflejen otros aspectos del trastorno. Una posibilidad es que reflejen la vulnerabilidad a la enfermedad y, dado que uno de los principales factores de riesgo es la genética, se plantea la cuestión de si los cambios cerebrales funcionales en eutimia también se puedan detectar en los familiares de pacientes que no han desarrollado el trastorno. Por otro lado, es posible que el deterioro cognitivo presente en eutimia se relacione con los cambios funcionales y/o estructurales cerebrales encontrados, pero hasta la fecha los resultados han sido inconsistentes.

El objetivo de este trabajo es, por tanto, examinar los cambios en el funcionamiento cerebral en cada una de las tres fases del trastorno bipolar; determinar qué cambios en el funcionamiento cerebral están presentes en familiares sanos de primer grado de los pacientes; y determinar si, y en qué medida, el deterioro cognitivo en pacientes eutímicos se asocia con cambios cerebrales funcionales y/o estructurales.

Nuestros resultados indican que los cambios funcionales cerebrales en el trastorno bipolar se pueden dividir en aquellos que están relacionados con el estado y los que son marcadores rasgo. La corteza parietal mostró evidencia de pertenecer a la primera categoría mientras que la corteza prefrontal dorsolateral mostró una combinación de ambas características: exhibe una activación reducida en ambas fases agudas de la enfermedad, pero sin normalizarse completamente en la eutimia. El fallo en la desactivación en la corteza frontal medial, correspondiente con el nodo anterior de la red neuronal por defecto, mostró una clara evidencia de ser un marcador rasgo para el trastorno. Esta alteración, se observó igualmente, pero de forma menos marcada, en los hermanos no afectados. Sin embargo, su disfunción no parece ser responsable del deterioro cognitivo presente en el trastorno, que en cambio sí que se relaciona con una activación reducida en la corteza prefrontal dorsolateral derecha.

En conclusión, estos resultados ponen de relieve la implicación de la red neuronal por defecto en el trastorno bipolar. Sin embargo, la naturaleza de esta disfunción y su relación con la sintomatología de este trastorno es aún desconocida.

7 Summary

1. INTRODUCTION

1.1. GENERAL INTRODUCTION

Bipolar disorder is a mood disorder characterized by alternating periods of remission and manic or hypomanic and depressive relapses. It has a prevalence of between 1-2%, this being relatively consistent across different cultures and regions and similar between men and women (Ferrari et al 2011, Goodwin et al 2008a, Merikangas et al 2011). It usually develops in young adult life, in the majority of cases before age 25 (Kessler et al 2005). There is sometimes a progression to refractory illness, where sustained periods of clinical remission are no longer evident (Berk et al 2007, Kapczinski et al 2009, Reinares et al 2013).

There is a high prevalence of comorbidity between bipolar disorder and other DSM axis I and II disorders (George et al 2003, Grant et al 2005). There is also an increased risk of physical illnesses, particularly cardiovascular and endocrine disorders (Beyer et al 2005, Forty et al 2014, Krishnan 2005). These comorbidities add to the mortality of the disorder (Carlborg et al 2015); which is already significant due in part to the high rate of suicide (Osby et al 2001, Tondo & Baldessarini 2005).

The mainstay of treatment is pharmacological. This aims to manage acute episodes of depression and mania and to prevent the emergence of new episodes. Typical treatments are mood stabilizers such as lithium and anticonvulsants, and also atypical antipsychotics, or antidepressants (NICE guidelines, 2015). As adjuncts to pharmacological treatment, psychotherapies have also been developed (for a review see Yatham et al (2005) and Yatham et al (2006)).

Studies over the last two decades have demonstrated that a proportion of patients with bipolar disorder show cognitive impairment that persists beyond episodes of illness into euthymia (Arts et al 2008, Bourne et al 2013, Mann-Wrobel et al 2011, Robinson et al 2006, Torres et al 2007). The deficits are wide ranging (Mann-Wrobel, 2011), but may involve executive function and long-term memory particularly (Robinson, 2006), and they are associated with impaired functioning in daily life (Depp et al 2012).

1.2. THE PATHOPHYSIOLOGY OF BIPOLAR DISORDER

Many factors are involved in the etiology and pathophysiology of bipolar disorder, and the aetiolgy is widely considered to be multifactorial (for reviews see Maletic & Raison (2014) and Miller & Raison (2016)). An initial wave of genetic studies examined the frequency of the disorder in first degree relatives and co-twins of patients and, to a lesser extent, adoption studies. These studies revealed that first-degree relatives of people with bipolar disorder are around 10 times more likely to develop the disorder (Craddock & Jones 1999, Lichtenstein et al 2009) and the heritability is about 60-93% (Kieseppa et al 2004, Lichtenstein et al 2009, McGuffin et al 2003). More recent studies focused on candidate genes and contemporary GWAs studies point to the disorder having a mainly polygenic basis (Chen et al 2013, Cichon et al 2011, Ferreira et al 2008, Muhleisen et al 2014, Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011, Seifuddin et al 2012, Sklar et al 2008, Szczepankiewicz 2013, Wellcome Trust Case Control 2007). Environmental factors that have been studied for their possible role as risk factors include exposure to viral infection during pregnancy, substance abuse or history of traumatic events (Marangoni et al 2016, Tsuchiya et al 2003). Additionally, there is evidence for alterations of neuroendocrine (Belvederi Murri et al 2016) and immune (Pace & Miller 2009, Rosenblat et al 2014) mechanisms.

1.3. NEUROIMAGING STUDIES IN BIPOLAR DISORDER

1.3.1. Structural brain abnormalities

Studies using whole-brain techniques such as voxel-based morphometry (VBM) have found evidence for volume reduction in the anterior cingulate cortex, the insula and the inferior frontal cortex, among other regions (Bora et al 2010a, Ellison-Wright & Bullmore 2010, Houenou et al 2011, Selvaraj et al 2012, Wise et al 2016b). A recent mega-analysis conducted by the ENIGMA consortium in a sample of 1710 patients and 2594 controls found reduced volume in hippocampus, thalamus, amygdala (only in the case of patients type I), along with an increased lateral ventricles volume (Hibar et al 2016). White matter changes are also well documented in bipolar disorder, it has been reported subcortical signal hyperintensities (Beyer et al 2009, Kempton et al 2008), reduced white matter volume in prefrontal regions (Mahon et al 2010) and reduced fractional anisotropy most consistently in the right temporo-parietal and the left anterior and mid-cingulate regions (Nortje et al 2013,

Wise et al 2016a) and more extensively when advanced techniques were applied (Canales-Rodriguez et al 2014, Emsell et al 2013).

