UNIVERSITAT DE BARCELONA

Unravelling Neural Heterogeneity in Mental Disorders: The Role of Genetics, Cognition, and Comorbidities

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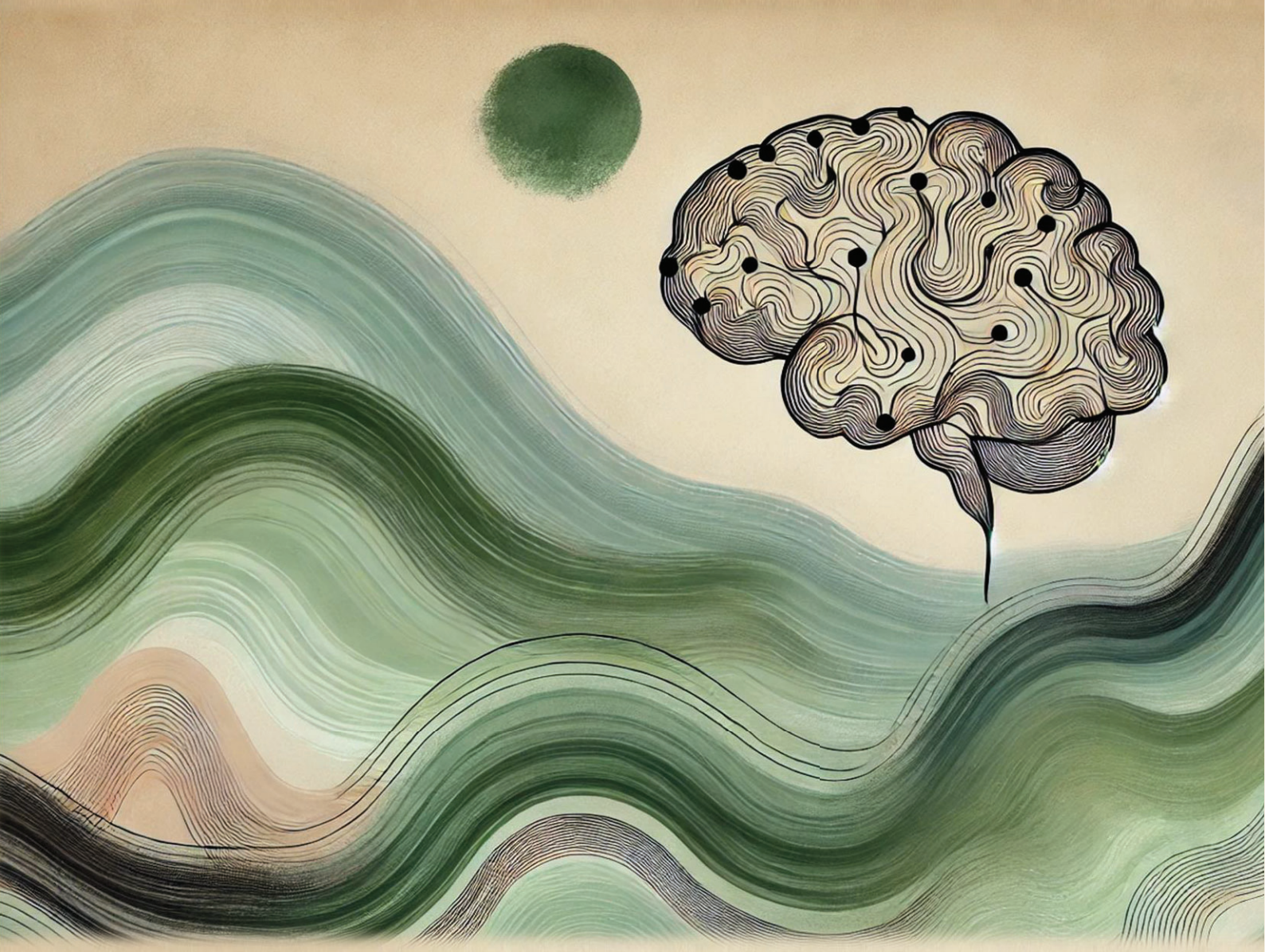

Unravelling Neural Heterogeneity in Mental Disorders: The Role of Genetics, Cognition, and Comorbidities

LYDIA FORTEA

Unravelling Neural Heterogeneity in Mental Disorders: The Role of Genetics, Cognition, and Comorbidities

Doctoral thesis dissertation presented by Lydia Fortea González to apply for the degree of doctor at the University of Barcelona

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Abbreviations

DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th version

ICD-11: International Classification of Diseases, 11th version

WHO: World Health Organization

BD: bipolar disorder

MDD: major depressive disorder

ASD: autism spectrum disorder

ADHD: attention-deficit/hyperactivity disorder

OCD: obsessive-compulsive disorders

PTSD: post-traumatic stress disorder

MRI: Magnetic resonance imaging

fMRI: Functional magnetic resonance imaging

VBM: Voxel-based morphometry

GMV: Grey matter volume

SPM: Statistical Parametric Mapping

BOLD: blood-oxygen-level dependent

RSN: resting-state networks

ICA: independent component analyses

SSD: schizophrenia spectrum disorder

RSN: resting-state networks

DMN: default mode network

CEN: central executive network

ENIGMA: Enhancing neuroimaging genetics through meta-analysis

PFC: prefrontal cortex

ACC: anterior cingulate cortex

BDNF: brain-derived neurotrophic factor

ADGRL3: Adhesion G Protein-Coupled Receptor L3

BPD: borderline personality disorder

SSD: schizophrenia spectrum disorders

DTI: diffusion tensor imaging

MRS: magnetic resonance spectroscopy

List of articles

Thesis in compendium of publications format. The thesis consists of six objectives and four articles:

Study I

Moreno-Alcázar A, Ramos-Quiroga JA, Ribases M, Sánchez-Mora C, Palomar G, Bosch R, Salavert J, **Fortea L**, Monté-Rubio GC, Canales-Rodríguez EJ, Milham MP, Castellanos FX, Casas M, Pomarol-Clotet E, Radua J. Brain structural and functional substrates of ADGRL3 (latrophilin 3) haplotype in attention-deficit/hyperactivity disorder. *Scientific reports*. 2021;11(1):2373.

IF 2021: 4.996, Q1 in Multidisciplinary Sciences.

Study II

Fortea L, Ysbaek-Nielsen AT, Macoveanu J, Petersen JZ, Fisher PM, Kessing LV, Knudsen GM, Radua J, Vieta E, Miskowiak KW. Aberrant resting-state functional connectivity underlies cognitive and functional impairments in remitted patients with bipolar disorder. *Acta psychiatrica Scandinavica*. 2023;148(6):570-582.

IF 2023: 5.3, Q1 in Psychiatry and Mental Health.

Study III

Fortea L, Albajes-Eizagirre A, Yao YW, Soler E, Verdolini N, Hauson AO, Fortea A, Madero S, Solanes A, Wollman SC, Serra-Blasco M, Wise T, Lukito S, Picó-Pérez M, Carlisi C, Zhang J, Pan P, Farré-Colomés Á, Arnone D, Kempton MJ, Soriano-Mas C, Rubia K, Norman L, Fusar-Poli P, Mataix-Cols D, Valentí M, Via E, Cardoner N, Solmi M, Shin JI, Vieta E, Radua J. Focusing on Comorbidity-A Novel Meta-Analytic Approach and Protocol to Disentangle the Specific Neuroanatomy of Co-occurring Mental Disorders. *Frontiers in psychiatry*. 2022;12:807839.

IF 2022: 4.52, Q1 in Psychiatry and Mental Health.

Fortea L, Ortuño M, De Prisco M, Oliva V, Albajes-Eizagirre A, Fortea A, Madero S, Solanes A, Vilajosana E, Yao Y, Del Fabro L, Galindo ES, Verdolini N, Farré-Colomés A, Serra-Blasco M, Picó-Pérez M, Lukito S, Wise T, Carlisi C, Arnone D, Kempton M, Hauson AO, Wollman

S, Soriano-Mas C, Rubia K, Norman L, Fusar-Poli P, Mataix-Cols D, Valentí M, Via E, Cardoner N, Solmi M, Zhang J, Pan P, Shin JI, Fullana MÀ, Vieta E, Radua J. Atlas of gray matter volume differences across psychiatric conditions: A systematic review with a novel meta-analysis that considers co-occurring disorders. *Biological Psychiatry*. 2024 Nov 2:S0006-3223(24)01729-3. Epub ahead of print.