1.3.2. Functional brain abnormalities

Findings from many functional imaging studies in bipolar disorder have led to a consensus that it is characterized by reduced resting and task-related activity in the prefrontal cortex and some other cortical regions, coupled with overactivity in the amygdala, hippocampus and parahippocampal gyrus and the basal ganglia (Green et al 2007, Savitz & Drevets 2009, Strakowski et al 2012, Strakowski et al 2005). Recent meta-analyses suggest that this pattern is seen both at rest and in studies using task activation, although the pattern differs to some extent depending on whether cognitive or emotional tasks (typically facial emotion processing) are used (Chen et al 2011, Kupferschmidt & Zakzanis 2011). What remains less clear is the 'state' v. 'trait' characteristics of functional imaging abnormality in bipolar disorder, i.e. whether there are differences between patients in manic and depressed episodes and to what extent changes seen in both phases of illness persist into euthymia. In Kupferschmidt and Zakzanis (2011)' meta-analysis of 55 studies that pooled conventional effect-size data, resting and task-related changes were seen in episodes of illness and in euthymia but the differences between phases were complex. Cortical hypoactivity and limbic hyperactivity was found to be greater in patients in a manic phase than in euthymia, and patients in a depressed phase showed greater hypoactivation in frontal regions than in euthymia. However, patients in euthymia showed more evidence of limbic hyperactivity than those with depression. Abnormalities were also more pronounced in patients in a manic than in depressed phase. Rather differently, Chen et al (2011)'s meta-analysis of voxel-based functional magnetic resonance imaging (fMRI) studies found decreased activation in the inferior frontal gyrus in mania, no changes in depression and reduced activation was restricted to the lingual gyrus in 26 studies carried out on participants in a euthymic phase.

There are relatively few state vs. trait studies involving participants in different phases using cognitive paradigms. The n-back has been one of the most widely used paradigm of working memory and a review of 8 studies in euthymic bipolar patients type I showed a pattern of changes in the dorsolateral and ventrolateral prefrontal cortex as well as temporo-parietal regions (Cremaschi et al 2013). However, in what appears to be the only contemporary study to directly compare patients across phases using this task, Townsend et al (2010) examined

13 patients in a manic phase, 14 in a depressed phase and 15 in a euthymic phase, as well as 14 healthy controls. Citing a lack of availability of methods for analysing differences among four groups at the whole-brain level, the authors only examined two predetermined regions of interest (ROIs), the left and right dorsolateral prefrontal cortex and the left and right posterior parietal cortex. They found reduced activation in both ROIs in mania, depression and euthymia, with no significant variation across phases.

1.3.3. The default mode network

Over the past decade the importance not only of task-related activations but also de-activations has become increasingly recognised. This follows the discovery of the so-called default mode network, an interconnected set of brain regions that are highly active at rest but de-activate during performance of a wide range of attention- demanding tasks (Andrews-Hanna et al 2010, Buckner et al 2008, Raichle et al 2001). Prominent among these regions are two midline cortical areas, the medial frontal cortex anteriorly and the posterior cingulate cortex/precuneus posteriorly. Beyond this, evidence from studies using a small number of tasks that have been found to activate parts of the default mode network rather than deactivate it suggests that it has roles as diverse as autobiographical recall, thinking about the future, theory of mind, moral decision-making and making judgments about characteristics that apply to oneself vs. others (Buckner et al 2008).

Failure of de-activation in parts of this network has been found in a range of neurologic and psychiatric disorders, including schizophrenia and major depression (for a review see Buckner et al (2008) and Whitfield-Gabrieli & Ford (2012)). Recent evidence suggests that bipolar disorder may also be characterised by de-activation changes in the default mode network in mania (Pomarol-Clotet et al 2012, Strakowski et al 2008) or depression (Fernandez-Corcuera et al 2013). In euthymia, Allin et al (2010) and Costafreda et al (2011) using a verbal fluency task found that the region affected was the posterior cingulate gyrus/precuneus, corresponding to the posterior midline node of the network.

1.3.4. Brain functional changes in relatives of patients with bipolar disorder

Since bipolar disorder has a hereditary component, the question arises of whether brain functional changes, perhaps similar to those seen in euthymic patients, might also be seen in their first-degree relatives.

A recent review by Fusar-Poli et al (2012) showed that despite no significant difference in gray matter volume, relatives showed increased activation in medial and superior frontal and in the left insula. These results indicate that changes in brain function might be better candidates for identifying endophenotypes associated with the disorder. Studies using cognitive paradigms have been relatively few and have mixed findings. Drapier et al (2008) found increased activation in the left frontopolar cortex in 20 unaffected first-degree relatives of bipolar patients compared with 20 healthy controls during the performance of the n-back task. Thermenos et al (2010) also used the n-back task and found a pattern of increased activation in the left frontopolar cortex, the anterior insula and the right parietal lobe in 18 first-degree relatives compared with 19 controls. Pompei et al (2011) examined 25 relatives and 48 controls using the Stroop task and found reduced activation affecting the superior and inferior parietal cortex. In contrast, other studies failed to find any cortical activation differences between relatives and controls (Costafreda et al 2009, Whalley et al 2011).

Currently, findings concerning DMN function in relatives of patients with bipolar disorder are few. Allin et al (2010) found failure of de-activation in the posterior cingulate cortex/precuneus in 18 euthymic bipolar patients and in 19 of their unaffected first-degree relatives, in a study using a verbal fluency task. In contrast, Sepede et al (2012), using the Continuous Performance Test, found increased de-activation of the posterior cingulate cortex in 22 relatives compared to 24 controls.

1.3.5. Brain correlates of cognitive impairment in bipolar disorder

Since patients with bipolar disorder show structural and functional brain changes, it is possible that some form of brain dysfunction presumably underlie the persistent cognitive impairment present in a proportion of patients with bipolar disorder. Relatively few studies have examined whether structural changes in bipolar patients are related to presence of cognitive impairment. Early studies reviewed by Bearden et al (2001) found some evidence

of associations with increased lateral ventricular volume and volume reductions in the prefrontal cortex, and more robustly with presence of white matter signal intensities. However, more recent studies examining multiple grey and white matter regions have generally found few significant correlations with executive, memory or other cognitive deficits (Haldane et al 2008, Hartberg et al 2011b, Killgore et al 2009, Moorhead et al 2007, Zimmerman et al 2006).