IF 2023/2024: 9.6, Q1in Psychiatry and Mental Health

Thesis summary (in Spanish)

Explorando la heterogeneidad neural en los trastornos mentales: el papel de la genética, la cognición y las comorbilidades

1. Introducción

Los trastornos mentales son una de las principales causas de discapacidad a nivel mundial, afectando significativamente la calidad de vida de las personas afectadas y generando una considerable carga económica y social. A pesar de los avances en diagnóstico y tratamiento, los mecanismos neurobiológicos subyacentes a estas afecciones siguen siendo poco comprendidos, dificultando su detección temprana, la estimación de su pronóstico y el diseño de intervenciones efectivas. Estudios de resonancia magnética (RM) han identificado alteraciones cerebrales asociadas a trastornos mentales, lo que ofrece un gran potencial para mejorar su comprensión y facilitar diagnósticos más precisos y tratamientos personalizados. Sin embargo, la heterogeneidad de estos hallazgos, derivada, entre otros, de la variabilidad clínica, predisposiciones genéticas, deterioros cognitivos y comorbilidades, representa un desafío significativo para la identificación de biomarcadores estables y robustos. Abordar esta heterogeneidad es, por tanto, esencial para mejorar la comprensión de los trastornos mentales y avanzar en el campo de la psiquiatría personalizada.

Esta tesis estudia como diversos factores, específicamente haplotipos genéticos, deterioro cognitivo y comorbilidades, contribuyen a la heterogeneidad en los estudios de neuroimagen, con el fin último de aumentar el conocimiento sobre las bases biológicas de los trastornos y así poder ofrecer una mejor cura a las personas afectadas.

2. Hipótesis

H1. Los correlatos neurales de los trastornos mentales dependen de la presencia de haplotipos genéticos.

H2. Los correlatos neurales de los trastornos mentales dependen de la presencia de deterioro cognitivo comórbido.

H3. Los correlatos neurales de los trastornos mentales dependen de la presencia de otros trastornos comórbidos.

H4. Existen haplotipos genéticos asociados a trastornos mentales que presentan correlatos neurales relevantes, lo que confunde el análisis de los correlatos neurales de dichos trastornos.

H5. Hay trastornos mentales comórbidos que confunden el análisis de los correlatos neurales de trastornos mentales, provocando resultados más difusos e inespecíficos.

3. Objetivos

O1. Evaluar si los correlatos neurales de un trastorno mental pueden depender de la presencia de un haplotipo genético.

O2. Evaluar si los correlatos neurales de un trastorno mental pueden depender de la presencia de deterioro cognitivo.

O3. Evaluar si los correlatos neurales de trastornos mentales dependen de la presencia de otros trastornos comórbidos.

O4. Evaluar si los haplotipos asociados a trastornos mentales pueden tener correlatos neurales relevantes cuando se consideran tanto los efectos de los trastornos mentales como de los haplotipos genéticos.

O5. Evaluar si el análisis de los correlatos neurales de trastornos mentales produce resultados más focalizados y específicos cuando se covaría por la presencia de comorbilidades.

O6. Desarrollar un atlas que mapee las alteraciones específicas y transdiagnósticas en el volumen de sustancia gris (VSG) asociadas estadísticamente con los principales trastornos mentales, teniendo en cuenta el efecto de confusión generado por trastornos comórbidos.

4. Métodos

El estudio I exploró los correlatos neurales del trastorno por déficit de atención e hiperactividad (TDAH) en adultos y del gen latrofilina 3 (ADGRL3, asociado al TDAH). Pacientes con TDAH (n=64) y controles (n=64), clasificados según su haplotipo de ADGRL3 (de riesgo y protector), completaron una RM estructural y funcional durante una tarea de memoria de trabajo (*n-back*).

Los datos se analizaron con FSL empleando un modelo lineal ajustado por edad, sexo y medicación, para investigar los correlatos neurales de TDAH, los haplotipos y su interacción.

El estudio II investigó correlatos funcionales en pacientes con trastorno bipolar (TB) asociados al deterioro cognitivo. Un total de 144 pacientes con TB en remisión, clasificados en cognitivamente deteriorados (n=83) y cognitivamente normales (n=61), y 50 controles completaron una RM funcional en estado de reposo. Utilizado FSL se analizó la conectividad funcional intra e interredes funcionales de la red por defecto (DMN), ejecutiva central (CEN) y de saliencia, ajustando por edad y sexo.

El estudio III desarrolló y validó una metodología innovadora de meta-análisis con SDM-PSI, diseñada para considerar el efecto de las comorbilidades. Se analizaron 433 estudios de VSG, incluyendo 19,718 pacientes y 16,441 controles, para identificar alteraciones estructurales asociadas a trastornos mentales, y compararla con los métodos estándar.

5. Resultados

El estudio I no identificó interacciones diagnóstico X haplotipo. Sin embargo, ambos haplotipos mostraron una hipo-activación durante la tarea n-back. Por lo tanto, los haplotipos del ADGRL3 pueden confundir los estudios sobre las bases neuronales del TDAH, ya que están asociados tanto al trastorno como a la neuroimagen.

El estudio II reveló que los pacientes con TB cognitivamente deteriorados exhibieron mayor hiper-conectividad en regiones de la DMN y menor hipo-conectividad en regiones de la ECN. Por lo tanto, los correlatos funcionales del TB están influenciados por la presencia de deterioro cognitivo comórbido.

El estudio III reveló que los correlatos de VSG de un trastorno mental están influenciados por la presencia de otros trastornos comórbidos. Además, utilizando la metodología innovadora se observó que las alteraciones eran más focalizadas y específicas cuando se covaría por los otros trastornos.

6. Conclusiones

C1. La presencia de haplotipos de ADGRL3 de protección o riesgo no influye en los correlatos estructurales y funcionales del TDAH.

C2. El deterioro cognitivo influye en los correlatos funcionales de pacientes con TB.

C3. Los correlatos estructurales de los trastornos mentales varían según la presencia de trastornos comórbidos.

C4. Los haplotipos de ADGRL3, asociados al TDAH, tienen correlatos funcionales cerebrales importantes, por lo que pueden actuar como factores de confusión en el análisis de los correlatos cerebrales del TDAH.

C5. Los trastornos comórbidos actúan como factores de confusión cuando se estudian las alteraciones estructurales en los trastornos mentales, generando patrones más amplios e hiper-correlacionados.

C6. Los correlatos neurales de los trastornos mentales están influenciados por varios factores, como el deterioro cognitivas y las comorbilidades.

C7. El análisis de los correlatos neurales en trastornos mentales puede estar sesgado por diversos factores de confusión, como los haplotipos genéticos y las comorbilidades.

C8. La presencia de efectos moderadores y de confusión al investigar los correlatos neurales de trastornos mentales complica la identificación de biomarcadores robustos y específicos, pero también abre nuevas posibilidades para futuras investigaciones.

7. Palabras clave

Neuroimagen, trastorno mental, heterogeneidad, haplotipos genéticos, deterioro cognitivo, trastornos comórbidos.

Thesis summary (in Catalan)

Explorant la heterogeneïtat neuronal en els trastorns mentals: el paper de la genètica, la cognició i les comorbiditats

1. Introducció

Els trastorns mentals són una de les principals causes de discapacitat a nivell mundial, impactant significativament la qualitat de vida de les persones afectades i generant una considerable càrrega econòmica i social. Malgrat els avenços en el diagnòstic i el tractament, els mecanismes neurobiològics subjacents a aquestes afeccions continuen sent poc compresos, fet que dificulta la seva detecció precoç, l'estimació del seu pronòstic i el disseny d'intervencions efectives. Els estudis de ressonància magnètica (RM) han identificat alteracions cerebrals associades als trastorns mentals, oferint un gran potencial per millorar-ne la comprensió i facilitar diagnòstics més precisos i tractaments personalitzats. No obstant això, la heterogeneïtat d'aquests resultats, derivada, entre altres factors, de la variabilitat clínica, les predisposicions genètiques, el deteriorament cognitiu i les comorbiditats, representa un repte significatiu per a la identificació de biomarcadors estables i robustos. Per tant, abordar aquesta heterogeneïtat és essencial per millorar la comprensió dels trastorns mentals i avançar en el camp de la psiquiatria personalitzada.

Aquesta tesi estudia com diversos factors, específicament haplotips genètics, deteriorament cognitiu i comorbiditats, contribueixen a la heterogeneïtat en els estudis de neuroimatge, amb l'objectiu final d'augmentar el coneixement sobre les bases biològiques dels trastorns i així poder oferir una millor cura a les persones afectades.

2. Hipòtesis

H1. Els correlats neurals dels trastorns mentals depenen de la presència d'haplotips genètics.

H2. Els correlats neurals dels trastorns mentals depenen de la presència de deteriorament cognitiu comòrbid.

H3. Els correlats neurals dels trastorns mentals depenen de la presència d'altres trastorns comòrbids.

H4. Existeixen haplotips genètics associats a trastorns mentals que presenten correlats neurals rellevants, fet que confon l'anàlisi dels correlats neurals d'aquests trastorns.

H5. Hi ha trastorns mentals comòrbids que confonen l'anàlisi dels correlats neurals dels trastorns mentals, provocant resultats més difusos i inespecífics.