Very few studies have investigated brain activations in relation to cognitive impairment in bipolar disorder (Oertel-Knochel et al 2013, Oertel-Knochel et al 2014b, Oertel-Knochel et al 2012, Oertel-Knochel et al 2015a). In one study that examined patients in the euthymic phase, Oertel-Knochel et al (2013) found that 26 euthymic bipolar patients were impaired on a verbal learning and recognition task, and also showed a pattern of reduced activation compared to healthy controls when they performed the same task while being scanned. The areas affected included the left middle and superior frontal gyrus during encoding, and the bilateral middle and inferior frontal gyrus, plus the parahippocampal and other posterior medial cortical areas during retrieval.

2. AIMS AND HYPOTHESIS

Studies carried out so far provide only an incomplete answer to the question of what functional imaging changes characterize bipolar disorder and the ‘state’ vs ‘trait’ characteristics of functional imaging abnormalities, i.e. whether there are differences between patients in manic and depressed episodes and to what extent changes seen in both phases of illness persist into euthymia. It was also noted that studies to date have mainly focused on activation changes, and little is known about changes in de-activation.

Since brain functional changes in euthymia are unrelated to the acute phases of the disorder, i.e. depression and mania, it seems likely that they reflect other aspects of the illness. One possibility is that they represent a risk factor, i.e. they reflect vulnerability to the disorder. Since one of the main factors conferring vulnerability to bipolar disorder is genetic, the question arises of whether brain functional changes can also be seen in relatives of patients with the disorder.

On the other hand, it seems likely that both structural and functional changes reported in the literature reflect the cognitive impairment present in euthymia. However, few studies to date have examined the neurobiological underpinning of this cognitive impairment and results have been inconsistent.

Thus, the aims are:

1) To examine patterns of activation and de-activation during performance of a working memory task in bipolar patients in different phases of illness: mania, depression and euthymia.

    - Bipolar patients will show reduced activation and, based on existing findings, this will affect the dorsolateral prefrontal cortex among other regions and will be present during both phases of illness and in euthymia.

    - Bipolar patients will show failure of de-activation in the medial frontal cortex and/or the posterior cingulate gyrus/precuneus. Due to the currently small number of studies of de-activation in bipolar disorder, no hypotheses are made concerning phase of illness.

2) To examine patterns of activation and de-activation in a group of first-degree relatives of euthymic bipolar patients during performance of a working memory task. As well as comparing them to healthy controls and also to their affected siblings.

    - Based on the small number of existing studies, it is hypothesized that siblings of patients with bipolar disorder will show activation changes although at present it is not possible to specify the regions affected, or whether the changes will take the form of relatively reduced or relatively increased activation.

    - It is hypothesized that the siblings of patients with bipolar disorder will show a changed pattern of de-activation in one or more areas of the default mode network compared to healthy controls. Given that there are few studies examining de-

activations in relatives, no hypotheses are made concerning the direction of the changes.

- The pattern of functional imaging changes in siblings of patients with bipolar disorder will show similarities to that seen in patients with the disorder in the euthymic phase.

3) To investigate the relationship between brain structural and functional changes and the cognitive impairment of euthymic bipolar patients. Gray and white matter volume will be examined using voxel-based morphometry, and functional changes will be evaluated using a working memory task.

   - Cognitively impaired patients will show reduced both gray and white matter volume compared to those patients without cognitive impairment.

   - Cognitively impaired patients will show brain functional changes compared to those patients without cognitive impairment. No hypotheses are made concerning whether these differences will affect activation, de-activation or both.

   - Both groups of patients will show structural and functional differences compared to matched healthy controls.

3. METHODS

All subjects gave written informed consent prior to participation in accordance to the Declaration of Helsinki and the research protocol was approved by the Clinical Research Ethics Committee. Patients were recruited from three hospitals: Hospital Benito Menni CASM, Hospital Clínic and Hospital General de Granollers. They all met DSM-IV criteria for bipolar I disorder and were excluded if a) they were left-handed, b) they were younger than 18 or older than 55; c) they had a history of brain trauma or neurological disease, d) they had shown alcohol/substance abuse within 12 months prior to participation; e) they had undergone electroconvulsive therapy in the previous 12 months; and f) they showed evidence of general intellectual impairment/handicap outside the normal range as measured using four

subtests of the Wechsler Adult Intelligence Scale III (WAIS-III) (vocabulary, similarities, block design, and matrix reasoning). Manic symptoms were assessed using the Young Mania Rating Scale (YMRS) (Young et al 1978). The participants in the mania subgroup were required to have an YMRS score > 18 and <8 for euthymic patients. Depressive symptoms were assessed using the Hamilton Rating Scale for Depression (21-items, HRSD) (Hamilton 1960) and those in the depression subgroup were required to a have a score > 18 and <8 for euthymic patients.

Healthy controls were recruited via poster and web-based advertisement in the hospital and local community, plus word-of-mouth requests from staff in the research unit. The controls met the same exclusion criteria as the patients. They were also excluded if they reported a history of mental illness or treatment with psychotropic medication, and/or had a first-degree relative with a psychiatric illness. The unaffected siblings met the same exclusion criteria as the patients and they were also excluded if they reported a history of mental illness and/or treatment with psychotropic medication as assessed using the Computerized Diagnostic Interview Schedule for the DSM-IV (C DIS-IV) (Robins et al 2000).

While being scanned, individuals performed a sequential-letter version of the n-back task (Gevins & Cutillo 1993). Two levels of memory load (1-back and 2-back) were presented in a blocked design manner. Each block consisted of 24 letters that were shown every 2 s (1 s on, 1 s off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within the blocks. Individuals had to indicate repetitions by pressing a button. 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 s. To identify which task had to be performed, characters were shown in green in 1-back blocks and in red in 2-back blocks. All participants first went through a training session outside the scanner. Task performance was measured using the signal detection theory index of sensitivity (d') of ability to discriminate targets from non-targets (Green & Swets 1966). Higher values of d' indicate better ability to discriminate between targets and distractors. Participants who had negative d' values in either or both of the 1-back and 2-back versions of the task, which suggests that they were not performing it, were a priori excluded from the study.