3. Objectius

O1. Avaluar si els correlats neurals d'un trastorn mental poden dependre de la presència d'un haplotip genètic.

O2. Avaluar si els correlats neurals d'un trastorn mental poden dependre de la presència de deteriorament cognitiu.

O3. Avaluar si els correlats neurals dels trastorns mentals depenen de la presència d'altres trastorns comòrbids.

O4. Avaluar si els haplotips associats a trastorns mentals poden tenir correlats neurals rellevants quan es consideren tant els efectes dels trastorns mentals com dels haplotips genètics.

O5. Avaluar si l'anàlisi dels correlats neurals dels trastorns mentals produeix resultats més focalitzats i específics quan es covaria per la presència de comorbiditats.

O6. Desenvolupar un atles que cartografiï les alteracions específiques i transdiagnòstiques en el volum de substància grisa (VSG) associades estadísticament amb els principals trastorns mentals, tenint en compte l'efecte de confusió generat per trastorns comòrbids.

4. Mètodes

L'estudi I va explorar els correlats neurals del trastorn per dèficit d'atenció i hiperactivitat (TDAH) en adults i del gen latrofilina 3 (ADGRL3, associat al TDAH). Pacients amb TDAH (n=64) i controls (n=64), classificats segons el seu haplotip d'ADGRL3 (de risc i protector), van completar una RM estructural i funcional durant una tasca de memòria de treball (*n-back*).

Les dades es van analitzar amb FSL utilitzant un model lineal ajustat per edat, sexe i medicació, per investigar els correlats neurals del TDAH, els haplotips i la seva interacció.

L'estudi II va investigar els correlats funcionals en pacients amb trastorn bipolar (TB) associats al deteriorament cognitiu. Un total de 144 pacients amb TB en remissió, classificats en cognitivament deteriorats (n=83) i cognitivament normals (n=61), i 50 controls van completar una RM funcional en estat de repòs. Utilitzant FSL, es va analitzar la connectivitat funcional intra i interxarxes funcionals de la xarxa per defecte (DMN), executiva central (CEN) i de saliència, ajustant per edat i sexe.

L'estudi III va desenvolupar i validar una metodologia innovadora de meta-anàlisi amb SDM-PSI, dissenyada per considerar l'efecte de les comorbiditats. Es van analitzar 433 estudis de VSG, incloent 19.718 pacients i 16.441 controls, per identificar alteracions estructurals associades als trastorns mentals i comparar-les amb els mètodes estàndard.

5. Resultats

L'estudi I no va identificar interaccions diagnòstic × haplotip. No obstant això, ambdós haplotips van mostrar una hipoactivació durant la tasca n-back. Per tant, els haplotips d'ADGRL3 poden confondre els estudis sobre les bases neuronals del TDAH, ja que estan associats tant al trastorn com a les troballes de neuroimatge.

L'estudi II va revelar que els pacients amb TB cognitivament deteriorats exhibien una major hiperconnectivitat en regions de la DMN i una menor hipoconnectivitat en regions de la CEN. Per tant, els correlats funcionals del TB estan influenciats per la presència de deteriorament cognitiu comòrbid.

L'estudi III va mostrar que els correlats de VSG d'un trastorn mental estan influenciats per la presència d'altres trastorns comòrbids. A més, mitjançant la metodologia innovadora es va observar que les alteracions eren més focalitzades i específiques quan es covariava per la presència d'altres trastorns.

6. Conclusions

C1. La presència d'haplotips d'ADGRL3 de protecció o risc no influeix en els correlats estructurals i funcionals del TDAH.

C2. El deteriorament cognitiu influeix en els correlats funcionals dels pacients amb TB.

C3. Els correlats estructurals dels trastorns mentals varien segons la presència de trastorns comòrbids.

C4. Els haplotips d'ADGRL3, associats al TDAH, tenen correlats funcionals cerebrals importants, de manera que poden actuar com a factors de confusió en l'anàlisi dels correlats cerebrals del TDAH.

C5. Els trastorns comòrbids actuen com a factors de confusió quan s'estudien les alteracions estructurals en els trastorns mentals, generant patrons més amplis i hiper-correlacionats.

C6. Els correlats neurals dels trastorns mentals estan influenciats per diversos factors, com el deteriorament cognitiu i les comorbiditats.

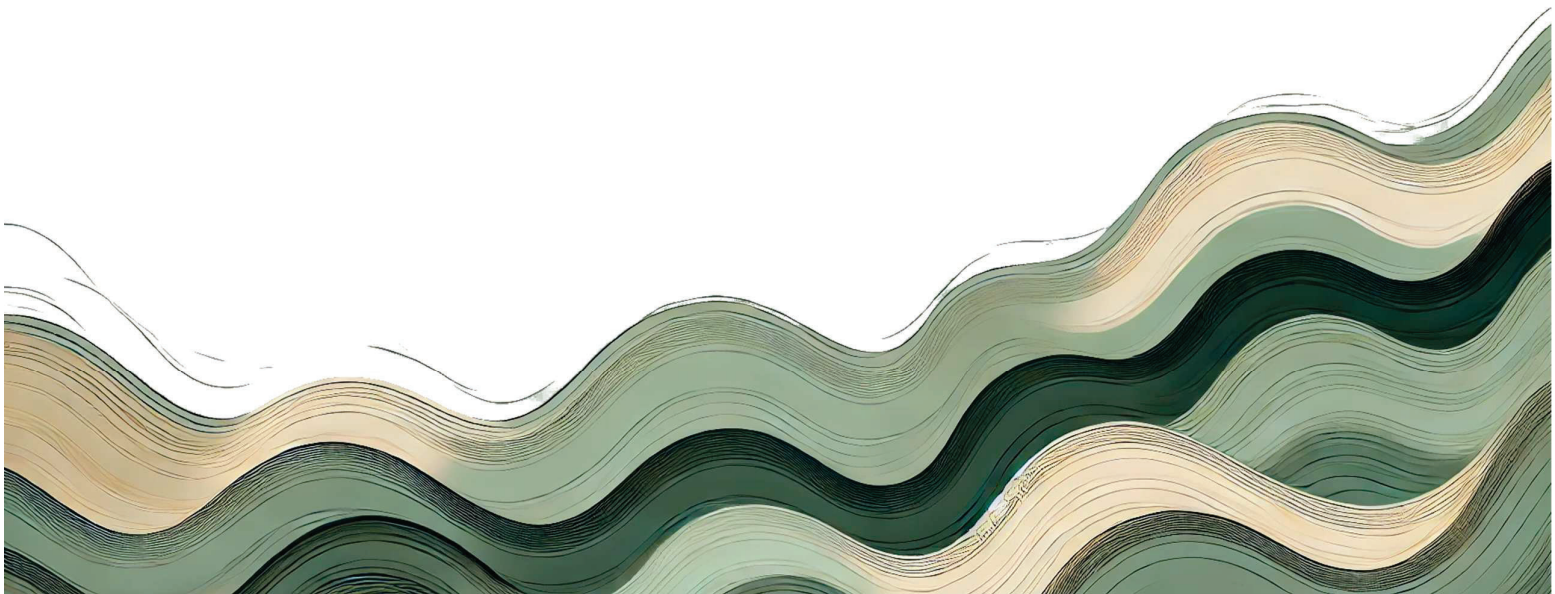
C7. L'anàlisi dels correlats neurals en trastorns mentals pot estar esbiaixat per diversos factors de confusió, com els haplotips genètics i les comorbiditats.

C8. La presència d'efectes moderadors i de confusió en la investigació dels correlats neurals dels trastorns mentals dificulta la identificació de biomarcadors robustos i específics, però també obre noves possibilitats per a futures investigacions.

7. Paraules clau

Neuroimatge, trastorn mental, heterogeneïtat, haplotips genètics, deteriorament cognitiu, trastorns comòrbids.

Introduction



In the introduction to this thesis, I will begin by reviewing the major mental disorders, followed by an overview of the key neuroimaging techniques used to explore their brain correlates. Next, I will summarize the main findings of neuroimaging studies that investigate these neural correlates. Finally, I will expose the problem of "heterogeneity" —specifically, the variability in neural correlates of a given disorder across different studies— and discuss potential reasons for this variability. The exploration and potential reduction of this heterogeneity will be the central theme of this thesis.

1. Mental disorders

Mental disorders are a broad range of mental health conditions that significantly impact an individual's mood, thinking, behavior, and overall well-being. These disorders often lead to considerable distress and impair the ability to function in everyday life, affecting areas such as social interactions, work performance, or other critical areas of functioning. Common symptoms associated with mental disorders include mood disturbances (e.g., depression, mania, and mood swings), anxiety (excessive worry or fear), cognitive impairments (difficulties with memory or concentration), behavioral changes (e.g., agitation or compulsive behaviors), and perceptual disturbances (e.g., hallucinations or delusions) (1).