All subjects underwent structural and functional MRI scanning using a 1.5 Tesla GE Signa scanner (General Electric Medical Systems, Milwaukee, Wis) located at the Sant Joan de Déu Hospital in Barcelona (Spain). For the functional neuroimaging data, in each individual scanning session 266 volumes were acquired. A gradient-echo echoplanar imaging (EPI) sequence depicting the blood oxygenation level-dependent (BOLD) contrast was used. Each volume contained 16 axial planes acquired with the following parameters:repetition time = 2000 ms, echo time = 20 ms, flip angle 70º, section thickness, 7 mm, section skip, 0.7 mm, in-plane resolution, 3x3 mm. The first 10 volumes were discarded to avoid T1 saturation effects.

Individual fMRI analyses were performed with the FEAT module, included in FSL software (Smith et al 2004). Pre-processing with FSL-FEAT included: a) motion correction (Jenkinson et al 2002); b) non-brain removal (Smith 2002); c) isotropic 5mm-FWHM Gaussian smoothing; d) high-pass temporal filtering; e) time-series statistical analysis with local autocorrelation correction (Woolrich et al 2001); and f) registration to the MNI 152 standard space (Jenkinson et al 2002, Jenkinson & Smith 2001). To minimize unwanted movement-related effects, participants with an estimated maximum absolute movement >3.0 mm or an average absolute movement >0.3 mm were excluded from the study.

General linear models were fitted to generate individual activation maps for the following contrasts: 1-back vs baseline, 2-back vs baseline and 2-back vs 1-back. Differences in fMRI activation maps between patients and controls were generated within the FEAT module, using mixed effects GLM models (Beckmann et al 2006). FEAT uses Gaussian random field theory to properly account for the spatially distributed patterns when performing statistical tests. Specifically, the analyses were performed with the FLAME stage 1 with default height threshold ($z > 2.3$) (Beckmann et al 2003, Woolrich et al 2001) and a p-value < 0.05 corrected for multiple comparisons (Woolrich et al 2004, Worsley 2001).

4. RESULTS

4.1. Brain functional changes across the different phases of bipolar disorder

Participants with bipolar disorder in mania (n = 38), depression (n = 38) and euthymia (n = 38), as well as healthy controls (n = 38) were compared during performance of the n-back

working memory task. Compared with the controls, the mania and depression subgroups, but not the euthymia subgroup, showed reduced activation in the dorsolateral prefrontal cortex, the parietal cortex and other areas. Compared with the euthymia subgroup, the mania and depression subgroups showed hypoactivation in the parietal cortex. All three bipolar subgroups showed failure of de-activation in the ventromedial frontal cortex. Linear mixed-effects modeling revealed a further cluster of reduced activation in the left dorsolateral prefrontal cortex in the patients; this was significantly more marked in the mania than in the euthymia subgroup.

4.2. Brain functional changes in first-degree relatives of patients with bipolar disorder: evidence for default mode network dysfunction

This study compared 20 euthymic patients with bipolar disorder, 20 of their unaffected siblings and 40 healthy controls during performance of the n-back working memory task. We found that euthymic bipolar patients showed failure of de-activation in the medial frontal cortex, an area which constitutes the anterior midline node of the default mode network. This was not accompanied by any activation changes. A similar, though less marked failure of de-activation, again with no activation changes, was also seen in the unaffected siblings of patients with the disorder.

4.3. Structural and functional correlates of cognitive impairment in euthymic patients with bipolar disorder

Thirty-three euthymic bipolar patients with preserved memory and executive function and 28 euthymic bipolar patients with significant memory and/or executive impairment, plus 28 healthy controls underwent structural MRI using voxel-based morphometry. The cognitively preserved patients showed significantly reduced grey matter volume in a single small cluster located in the right precentral gyrus and they also showed bilaterally symmetrical clusters of significantly reduced white matter volume compared to the controls in the genu of corpus callosum. No clusters of grey or white matter volume difference were found between the two patient groups.

Twenty-seven of the cognitively preserved patients, 23 of the cognitively impaired patients and 28 controls also underwent fMRI during performance of the n-back working memory

task. The cognitively impaired patients showed hypoactivation compared to the cognitively preserved patients in a circumscribed region in the right dorsolateral prefrontal cortex. The cognitively preserved patients showed failure of de-activation in the medial frontal cortex compared to the healthy controls.

5. DISCUSSION

This thesis has examined changes in activation and deactivation in bipolar disorder during the execution of a working memory task. The analyses carried out provide evidence that bipolar disorder is characterized by both mood-state-dependent and mood-state-independent functional imaging abnormalities. Thus, reduced activation in the dorsal parietal cortex was seen in both mania and depression but not in euthymia. Reduced activation was also seen in the dorsolateral prefrontal cortex, but here the changes showed a more complicated relationship with phase of illness – activation was reduced across all three phases of illness, although with greater reductions in mania (but not depression) than in euthymia. On the other hand, failure of de-activation in the medial frontal cortex was seen in all three illness phases and so seems to represent a trait-like abnormality.

The second study found that a similar, though less marked failure of de-activation, again with no activation changes, was also seen in the unaffected siblings of patients with the disorder. Therefore, failure to de-activate the medial prefrontal cortex in both euthymic bipolar patients and their unaffected siblings adds to evidence for default mode network dysfunction in the disorder, and suggests that it may act as a trait marker.

Finally, our last study suggests that cognitive impairment in the euthymic phase is unrelated to structural brain abnormality and the DMN dysfunction does not seem to be responsible for it. However, we find evidence that it might be related to functional changes in the dorsolateral prefrontal cortex.

5.1. Mood-state dependent brain functional changes

Our finding of mood-state dependent changes in the dorsal parietal cortex is unexpected– this region was not identified in Kupferschmidt and Zakzanis (2011)'s or Chen et al (2011)'s meta-analyses, including in their subanalyses directed to mood state. One possible

explanation for this relates to the fact that the parietal cortex forms part of the 'working memory network' activated the n-back task (Owen et al 2005) and, although both meta-analyses pooled data from studies using a range of different cognitive tasks, relatively few of them employed the n-back or other working memory tasks (10/32 and 7/29 respectively).

Among studies that did use the n-back task, Pomarol-Clotet et al (2012) found reduced activation in the parietal cortex along with other parts of the working memory network in patients in a manic phase, and Fernandez-Corcuera et al (2013) had similar results in bipolar depression (it should be noted that both these studies were carried out on samples that overlapped with the present study). With respect to euthymia, Cremaschi et al (2013) reviewed eight studies using the n-back task in this phase of illness and found reduced parietal activation only in one of them (Townsend et al 2010) whereas the rest did not find differences or found an opposite pattern of increased activation. This study was the only study to date that had examined patients in all three illness phases during performance of the n-back task. Their findings were quite different to ours in that they failed to find significant variation across phase in either the parietal cortex or the dorsolateral prefrontal cortex, although activation was reduced in all three patient groups compared with controls.