For practical purposes, these conditions are categorized according to their clinical symptoms. Mental health professionals primarily refer to two authoritative classifications: the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) (2), published by the American Psychiatric Association and the *International Classification of Diseases* (ICD-11) (3), published by the World Health Organization (WHO). These guides categorize mental disorders into distinct types, each with unique symptoms and diagnostic criteria. Below is an overview of the major categories of mental disorders, also represented in Figure 1.

1. Anxiety disorders. These disorders are characterized by excessive fear, anxiety, and related avoidance and behavioral disturbances. These disorders can significantly impair daily functioning and quality of life, often leading to avoidance behaviors that worsen over time. Individuals with anxiety disorders may also experience physical symptoms such as increased heart rate, trembling, or difficulty breathing, along with mental symptoms like racing thoughts or irrational fears. There are several types of anxiety disorders, each differing based on the specific triggers or manifestations of fear. For

example, social anxiety disorder entails an intense fear of being judged or embarrassed in social situations; panic disorder involves recurrent unexpected panic attacks with symptoms like chest pain, dizziness, and a sense of impending doom; agoraphobia is characterized by the fear of situations or places where escape might be difficult, or help might not be available, often leading to avoidance of public places; generalized anxiety disorder is characterized by chronic and excessive worry about everyday issues such as health, finances, or relationships; and specific phobias involve an irrational and excessive fear of particular objects or situations (e.g., spiders, heights), often triggering an immediate anxiety response.

2. Mood disorders. These disorders are categorized by significant disturbances in a person's emotional state, often involving prolonged periods of extreme sadness, euphoria, or both. These disorders can lead to significant impairments in daily life, and their severity can range from mild to life-threatening. Common symptoms include persistent sadness, feelings of hopelessness, irritability, and fluctuations between extreme highs (mania) and lows (depression). Specific mood disorders include bipolar disorder (BD), characterized by alternating periods of mania (elevated mood, increased energy, and impulsive behavior) and depressive episodes (sadness, low energy, and feelings of hopelessness), and major depressive disorder (MDD), which involves persistent sadness, loss of interest in activities, and feelings of worthlessness, often accompanied by physical symptoms like changes in appetite or sleep.
3. Schizophrenia spectrum and other psychotic disorders. These disorders are characterized by a disconnection of reality, marked by distorted thinking, perceptions, and behavior. Symptoms often include hallucinations (hearing or seeing things that aren't present, typically voices), delusions (strongly held false beliefs, such as paranoia or grandiosity), severely disorganized thinking or speech, and negative symptoms (e.g., diminished emotional expression, lack of motivation). These disorders significantly impair a person's ability to function and can be chronic and debilitating. Examples include schizophrenia and schizoaffective disorder, which combine symptoms of schizophrenia and mood disorders.
4. Neurodevelopmental disorders. These disorders originate during the developmental period, typically before a child enters grade school, and are characterized by developmental deficits that cause impairments in personal, social, academic, or occupational functioning. These deficits can be intellectual, communicative, motor-related, or behavioral. Examples include autism spectrum disorder (ASD),

characterized by difficulties in understanding social interaction, communication, and repetitive behaviors or restricted interests, and attention-deficit/hyperactivity disorder (ADHD), which involves persistent patterns of inattention (e.g., difficulty sustaining focus), hyperactivity (e.g., excessive movement), or impulsiveness (e.g., interrupting others).

5. Obsessive-compulsive and related disorders. These disorders are defined by the presence of obsessions (recurrent, persistent, intrusive thoughts) and/or compulsions (repetitive behaviors or mental acts). The behaviors are often time-consuming, cause significant distress, and interfere with daily life. Examples include obsessive-compulsive disorder (OCD), characterized by unwanted thoughts and repetitive behaviors, and body dysmorphic disorder, which involves an excessive preoccupation with perceived flaws in appearance, often leading to repetitive behaviors like mirror checking or skin picking.
6. Trauma- and stressor-related disorders. These disorders develop after exposure to a traumatic or highly stressful event involving death, serious injury, or sexual violence. They are characterized by intrusive thoughts, flashbacks, and avoidance behaviors or situations related to the trauma. Individuals may also experience heightened arousal and negative changes in mood and cognition. Examples include post-traumatic stress disorder (PTSD), characterized by persistent distress and functional impairment following trauma, with symptoms lasting more than a month, and acute stress disorder, which is similar to PTSD but with symptoms resolving within a month.
7. Eating disorders. These disorders are characterized by persistent and severe disturbance in eating behavior and related thoughts and emotions, often driven by an intense preoccupation with body image and weight. These disorders can result in serious health complications, including malnutrition, heart problems, and, in several cases, death. They are often linked to issues with body image, self-esteem, and emotional regulation. Examples include anorexia nervosa, characterized by an intense fear of gaining weight, leading to extreme food restriction and weight loss, and bulimia nervosa, which involves episodes of binge eating followed by compensatory behaviors like vomiting or fasting.

Figure 1. Classification of major non-substance use mental disorders

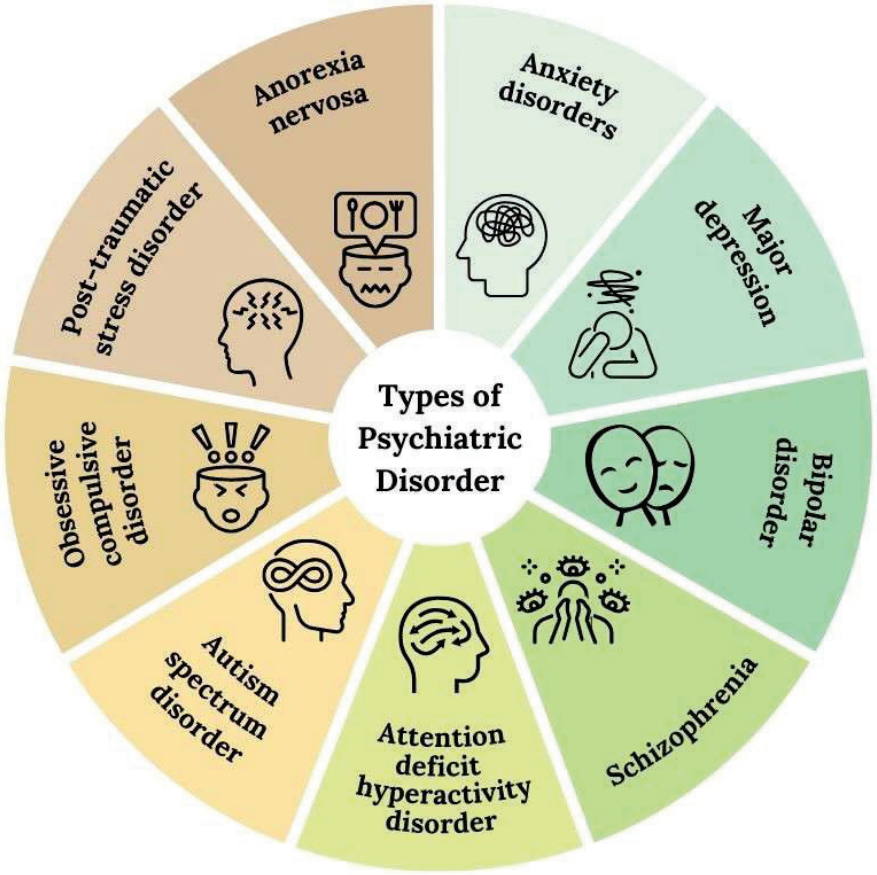


Figure created by the doctoral student

1.1. Epidemiology and risk factors

Mental disorders are a significant global health concern, affecting individuals across all demographics, regardless of age, gender, or socio-economic status. According to the WHO, approximately one in four individuals worldwide will experience a mental health disorder at some point in their lives, highlighting the widespread nature of these conditions (4). Anxiety and depression disorders are amongst the most common mental disorders worldwide (1). Surveys have shown that the average lifetime prevalence of anxiety disorders worldwide is around 7% (5), and for depression, it is roughly 5% of the global population (6). However, these rates may vary significantly depending on the region studied and the methodology used. For instance, the National Comorbidity Survey conducted in the United States estimated much higher lifetime prevalences (31% for anxiety disorders and 17% for depression) (7,8).

Psychiatry disorders arise from a complex interplay of genetic, biological, environmental, and psychological factors. Due to this multifactorial etiology, specific populations are more vulnerable to developing these conditions. Genetic predisposition plays a significant role as a risk factor in developing mental disorders, particularly those with a strong hereditary component, such as ADHD and ASD (9). Individuals with a family story of mental illness are at significantly higher risk of developing similar or even different mental disorders themselves. For instance, a large-scale meta-analysis found that offsprings of affected parents have a significantly higher lifetime ratio of developing any mental disorder, as well as the same mental disorder diagnosed in the parent (10).