We also found reduced activation in the dorsolateral prefrontal cortex, which showed ambiguous evidence of state-like characteristics. It did not appear in any of the contrasts between pairs of bipolar subgroups, but emerged in the ANOVA comparing all three bipolar subgroups and the controls. Reduced prefrontal cortex activation has been a regular finding in bipolar disorder, although it has mainly been documented in the orbitofrontal cortex and the ventrolateral prefrontal cortex perhaps reflecting the nature of the tasks used in these studies – the go/no-go task and the Stroop task (Hajek et al 2013). Consistent with such an interpretation, all of a small number of studies that have used working memory tasks have found reduced activation in or close to the dorsolateral prefrontal cortex in mania (Pomarol-Clotet et al 2012), depression (Fernandez-Corcuera et al 2013) and euthymia (Lagopoulos et al 2007, Monks et al 2004, Townsend et al 2010).

5.2. Trait-like brain functional changes

The final finding of this study was that failure of de-activation in the medial frontal cortex distinguished the patients from the controls and it was present to a similar degree in all three

phases of illness. This finding was replicated in the second and the last study and adds to evidence for default mode network dysfunction in the disorder.

This finding is in line with those of our previous studies in mania (Pomarol-Clotet et al 2012) and bipolar depression (Fernandez-Corcuera et al 2013) and to that found in a mixed group of patients with bipolar disorder (Calhoun et al 2008). However, Strakowski et al (2008) found greater de-activation in the posterior cingulate cortex in patients in a first-episode of mania. In euthymia, two studies found that the region affected was the posterior cingulate cortex (Allin et al 2010, Costafreda et al 2011). Resting state connectivity studies have also implicated the default mode network in bipolar disorder (Vargas et al 2013).

5.3. Brain functional changes in first-degree relatives

Our second study found that relatives of bipolar patients also showed failure of de-activation in the medial frontal cortex and was less marked than that seen in the patients. Previous studies have also found deactivation changes in relatives: Allin et al (2010) found failure of de-activation, although this was in the posterior cingulate cortex/precuneus rather than in the medial prefrontal cortex as in our study. In contrast, Sepede et al (2012) found exaggerated deactivation in the same area. Also relevant here is the study of Thermenos et al (2010) which found four areas of what the authors considered to be increased activation in relatives of bipolar patients; however, in two of these regions, the left orbitofrontal cortex and the parietal cortex, plots of mean activations revealed that this actually represented failure of de-activation. Therefore, failure to de-activate the medial prefrontal cortex in both euthymic bipolar patients and their unaffected siblings adds to evidence for default mode network dysfunction in the disorder, and suggests that it may act as a trait marker.

5.4. Neural correlates of cognitive impairment

Several findings from these studies might be candidates for the neural correlates of cognitive impairment in bipolar disorder. The activation changes between illness and euthymia we found in the dorsal parietal cortex, and more equivocally between mania and euthymia in the dorsolateral prefrontal cortex, could have reflected either the obvious symptomatic differences between the two states, or alternatively improvement in cognitive function taking place with recovery. Of the two, the latter seems intuitively more likely, given that we used a

cognitive as opposed to an emotional task. On the other hand, all three studies found evidence of failure of de-activation in the anterior node of the DMN, which also seems to exert a general influence on cognitive function (Anticevic et al 2012).

Thus, in our last study we compared two groups of cognitively impaired and preserved euthymic patients. The fact that we found that medial frontal failure of de-activation did not distinguish cognitively preserved from cognitively impaired euthymic patients, suggests that this general modulatory function carried out by the default mode network dysfunction does not play a role in the cognitive impairment seen in euthymic patients with bipolar disorder.

We did find evidence that cognitive impairment in euthymic bipolar patients was associated with brain functional changes, specifically reduced activation in a region that conformed reasonably closely to the right dorsolateral prefrontal cortex, although this was only seen in the 2-back vs. 1-back contrast. Our findings here show a notable similarity to those of Oertel-Knochel et al (2013) described in the Introduction—they found reduced activation in the left middle superior frontal gyrus in 26 euthymic bipolar patients, who as a group showed poor memory test performance, during the encoding phase of a memory task (reduced activation was seen in other lateral frontal regions during retrieval). The dorsolateral prefrontal cortex is implicated in both the cognitive, i.e. executive, aspects of frontal lobe function (Elliott 2003) and in long-term memory (Blumenfeld & Ranganath 2007), and so is a plausible location for brain functional changes associated with performance of both types of task in bipolar disorder.

5.5. Conclusions

The results of the studies reported in this thesis highlight the involvement of the default mode network in bipolar disorder. However, the nature of this dysfunction, its relation to symptoms, and subsequent course of the illness are unknown and, therefore, future studies are needed to determine its role in this disorder.

5.6. Limitations

The studies reported have a number of limitations that should be acknowledged. Most importantly, the relatively small samples sizes, particularly in the second and third study, may

have influenced the results. In particular, it is possible that larger samples of patients and controls might have revealed changes in activation as well as in de-activation. The sample sizes in the structural imaging study comparing euthymic patients with and without cognitive impairment may have been too small to detect subtle volume differences between the two patient groups. A related issue here is that the participants were scanned at 1.5 Tesla.

Secondly, the cross-sectional nature of the studies means they may be susceptible to sampling biases. Thus, in the first study the patients were taking medication, which differed in dosage and type in the different phases of illness. Also most patients in this study had bipolar I disorder, and they were not preselected to exclude psychotic forms of illness. In the third study the recruitment strategy meant that the cognitively preserved patients were not explicitly matched with the healthy controls for cognitive function, and ended up being only relatively cognitively preserved.

Finally, the finding that the relatives showed an intermediate level of medial frontal de-activation between the bipolar patients and the controls depended on ROI analysis. When reported clusters are large (which was not the case in our study) they may contain functionally and anatomically heterogeneous ensembles of voxels, which therefore may not be well characterized by a single ROI (Poldrack 2007).