Gender is another critical factor in the prevalence of mental disorders. Women are nearly twice as likely as men to suffer from anxiety and mood disorders (11), while men are more likely to suffer from substance use disorders or die from suicide (12,13). This gender disparity may be influenced by several factors, including hormonal differences, such as fluctuations in estrogen and progesterone levels and the use of different maladaptive coping strategies (e.g., rumination in women and substance abuse in men). Social stressors, such as gender-based violence, disproportionately affect women, increasing their vulnerability to mental health issues (14). Conversely, societal expectations of masculinity often discourage men from seeking help for emotional distress, leading to underdiagnosis and greater reliance on unhealthy coping mechanisms (15). Cultural norms also shape how men and women perceive and report mental health symptoms, influencing both diagnosis and treatment.

Age also plays a crucial role in the onset and diagnosis of mental disorders. Younger individuals, particularly adolescents and young adults, are more frequently diagnosed with disorders like anxiety, mood disorders, and first-episode psychotic disorders (11). Adolescence is a period of significant neurological and psychological development, during which the brain undergoes changes in regions related to emotion regulation and decision-making (16). This developmental phase coincides with the increasing stressors associated with modern life, such as academic pressures, social media influences, or bullying, which have been suggested as contributors to the rising rates of mental health disorders among younger populations (17,18). Early identification and intervention in younger populations are critical, as untreated mental health conditions during adolescence can lead to long-term functional impairments, substance use, and increased risk of suicide.

Socio-economic factors further contribute to the risk of developing mental disorders. Poverty, unemployment, and limited access to education and healthcare disparities increase vulnerability to mental health problems (19). Chronic financial stress and insecurity can lead to feelings of hopelessness, anxiety, and depression. Additionally, people living in lower socioeconomic conditions also face barriers to accessing mental health care, such as high costs, long waiting times, and stigma surrounding treatment (19). The cumulative effect of these stressors contributes not only to the onset of mental disorders but also to their persistence and severity.

Additionally, childhood adversity is strongly associated with the development of mental disorders throughout different stages of life (20). Experiences of abuse, neglect, or trauma in early childhood, particularly within a dysfunctional family environment, significantly elevate the risk of developing a range of mental disorders, including depression, anxiety, schizophrenia, and PTSD. Adverse childhood experiences may disrupt normal brain development and shape an individual's coping mechanisms, emotional regulation, and stress responses, making them more susceptible to mental health issues throughout different stages of life (21).

1.2. Impact of mental disorders

Mental disorders profoundly impact individuals and society, affecting various aspects of life, including work, relationships, and overall well-being. These conditions not only impose a significant personal burden on those who suffer from them but also have far-reaching effects on families, communities, and societies. Mental disorders are a leading cause of disability worldwide, with the WHO identifying depression as the single largest contributor to disability globally. Depression significantly impairs an individual's ability to perform daily activities and limits their participation in both social and economic life (22).

The stigma surrounding mental disorders exacerbates the challenges faced by those affected. This stigma leads to discrimination, reduced employment opportunities, and difficulties in forming and maintaining social relationships. Stigma not only affects personal well-being but also perpetuates a cycle of social and economic marginalization. As a result, individuals with mental disorders experience diminishing quality of life, which can exacerbate feelings of isolation, hopelessness, and social exclusion (23).

One of the most alarming consequences of mental disorders is their strong association with suicide. Approximately 90% of suicides are linked to mental health conditions (24). While the global suicide rate is estimated to be around 11.1 per 100,000 people (25), the risk of suicide among individuals with mental disorders is substantially higher. Depression carries the highest suicide rate, with 534.3 per 100,000 person-years, followed by schizophrenia at 352.2 per 100,000 person-years (26). These statistics underscore the severe risk psychiatric conditions pose to life expectancy and mental health.

Beyond the personal and social impact, mental disorders impose a substantial economic burden worldwide. The financial impact associated with mental health includes both direct and indirect expenses. Direct costs include healthcare-related expenses such as medication, therapy, and hospitalization. Due to the chronic nature of many mental health conditions, these healthcare costs can be substantial. For instance, in the United States, the total cost of mental health care exceeded $200 billion in 2013, accounting for a significant portion of overall healthcare spending (27). Similarly, in Europe, the annual costs of mental disorders are estimated at €798 billion, making them some of the most expensive health conditions to manage (28).

However, the indirect costs of mental disorders are often more substantial. These costs include lost productivity, absenteeism, and premature mortality. Depression and anxiety disorders alone are estimated to cost the global economy $1 trillion annually in lost productivity, as individuals affected by these conditions often struggle to work or perform at their full potential (29,30). Unemployment rates are also disproportionately high among individuals with mental disorders. For instance, individuals with schizophrenia face employment rates as low as 10-20% in many countries, influenced by the chronic nature of the illness, as well as barriers such as stigma, discrimination, fear of losing benefits, and lack of appropriate professional support (31,32).

1.3. Challenges on the neurobiology basis

The neurobiological basis of mental disorders is an area of intense research, yet it remains poorly understood. While there has been significant progress in identifying brain regions, neurotransmitter systems, and neural circuits involved in mental disorders such as anxiety, mood, and psychotic disorders, knowledge about the precise mechanisms underlying these conditions is still limited. These challenges are compounded by the complexity of brain function, the dynamic interactions between environmental and genetic factors, and the influence of developmental and life-course changes on brain structure and function.

A significant obstacle in understanding these mechanisms is the heterogeneity among individuals diagnosed with the same label. Mental disorders often encompass a wide range of symptoms, severities, and underlying etiologies, making it difficult to identify universal neurobiological markers. This heterogeneity underscores the need for more refined diagnostic tools that can classify psychiatric conditions into biologically meaningful subtypes. Identifying specific genetic markers, neuroimaging patterns, or biochemical changes associated with the different psychiatric sub-conditions could significantly enhance our knowledge about their biological processes, leading to more accurate diagnoses (33).

The identification of biological markers could not only improve diagnostic accuracy but also help predict treatment responses and personalize care. For instance, specific biomarkers might allow clinicians to determine which patients will likely respond to particular treatments, reducing the current trial-and-error approach in psychiatric care. This would be particularly impactful in conditions like bipolar disorder or schizophrenia, where treatment response often varies significantly among individuals (34). Advances in neuroimaging can help map anatomical and functional disruptions in brain networks associated with these disorders (35,36). At the same time, genetic studies may uncover variants that predispose individuals to certain conditions or treatment outcomes and reveal neural correlates associated with distinct genetic patterns (37). Similarly, biochemical analysis of blood or other biomarkers could provide insights into neuroinflammatory or neuroendocrine pathways involved in mental disorders (38).

Addressing the complexity of understanding the neurobiological basis of mental disorders requires a multidisciplinary approach, integrating neuroimaging, genetics, biochemical analysis, and other advanced methodologies. Leveraging machine learning and big data analytics to analyze these diverse data can unravel the intricate interactions between biological, environmental, and genetic factors, ultimately paving the way for precision psychiatry and improved diagnostic, therapeutic, and preventive strategies.

2. Magnetic resonance imaging

Magnetic Resonance Imaging (MRI) is a non-invasive imaging technique that provides detailed information about the brain's anatomy, function, and physiological processes without ionizing radiation (see Figure 2). This versatile method includes various specialized techniques,

including structural MRI, functional MRI (fMRI), diffusion tensor imaging, and magnetic resonance spectroscopy, each offering unique insights into brain function and structure. Additionally, the development of advanced software for neuroimaging data processing and analysis has enabled the implementation of automated procedures and sophisticated statistical models with high reliability for each imaging modality.

Figure 2. Magnetic resonance scanner (A), structural MRI (B), time-series for the anterior cingulate cortex (ACC) obtained by fMRI (C)

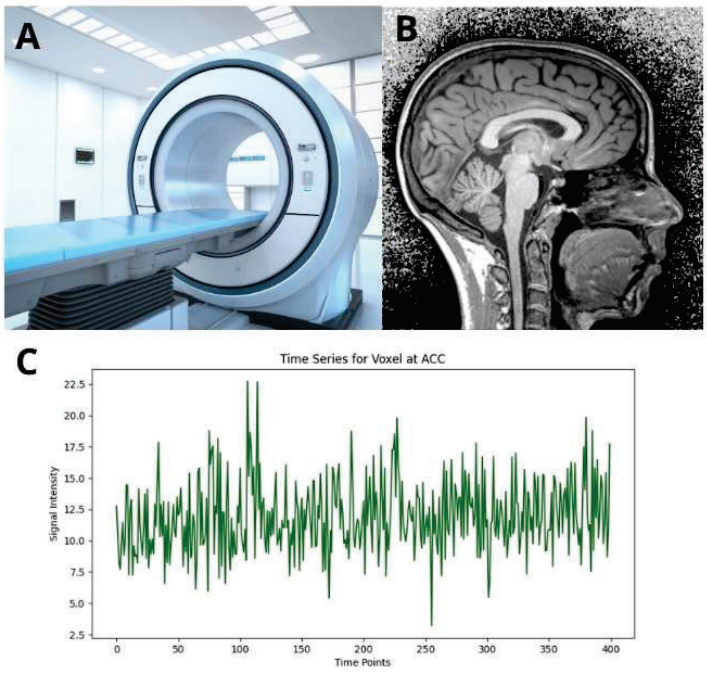


Figure created by the doctoral student. A) is obtained from Canva and is free from copyright restrictions.