5.7. Future investigations

While the studies reported in this thesis highlight the possible role of the DMN in the underlying neurobiology of bipolar disorder, the results are preliminary and subject to limitations. Therefore, it would be desirable to explore the findings further, perhaps using longitudinal approaches to compare the same patients when ill and in euthymia, and establishing whether changes in the DMN are present at first-episode or develop later. This could shed light on the possible link between this abnormality with genetic factors, neurodevelopment and neurodegenerative processes.

As noted previously, DMN abnormality has been found in other psychiatric disorders, including schizophrenia and major depression. It will therefore also be desirable to determine the specificity or otherwise of medial frontal failure of de-activation.

Finally, it should be noted that there is a need for multi-modal studies to further characterize the biological processes involved in DMN dysfunction. Such studies can establish whether functional imaging changes in the DMN and elsewhere, have correlates in other aspects of neurobiology, such as changes in gray matter structure and white matter integrity and connectivity.

8 Anexo

Tabla 1. Resumen de los estudios de fMRI longitudinales y de comparación de muestras independientes de pacientes bipolares en diferentes fases.

Autor	Año	Tarea	Diseño	N Ctrl	N Bip	YMRS	HDRS	Edad	Edad Ctrl	Sexo (H/M)	Sexo Ctrl	Resultados
Blumberg	2003	Stroop	Transversal	20	11 Man 10 Dep 15 Eut	19 1.9 4.1	6.8 28.2 7.3	20-55 21-50 26-53	-	6/5 5/5 7/8	10/10	**Mania vs Eut** ↓ VPFC dcho **Dep vs Eut** ↑ VPFC izqdo **Dep vs Ctrl** ↑ VPFC izqdo **Bip vs Ctrl** ↓ VPFC
Chen	2006	FA	Transversal	8	8 Man 8 Dep	24.13 0.43	2 18.38	39 41.88	38.75	8/0 5/3	2/6	**Mania vs Dep, Ctrl** *Caras tristes* ↑ Fusiforme ↑ Frontal Superior ↑ Temporal Medio ↑ Temporal Superior ↑ Cingulado Medio ↑ Ínsula ↑ Hipocampo ↑ Amígdala **Dep vs Man, Ctrl** *Caras felices* ↑ Frontal Superior ↑ Opérculo Rolándico ↑ Precentral ↑ Frontal Inferior Orbital ↑ Temporal Medio ↑ Calcarine ↑ Lingual ↑ Cingulado Medio

												↑ Putamen ↑ Tálamo **Mania, Dep vs Ctrl** *Caras de miedo* ↑ Precentral ↑ Postcentral ↑ Temporal Medio ↑ Parahipocampo ↑ Caudado ↑ Putamen ↑ Tálamo ↑ Tallo cerebral
Marchand	2007	Stroop Motor	Longitudinal	-	T1 10 Dep T2 10 Eut	- 0.5	- 1.9*	43.4	-	10/0		**Eut vs Dep** *Motor no-dominante* ↑ Cingulado Anterior
Kaladjian	2009	Go/NoGo	Longitudinal Intervalo: 142.5 días	10	T1 10 Man T2 10 Eut	24.6 2.1	4.3 2.2	40.1	41.5	5/5	5/5	**Man vs Eut** ↑ Amígdala **Eut vs Ctrl** ↓ Amígdala **Man, Eut vs Ctrl** ↓ Putamen
Chen	2010	FA	Longitudinal Intervalo: 6.33 meses	T1 12 T2 9	T1 12 Man T2 9 Eut	29.17 0.44	0.67 3.11	37.92	38	9/3 7/2	8/4 6/3	**Man vs Eut** ↓Hipocampo ↓Amígdala **Bip vs Ctrl** ↑Frontal Medio Orbital ↓Cingulado Posterior **Man vs Ctrl** ↑ Frontal Medio Orbital ↑ Caudado **Eut vs Ctrl** ↑ Hipocampo ↑ Amígdala

												↑ Ínsula ↑ Frontal Superior Orbital
Townsend	2010	N-back	Transversal	14	13 Man 14 Dep 15 Eut	15.9 3.1 1.7	5.3 21 3.8	38.5 38.7 37	30.8	5/8 7/7 7/8	6/8	**Man, Dep, Eut vs Ctrl** ↓ Frontal Inferior Triangular ↓ Angular No diferencias entre fases
Van der Schot	2010	FA	Transversal	18	12 Man 12 Dep 18 Eut	15.1 1.1 0.38	16,7 ** 44.3 9.6	38 43 36	33.6	6/6 6/6 8/10	8/10	**Ctrl, Dep vs Man, Eut** ↓ Amígdala ↓ Polo Temporal **Dep vs Man** ↓ Polo Temporal ↓ Frontal Inferior Orbital **Ctrl, Dep, Eut vs Man** ↓ Frontal Medio **Man, Dep, Eut vs Ctrl** ↑ Frontal Inferior Orbital
Bermpohl	2010	Recompensa	Longitudinal Intervalo: 38 semanas	26	T1 15 Man T2 7 Eut	18.9 3.2		38.6 36.1	38.7	8//7 3/4	15/11	**Man vs Eut** ↑ Frontal Medio Orbital **Man vs Ctrl** ↓ Lingual ↑ Frontal Medio Orbital
Fleck	2011	Go/NoGo	Transversal	10	10 Mixto 10 Dep	24 9	22* 29	30 34	33	4/6 5/5	2/8	**Man vs Dep** ↑Tálamo ↑Cerebelo ↑Frontal Inferior **Man vs Ctrl** ↑Amigdala* ↑Frontal Medio ↑Frontal Medial
Hulvershorn	2012	FA	Transversal	30	30 Man 30 Dep	16 3	6 20	34 35	32	11/19 12/18	11/19	**Man vs Dep** ↑ Cingulado Anterior

					15 Eut	2	7	31				**Man vs Eut** ↓ Frontal Medio Orbital **Eut vs Ctrl** ↑ Putamen ↑ Ínsula ↑ Amígdala **Man vs Ctrl** ↑ Putamen ↑ Ínsula ↑ Cingulado Anterior ↓ Frontal Medio Orbital **Dep vs Ctrl** ↑ Putamen ↑ Amígdala
Perlman	2012	FA	Transversal	25	21 Dep 31 Eut	4 2.39	24.62 7.29	33.09 32.36	31.75	2/19 10/21	11/14	**Dep vs Ctrl** *Caras de miedo* ↑ Amígdala **Eut vs Ctrl** *Caras tristes, de enfado y miedo* ↑ Amígdala No diferencias entre fases
Liu	2012	FA	Transversal	58	18 Man 19 Dep 39 Eut			31.4 34.2 32.1	30	8/10 5/14 17/22	24/34	**Dep vs Ctrl, Eut** Caras de miedo ↑ Frontal Inferior Orbital **Bip vs Ctrl** Caras felices y neutrales ↓ Frontal Medial Orbital ↓ Caudado **Man vs Ctrl**