2.1. Structural MRI

Structural MRI uses the T1 sequence to generate high-resolution images that distinguish between different brain tissues, such as grey matter, white matter, and cerebrospinal fluid. It also helps identify specific brain regions like the cerebellum, thalamus, and frontal cortex. Structural MRI has been instrumental in uncovering brain anatomical anomalies associated with mental disorders (35,39,40), providing valuable insights into the structural brain differences often presented across various psychiatric conditions. There are several techniques to process and analyze structural MRI data, with voxel-based morphometry (VBM) and

surface-based morphometry being the most widely used methods for whole-brain and region-of-interest analyses, respectively.

2.1.1. Voxel-based morphometry

VBM is a straightforward technique that evaluates small-scale differences in gray or white matter (41). The most common variable investigated with VBM is gray matter volume (GMV), which refers to the amount of gray matter tissue in a specific region or across the whole brain. The VBM process involves several steps: (i) segmentation of brain images into gray matter, white matter, and cerebrospinal fluid, (ii) creation of a template in a common stereotactic space, (iii) spatial normalization of all brain images to align with the template, (iv) modulation of the normalized brain images to preserve tissue volume changes, (v) smoothing the modulate images using Gaussian kernel to ensure that each voxel represents surroundings voxels and (vi) voxel-wise statistical analysis using general linear models to investigate group differences and corrected for multiple comparisons if necessary.

The modulation step preserves the volume of a particular tissue that may grow or shrink after normalization. In effect, analyzing modulated data is thought to assess regional differences in the absolute grey matter volume. In contrast, unmodulated data to evaluate regional differences in grey matter concentration (41), though this idea has been debated (42). The outcome of VBM is a statistical parametric map that highlights regions where gray matter concentration or volume significantly differs between groups. Software that implements VBM on brain image data sequences is Statistical Parametric Mapping (SPM) software (https://www.fil.ion.ucl.ac.uk/spm), FSL (https://fsl.fmrib.ox.ac.uk/fsl/docs/#/) or ANTs (https://github.com/stnava). Figure 3 presents a graphical representation of a group comparison conducted using VBM.

Figure 3. Brain imaging of voxel-based differences between groups depicted in green

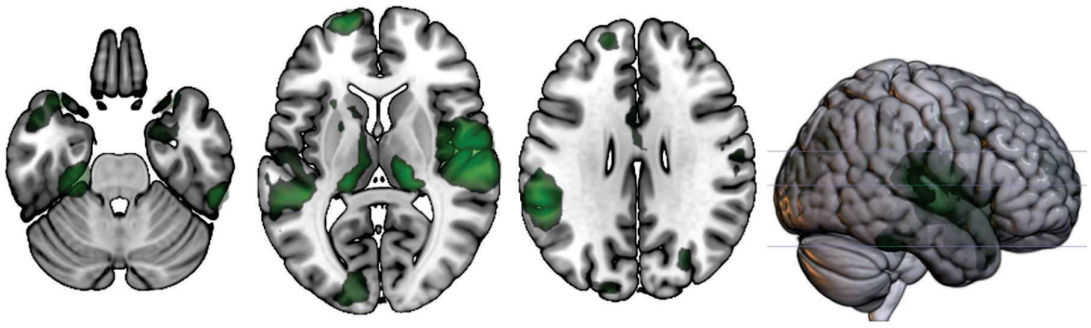


Figure created by the doctoral student

2.1.2. Surface-based morphometry

Surface-based morphometry is a set of techniques to analyze surfaces representing boundaries within the cerebral cortex, providing measures such as cortical thickness, surface area, and others (43). The most widely used software for these analyses is FreeSurfer (http://surfer.nmr.mgh.harvard.edu). However, this thesis focuses specifically on GMV for structural measures, so I will not go into detail on the other surface-based measures.

2.2. Functional MRI

fMRI measures differences in brain activity across time by detecting changes associated with blood flow, offering real-time insights into the functioning of different brain regions. This technique primarily relies on blood-oxygen-level dependent (BOLD) contrast, which detects changes in signal intensity caused by variations in oxygenated and deoxygenated blood. When neurons are active, they consume glucose and oxygen, increasing local blood flow. This process involves two key factors: (i) the over-supply of oxygen to the active area (hyperperfusion) and (ii) the differing magnetic properties of oxygenated and deoxygenated blood. This increase in oxygenated blood alters the MRI signal, allowing brain activity to increase detection.

fMRI has been crucial in studying normal brain function and alterations associated with mental disorders (36,44). There are two main approaches to detecting BOLD response: task-based fMRI, which measures the brain activity changes in response to specific tasks or stimuli, and resting-state fMRI, which measures the baseline brain activity fluctuations when the subject is not engaged in any task.

Pre-processing fMRI data, whether for task-based or resting-state analysis, involves several common steps: (i) slice time correction to adjust for temporal offsets between slices, (ii) motion correction to adjust for subject head motion, (iii) temporal filtering to remove low-frequency drifts and high-frequency noise, (iv) nuisance and physiological noise correction (e.g., cardiac and respiratory artifacts), (v) co-registration with the subject's anatomical MRI scan, (vi) spatial normalization into a common stereotactic space, and (vii) smoothing the normalized images. The specific subject- and group-level analyses differ depending on whether task-based or resting-state fMRI data is being processed. Standard software tools for pre-processing fMRI data include SPM (https://www.fil.ion.ucl.ac.uk/spm), FSL (https://fsl.fmrib.ox.ac.uk/fsl/docs/#/), AFNI (https://afni.nimh.nih.gov/) and FMRIprep (https://fmriprep.org/en/stable/).

2.2.1. Task-based fMRI

Task-based fMRI involves scanning the brain while a subject engages in specific tasks or sensory activities. This method helps identify which regions are activated during various tasks, offering valuable information on the functional specialization of different brain areas. Task-based MRI is widely used to study cognitive and emotional functions such as working memory, attention, emotion recognition, and motor function in healthy individuals and those with mental disorders (45,46).

The analysis of task-based fMRI data typically begins by measuring the BOLD signal as the subject performs a designated task, then comparing these brain activation patterns to those recorded during baseline or control conditions (e.g., comparing the brain activation when observing an angry face versus a neutral face). After pre-processing the fMRI data, a task design matrix is created for each subject to run the first-level (subject-level) analysis (47), including regressors based on the experimental paradigm. Then, a contrast matrix is created to specify the contrast of interest between different conditions. For example, in the previous example, the design matrix would include a regression for both types of stimuli (angry faces and neutral faces), and the contrast matrix would represent the difference in activation between them (e.g., angry faces > neutral faces). Once the first-level analysis is conducted and the images representing the contrast of interest are generated for each subject, a second-level (group-level) analysis is conducted. This step involves performing voxel-wise statistical analysis using general linear models to investigate the average response in a group or the differences between two groups and correct for multiple comparisons, if necessary.

2.2.2. Resting-state fMRI

Resting-state fMRI examines brain activity while the subject is at rest, not engaged in any specific task. This method measures the low frequency (<0.1 Hz) fluctuations in the BOLD signal. Resting-state fMRI provides valuable insights into the brain's intrinsic functional architecture by revealing networks of spatially distinct brain regions that show synchronized activity, even without external stimuli. These functionally connected areas are known as resting-state networks (RSN) and are consistently observed across individuals (48,49).

One of the most common measures obtained from resting-state fMRI is functional connectivity, which assesses the temporal correlation in BOLD signal between different brain regions. Several methods exist to analyze functional connectivity, such as seed-based or independent

component analyses (ICA) (50). The seed-based analysis involves selecting a specific “seed” region and correlating the average BOLD time course of voxels within the seed regions with the times courses of all other voxels in the brain. ICA is a data-driven technique that decomposes pre-processed resting-state fMRI data into spatially and temporally independent components. This approach separates the mixed fMRI signals into underlying source signals or noise, allowing researchers to identify distinct RSNs without requiring a priori selection of specific brain regions.

Some of the most extensively studied RSNs in both healthy individuals and those with mental disorders include the default mode network (DMN), which is active during introspection and mind-wandering; the central executive network (CEN), which is associated with cognitive control and decision-making; and the salience network, which is involved in detecting and filtering salient stimuli. Recent research is investigating alterations in these networks in mental disorders to understand their underlying neurophysiological mechanisms better. For instance, alterations in the DMN have been frequently observed in individuals with depression, highlighting changes in brain functional connectivity that may underlie some of the symptoms of this disorder, such as rumination (44).

2.3. Meta-analysis of MRI data

Beyond the individual-level structural and functional brain information acquired through MRI techniques, the development of advanced software like SDM-PSI (https://www.sdmproject.com) has enabled the integration of the results from multiple studies reporting brain MRI results. This meta-analytical software considers sample size and study heterogeneity, using mixed-effects models to calculate effect sizes for each voxel across the brain and permutations to determine the statistical significance of these effects, correcting for multiple comparisons (51,52). It also includes methods for detecting potential publication bias. SDM-PSI mainly relies on statistical maps of brain images or peaks’ coordinates from results published by the included studies. This approach is especially useful since neuroimaging studies often have relatively small sample sizes due to these procedures’ high costs and complexity. By aggregating data across studies, SDM-PSI facilitates more robust and comprehensive conclusions in neuroimaging research.

3. Brain alterations in mental disorders

Structural and functional brain alterations play a crucial role in understanding the neurobiological basis and pathophysiology of mental disorders. These alterations often highlight differences in brain regions and neural circuits implicated in the symptomatology of mental health conditions. For instance, differences in the size, shape, and connectivity of areas like the prefrontal cortex (PFC), amygdala, hippocampus, and thalamus have been associated with disorders such as schizophrenia, MDD, BD, and anxiety disorders (53). Large-scale meta-analyses and international collaborations, such as the ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis, https://enigma.ini.usc.edu/) consortium, are crucial in advancing this field. By integrating hundreds of datasets from around the globe, these efforts aim to uncover reliable biomarkers and elucidate the neurobiological basis of mental disorders, providing valuable insights into their development, progression, and potential therapeutic targets.

Figure 4. Cortical gray matter thickness alterations mapped across mental disorders.

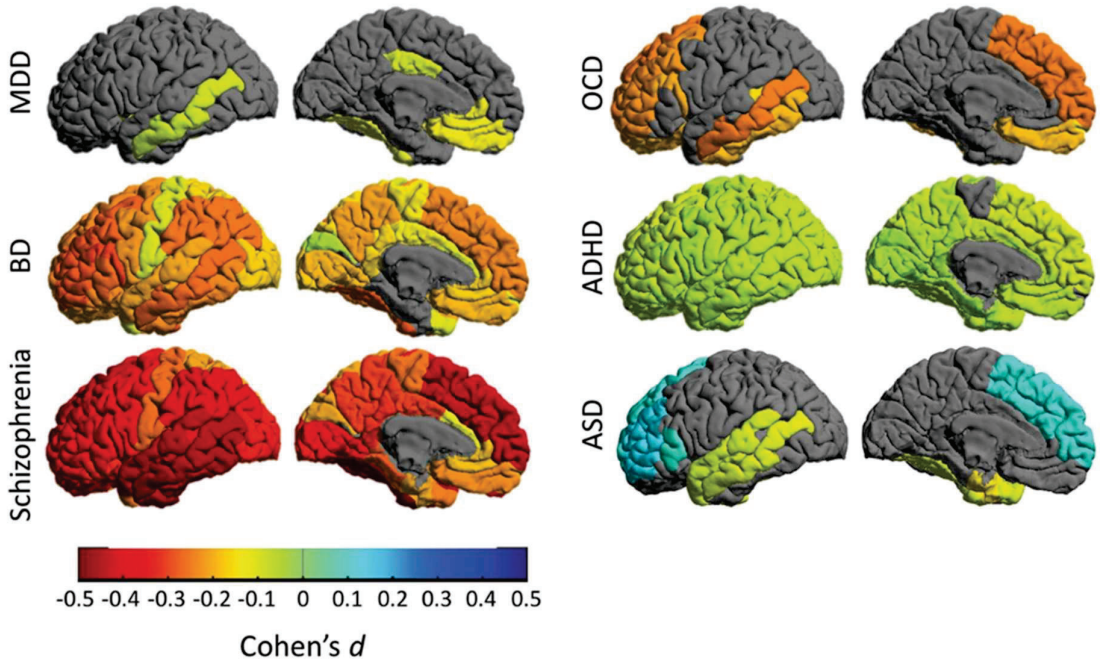


Figure adapted from Thompson et al. (53)*, under the Creative Commons Attribution 4.0 International License (CC BY 4.0). Modifications include displaying only six mental disorders from the original image to fit the thesis objectives. For details on the license, visit http://creativecommons.org/licenses/by/4.0/. Abbreviations: ADHD, attention-deficit/hyperactive disorder; ASD, autism spectrum disorder; BD, bipolar disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder.*

3.1. Anxiety disorders

Anxiety disorders are associated with structural and functional changes in brain regions involved in emotion processing, fear regulation, and executive control, such as the amygdala, PFC, and hippocampus. These areas play crucial roles in managing anxiety and processing memories. Structural neuroimaging studies have commonly reported reductions in GMV in the PFC and hippocampus in specific subtypes of anxiety disorders such as generalized anxiety disorder (35,54). In this context, the likely main role of the PFC is cognitive control, while the likely main role of the hippocampus is contextualizing fear. These structural alterations may thus underlie the difficulties in controlling anxiety and regulating fear responses observed in these disorders.

Similarly, functional neuroimaging studies often find hyperactivity in the amygdala and insula during fear processing in individuals with anxiety disorders, explaining the heightened emotional reactivity and sensitivity to perceived threats (55). This hyperactivity is typically accompanied by a hypoactivation of the PFC, which disrupts the connectivity between these regions, leading to a failure to inhibit the amygdala when regulating emotional and fear responses (56,57). This disruption may contribute to the excessive worry and hypervigilance characteristic of anxiety disorders.

3.2. Mood disorders

Mood disorders, including MDD and BD, are associated with structural and functional changes in several brain regions involved in mood regulation, emotional processing, and cognitive functions, such as the PFC, hippocampus, and amygdala (58).

For MDD, structural neuroimaging studies consistently report reduced volume in the PFC, which seems to be involved in cognitive control and decision-making, and the hippocampus, likely involved in memory formation (35,53). Similarly, functional neuroimaging studies also show decreased activity in these areas and the insula and striatum, which are involved in emotional regulation and motivation (44,59). These structural and functional alterations may underlie some of the core symptoms of MDD, including impaired cognitive function, memory deficits, and difficulties in regulating emotions.

For BD, structural neuroimaging studies also reported reduced GMV in the PFC and hippocampus, but these reductions are generally less pronounced than those seen in MDD (60,61). This discrepancy might reflect differences in the neurobiological basis of the two

disorders. In contrast with MDD, functional neuroimaging studies often show increased functional activity in the PFC, insula, and striatum, which may correspond to the heightened emotional reactivity and impulsivity often observed in manic episodes (44,62). Additionally, BD is associated with alterations in brain networks involved in emotion processing and reward, such as increased activity in the amygdala and altered connectivity within the fronto-limbic circuitry (63,64). These differences in brain structure and function may reflect the distinct clinical presentations of MDD and BD, such as the persistent low mood and anhedonia seen in MDD versus the fluctuating mood states and heightened impulsivity characteristic of BD.

3.3. Psychotic disorders

Psychotic disorders, such as schizophrenia, are characterized by widespread structural and functional changes, particularly in the PFC, hippocampus, thalamus, and temporal lobes (40,65). These regions seem to play a critical role in higher cognitive functions, memory, and sensory processing. Structural neuroimaging studies have often reported reduced GMV across cortical and subcortical areas, with more pronounced effects in the PFC and temporal lobes. These reductions are believed to contribute to the cognitive deficits and hallucinations commonly observed in these disorders (40,65).

Similarly, functional neuroimaging studies have also revealed abnormal brain activity patterns in these areas, even in individuals experiencing their first episode of psychosis (66). Specifically, they showed hypoactivation in the PFC, particularly in the dorsolateral regions, associated with impairments in executive functioning and working memory. In contrast, hyperactivity in the thalamus and temporal lobes, including the auditory cortex, has been associated with positive symptoms of psychosis, such as auditory hallucinations and delusions (67). Additionally, disrupted connectivity between the PFC and other brain regions, particularly the hippocampus and thalamus, is often observed, which may lead to difficulties in filtering relevant information, disorganized thinking, and maintaining cognitive control, further exacerbating the symptoms of psychotic disorders (68).

3.4. Neurodevelopmental disorders

Neurodevelopmental disorders, including ADHD and ASD, are often associated with atypical brain development and connectivity patterns.