												Fear, Neutral ↓Frontal Sup Med
Hummer	2013	Go/NoGo E	Transversal	30	30 Man 30 Dep 14 Eut	16 3 2	6 20 7	34 35 31	32	11/19 12/18 4/10	11/19	**Man, Dep vs Eut, Ctrl** ↑ Putamen **Man vs Eut** ↓ ↑Ínsula ↓ Temporal Superior ↑ Putamen **Dep vs Eut** ↓ Ínsula ↓ Temporal Superior ↓ Frontal Medial Orbital ↑ Putamen **Dep vs todos** ↓ Temporal Superior **Man vs todos** ↓ Precuneus **Man, Dep vs Ctrl** ↑ Ínsula ↑ Frontal Inferior Orbital **Eut vs Ctrl** ↑ Postcentral ↑ Frontal Inferior Orbital ↑ Frontal Medial Orbital
Rey	2014	FA interferencia	Longitudinal Intervalo: 2.8 meses	12	9 Man 9 Dep 11 Eut	13.3 0.5 1.9	1.6 * 15.3 4.3	42.6	41.3	8/4	8/4	**Dep vs Eut** ACC desactivación en Eut **Man vs Eut** ↓ Tálamo ↓ Frontal Medio y Sup Medial ↓ Precentral ↓ Angular

												↓ Precuneus *Desactivaciones diferenciales* Área Motora Suplementaria Frontal Medio Cingulado Medio **Dep vs Man** ↑ Temporal Medio ↑ Frontal Inferior Triangular **Eut vs Ctrl** ↓ Frontal Inferior Opercular ↓ Cingulado Medio ↓ Área motora suplementaria ↓ Frontal Medio ↓ Precentral ↓ Parietal Inferior ↓ Angular *Desactivaciones en Eut* Cingulado Anterior y Posterior ***Man vs Hc*** ↓ Precentral ↓ Frontal Inferior ↓ Cingulado Medio ↓ Parietal Superior e Inferior ↓ Temporal Medio ↓ Tálamo ↓ Putamen ↓ Pálido ↓ Ínsula ↓ Precuneus

												↓ Angular *Desactivaciones en Man* Cingulado Posterior **Dep vs Ctrl** ↓ Precentral ↓ Frontal Inferior Opercular ↓ Tálamo *Desactivaciones en Dep* Hipocampo

Ctrl: controles; Bip: bipolares; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale; H: Hombres; M: Mujeres; Man: Mania; Dep: Depresión; Eut: Eutimia; VPFC: corteza prefrontal ventrolateral; FA: tarea de reconocimiento facial emocional implícito o explícito; T1: primera sesión de resonancia; T2: segunda sesión de resonancia; E: tarea con estímulos emocionales; * MADRS: Montgomery-Asberg Depression Rating Scale; ** IDS: Inventory of Depressive Symptomatology; ↑: aumento de activación; ↓: reducción de activación. Las regiones cerebrales fueron identificadas en base a la localización de las coordenadas de los picos máximos de activación y el atlas AAL (Automated Anatomical Labeling).

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Tabla 2. Resumen de los estudios de fMRI de familiares de pacientes con trastorno bipolar.

Autor	Año	Tarea	Fase	Fam	N Bip	N Fam	N Ctrl	Edad Bip	Edad Fam	Edad Ctrl	Sexo Bip (H/M)	Sexo Fam (H/M)	Sexo Ctrl (H/M)	Resultados
Drapier	2008	N-back	Remisión	1er grado Relacionados *4 Padres* *10 Hermanos* *6 Hijos*	20	20	20	42.7	43	41.9	9/11	12/8	10/10	**Fam vs Ctrl** ↑ Frontal Superior Orbital ↑ Frontal Medio Orbital **Bip vs Ctrl** ↑ Frontal Medio Orbital ↑ Cuneus/Parietal Superior
Costafreda	2009	Fluencia verbal	-	Gemelos Mz	28	7	48	40	39.4	37.4	12/16	1/6	25/23	No diferencias
Allin	2010	Fluencia verbal	Eutimia	1er grado Relacionados *Padres* *Hermanos* *Hijos*	18	19	19	39.2	40.5	39.9	7/11	11/8	10/9	**Fam vs Ctrl** ↑ Precuneus* ↓ Precentral ↓ Cingulado Anterior **Bip vs Ctrl** ↑ Precuneus* ↓ Precentral **Bip vs Fam** ↑ Precentral ↑ Cingulado Anterior ↓ Precuneus*
Thermenos	2010	N-back	Estables	1er grado	19	18	19	41.1	-	39.2	57.8% H	44.4% H	47.4% H	**Fam vs Ctrl** ↑ Ínsula ↑ Opérculo Rolándico ↑ Postcentral **Bip vs Ctrl** ↑ Ínsula ↓ Frontal Superior **Bip vs Fam** ↓ Frontal Superior
Pompei	2011	Stroop	Eutimia	1er grado Relacionados *Hermanos* *Hijos*	39	25	48	39.43	35	36.33	19/20	13/12	25/23	**Bip, Fam vs Ctrl** ↓ Angular ↓ Parietal Inferior **Bip vs Ctrl, Fam** ↓ Caudado **Bip vs Todos** ↓ Frontal Inferior Orbital

Whalley	2011	Hayling test	-	1er grado	-	93	70		21.01	20.89	-	45/48	32/38	**Fam vs Ctrl** ↑ Amígdala
Frangou	2011	Stroop	Eutimia	1er grado *Hermanos* *Hijos*	47	48	71	46.2	36.5	39.8	21/26	25/25	36/35	**Fam vs Ctrl** ↓ Parietal **Bip vs Ctrl** ↓ Angular ↓ Parietal Superior ↓ Parietal Inferior ↓ Postcentral ↓ Caudado ↓ Frontal Inferior Orbital
Linke	2012	Recompensa	Eutimia	1er grado *9 Hermanos* *13 Hijos*	19	22	22	45	28	28	8/11	11/11	11/11	**Fam vs Ctrl** ↑Frontal Medial Orbital ↑Amígdala ↑Cingulado Anterior **Bip vs Ctrl** ↑ Rectus ↑ Frontal Inferior Orbital ↑ Cingulado Anterior ↑ Amígdala ↑ Putamen **Bip vs Fam** ↑Putamen ↓Amígdala
Sepede	2012	CPT	Eutimia	1er grado No relación *10 Hermanos* *12 Hijos*	24	22	24	34.8	31.5	35.2	10/14	7/15	8/16	**Fam vs Bip, Ctrl** ↑ Cingulado Posterior* ↑ Supramarginal ↑ Parietal Inferior ↑ Ínsula **Bip, Fam vs Ctrl** ↑ Ínsula ↑ Paracentral
Whalley	2013	Hayling	-	1er y 2do grado		78	58	-	21.12	20.78	-	42/36	25/33	**Fam vs Ctrl** No diferencias
Roberts	2013	Go/NoGo E	-	1er grado *Hermanos* *Hijos*		47	49	-	24.6	23.2	-	22/25	17/32	**Fam vs Ctrl** ↓ Corteza olfativa

Kanske	2013	Aritmética E	Eutimia	1er grado No relación *8 Padres* *5 Hermanos* *4 Hijos*	22	17	17	39.4	36.6	35.9	8/14	9/8	9/8	**Bip, Fam vs Ctrl** ↑ Parietal Superior
Erk	2014	Memoria verbal	-	1er grado *Padres* *Hijos* *Hermanos*		59	60	-	31.8	33.4	-	23/36	25/35	**Fam vs Ctrl** ↓ Hipocampo ↓ Cingulado Anterior
Sepede	2015	IAPS	Eutimia	1er grado No relación *10 Hermanos* *12 Hijos*	23	22	24	35.2	31.5	32.5	9/14	7/15	8/16	**Fam vs Ctrl** ↑ Temporal Superior y Medio ↑ Tálamo ↑ Fusiforme ↑ Cuneus ↑ Frontal Medio y Superior ↑ Ínsula ↑ Calcarine ↓ Lingual ↓ Cerebelo ↓ Cingulado Anterior* ↓ Supramarginal ↓ Área Motora Suplement **Bip vs Ctrl** ↑ Ínsula ↓ Hipocampo ↑ Temporal Superior y Medio ↑ Tálamo ↓ Fusiforme ↓ Cuneus ↓ Precuneus ↓ Supramarginal **Bip vs Fam** ↑ Ínsula ↑ Lingual ↑ Cerebelo ↑ Frontal Medio ↑ Cingulado Anterior* ↑ Area Motora Suplement ↓Hipocampo ↓ Calcarine

Kanske	2015	IAPS	Eutimia	1er grado No relación *8 Padres* *5 Hermanos* *4 Hijos*	22	17	17	39.4	36.7	35.94	8/14	9/8	9/8	**Fam vs Ctrl** ↑ Amígdala ↑ Cingulado Anterior ↑ Ínsula **Bip vs Ctrl** ↑ Amígdala
Willert	2015	TOM	Eutimia	1er grado	24	21	81	44.75	31	35.57	12/12	7/14	40/41	**Bip vs Ctrl, Fam** ↓ Temporal Medio

Bip: bipolares; Fam: familiares sanos; Ctrl: controles; H: Hombres; M: Mujeres; Mz: gemelos monocigóticos; FA: tarea de reconocimiento facial emocional implícito o explícito; E: tarea con estímulos emocionales; * Cambios en desactivaciones; ↑: aumento de activación; ↓: reducción de activación. Las regiones cerebrales fueron identificadas en base a la localización de las coordenadas de los picos máximos de activación y el atlas AAL (Automated Anatomical Labeling).

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Curriculum Vitae

Licenciada en Psicología por la Universidad de Deusto (Bilbao) y máster en Neuropsicología: diagnóstico y rehabilitación neuropsicológica (Universitat Autònoma de Barcelona) y en Neurociencias (Universitat de Barcelona). En 2012 obtuve el reconocimiento de especialista en Neuropsicología Clínica por parte del Colegio Oficial de Psicología de Catalunya.

Desde el 2010 realizo mi actividad investigadora en la fundación FIDMAG - Germanes Hospitalàries dirigida por Edith Pomarol-Clotet y pertenezco al grupo de investigación G15 del CIBERSAM dirigido por el Dr. Peter McKenna. Durante este tiempo me he formado en neuroimagen y neuropsicología de los trastornos mentales severos, y en concreto, del trastorno bipolar.

En 2011 obtuve una beca predoctoral PFIS (FI11/00221) gracias a la cual he desarrollado la tesis doctoral en el programa de Neurociencias Clínicas y Experimentales del doctorado de Medicina de la Universidad de Barcelona, bajo la codirección de los doctores Edith Pomarol-Clotet y Eduard Vieta. Fruto de esta beca pude realizar una estancia financiada de 9 meses en el Brain & Mental Health Laboratory (Melbourne, Australia) y en el Melbourne Neuropsychiatry Centre (Melbourne, Australia) para el aprendizaje de nuevas técnicas de neuroimagen. La estancia estuvo supervisada por el Prof. Chris Pantelis y el Prof. Murat Yücel.

Publicaciones |

2016

Brain functional changes in first-degree relatives of patients with bipolar disorder: evidence for default mode network dysfunction. Alonso-Lana S, Valentí M, Romaguera A, Sarri C, Sarró S, Rodríguez-Martínez A, Goikolea JM, Amann BL, Maristany T, Salvador R, Vieta E, McKenna PJ, Pomarol-Clotet E. *Psychological Medicine*. 2016; 46(12): 2513-2521.

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Brain structural changes in schizoaffective disorder compared to schizophrenia and bipolar disorder. Amann BL, Canales-Rodriguez EJ, Madre M, Radua J, Monte G, Alonso-Lana S, Landin-Romero R, Moreno-Alcazar A, Bonnin CM, Sarro S, Ortiz-Gil J, Gomar JJ, Moro N, Fernandez-Corcuera P, Goikolea JM, Blanch J, Salvador R, Vieta E, McKenna PJ, Pomarol-Clotet E. *Acta Psychiatr Scand*. 2016;133(1):23-33. doi: 10.1111/acps.12440.

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Common and specific brain responses to scenic emotional stimuli. Radua J, Sarro S, Vigo T, Alonso-Lana S**,** Bonnin CM, Ortiz-Gi l J, Canales-Rodriguez EJ, Maristany T, Vieta E, McKenna PJ,

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