In ADHD, structural neuroimaging studies have identified reduced GMV in the PFC, particularly in the dorsolateral and orbitofrontal regions, amygdala, and hippocampus, which

seem to be involved in cognitive functions like attention and impulse control (53,69). Interestingly, these structural alterations are predominantly observed in childhood and tend to diminish in adulthood, suggesting a delay in cortical maturation rather than permanent structural deficits (70). The reduced volume in the PFC and other areas is believed to contribute to the attentional deficits and impulsivity observed in individuals with ADHD. Functional neuroimaging studies have also revealed altered activation patterns in several regions of the fronto-striato-parietal and ventral attention networks. Hypoactivity in the PFC and anterior cingulate cortex (ACC) during tasks requiring executive functions and attention is commonly reported (69). These functional abnormalities may contribute to the difficulties with attention and impulsive control commonly reported in individuals with ADHD. Additionally, hyperactivity in the striatum and other subcortical regions has been observed, suggesting a compensatory mechanism or heightened sensitivity to reward. This increased activity may be associated with impulsive behaviors and difficulty in delaying gratification, often observed in ADHD (71).

In ASD, structural neuroimaging studies had commonly observed GMV alterations in brain regions associated with social cognition, including the amygdala, superior temporal sulcus, and medial PFC (53,69). Reductions in these regions may contribute to the difficulties with social cognition, social interaction, and emotional regulation commonly observed in individuals with ASD. Similarly, functional neuroimaging studies also report alterations in these regions (69,72). Hypoactivation in the amygdala and PFC is often observed during facial recognition and social processing tasks. These alterations may explain the difficulties individuals with ASD face in interpreting social cues and recognizing emotions in others (73).

3.5. Obsessive-compulsive disorder

OCD is associated with structural and functional changes in several brain regions, particularly within the cortico-striato-thalamo-cortical circuitry, which seems crucial for cognitive control, emotion regulation, and habit formation. Disruption in this circuit may contribute to the repetitive behaviors and cognitive rigidity characteristic of OCD. Structural neuroimaging studies have shown both increased and decreased GMV in individuals with OCD (74,75). Specifically, reduced GMV has been observed in cortical areas such as the orbitofrontal and ACC. At the same time, increased GMV has been found in subcortical areas like the putamen or thalamus. These regions are thought to be involved in regulating thoughts and behaviors,

which may contribute to the intrusive thoughts and compulsive behaviors characteristic of OCD (76).

Similarly, functional neuroimaging studies frequently report hyperactivity in the orbitofrontal cortex, ACC, and striatum, especially during error monitoring and conflict resolution tasks. This heightened activity may explain the concern for making mistakes and the repetitive checking behaviors associated with OCD (77). Additionally, altered connectivity between these regions, particularly between the orbitofrontal cortex and the basal ganglia, is often observed, suggesting a disruption in the normal inhibitory control over repetitive thoughts and actions (78).

3.6. Post-traumatic stress disorder

PTSD is associated with structural and functional changes in brain regions involved in fear processing, emotional regulation, and memory formation, including the amygdala, hippocampus, and PFC. Disruptions in these regions are thought to contribute to the heightened emotional reactivity and difficulties in regulating fear responses that are characteristic of PTSD. Structural neuroimaging studies often report reduced GMV in the hippocampus and PFC, which seem crucial for memory and executive function (35,59). These reductions may contribute to the intrusive memories and impaired emotional regulation commonly observed in individuals with PTSD.

Functional neuroimaging studies frequently show hyperactivity in the amygdala when individuals with PTSD are exposed to trauma-related stimuli, reflecting the heightened fear response and emotional reactivity (56,79). In contrast, hypoactivity is often observed in the PFC, particularly in the medial and dorsolateral regions, likely involved in cognitive control and the inhibition of inappropriate emotional responses through their interaction with the amygdala (56,79). Additionally, altered connectivity between the PFC and the amygdala is frequently observed, suggesting a disruption in the neural pathways that typically modulate fear responses and emotional regulation. This disruption may impair the ability to regulate fear and process traumatic memories, leading to persistent symptoms such as hypervigilance and re-experiencing traumatic events in individuals with PTSD (80,81).

3.7. Eating disorders

Eating disorders are associated with structural and functional changes in brain regions involved in reward processing, body image perception, and cognitive control, such as the insula, PFC,

and parietal lobes. However, the nature of these changes can vary depending on the specific subtype of the eating disorder. In anorexia nervosa, structural neuroimaging studies often show reduced GMV in these regions, which may reflect the effects of prolonged malnutrition and the associated cognitive and emotional symptoms observed in these individuals (82,83). The insula, likely involved in processing bodily sensations and self-perception, often exhibits significant volume reductions, potentially contributing to the distorted body image and altered interoceptive awareness characteristic of anorexia nervosa.

Functional neuroimaging studies have commonly observed hypoactivation in the insula and ACC during tasks involving taste, hunger perception, and emotional processing (84). These alterations may explain a diminished response to food-related stimuli and altered reward processing in anorexia nervosa. Conversely, hyperactivity in the orbitofrontal cortex and parietal lobes is often observed, especially in situations involving body image distortion and self-evaluation, which may underlie the obsessive concerns about weight and shape that are central features of anorexia nervosa (85). Additionally, there is often disrupted connectivity between the frontal regions and the limbic system, including the amygdala, suggesting impaired regulation of emotions and reward processing. This disruption may further contribute to the persistence of restrictive eating behaviors and anxiety about gaining weight (86).

3.8. Transdiagnostic brain alterations

Mental disorders had traditionally been defined by distinct symptoms thought to correlate with specific brain alterations. However, they also share common clinical features, suggesting the existence of potential transdiagnostic biomarkers (87). Indeed, favoring this view, genetic studies have revealed shared genetic polymorphisms across various mental disorders, blurring diagnostic boundaries and pointing to common biological pathways (88,89). Growing neuroimaging evidence further supports this idea, highlighting shared neural substrates in phenotypically related conditions like schizophrenia and BD (90,91). In this regard, several studies have identified a transdiagnostic pattern of gray matter loss in key brain regions, such as the anterior insula and dorsal ACC, across disorders including schizophrenia, BD, MDD, anxiety disorders, and OCD (90,91).

The anterior insula and dorsal ACC are core regions of the salience network, responsible for detecting and filtering relevant stimuli and facilitating the switching between the DMN and the CEN (92). The insula plays a significant role in integrating sensory information and emotional regulation, while the dorsal ACC is mainly associated with cognitive control and error motoring

(93–95). Volumetric reductions in these regions may disrupt cognitive and emotional processing integration, leading to attention, decision-making, and emotional regulation impairments. Given these associations, the common GMV loss observed in the anterior insula and dorsal ACC likely contributes to the emotional and cognitive dysfunctions often observed prevalent across psychiatric disorders rather than being diagnosis-specific symptoms (96–98).

4. The problem of heterogeneity

Despite numerous studies investigating brain features statistically associated with mental disorders, there are considerable inconsistencies across reported findings. These discrepancies highlight the complexity of unraveling the neurobiological underpinnings of these conditions, complicating the efforts to develop targeted and effective treatments or therapies. This variability can stem from several factors, including differences in sample size, imaging techniques, and study population. For instance, studies with smaller sample sizes often lack the statistical power to detect subtle brain alterations associated with mental disorders, while larger studies might.

Meta-analytic approaches and large-scale initiatives, such as the ENIGMA consortium, have aggregated data from multiple studies or sites, increasing overall sample size and population diversity to enhance the findings' reliability and generalizability (99). Notably, these large-scale approaches have confirmed that considerable variability exists between studies or sites, suggesting the existence of important sources of heterogeneity such as clinical symptomatology, the presence of cognitive impairments or comorbidities, neurobiological diversity of the mental disorder (i.e., the disorder is associated to more than one pattern of brain differences), medication use, among others (100–102).

Unfortunately, this heterogeneity may have hampered the finding of specific enough MRI biomarkers for individual mental disorders, posing a significant challenge to developing reliable machine-learning tools that could estimate risks to assist clinicians in diagnosing and distinguishing mental health conditions, ultimately leading to earlier and more effective treatments. Machine learning has shown potential in analyzing complex datasets, such as neuroimaging data, by uncovering patterns that traditional statistical methods might overlook (103). However, the heterogeneity of brain alterations among individuals with the same mental disorders, coupled with overlapping features between different disorders, significantly limits

the accuracy and reliability of these predictive models (104). Consequently, current machine-learning applications in psychiatry often struggle to achieve the precision required for clinical use (105).

This limitation underscores the necessity for identifying robust MRI biomarkers that indicate specific risks for specific disorders and developing more sophisticated machine learning algorithms capable of effectively handling the complex and multifaceted nature of mental disorders. Refining these tools has the potential to effectively support clinical decision-making and advance personalized medicine in psychiatry, ultimately improving patient outcomes and treatments.

4.1. Potential sources of this heterogeneity

Several factors may contribute to the observed heterogeneity in neuroimaging findings across mental disorders. One common source of variability is demographic differences within the study population, such as age or sex. For example, several meta-analyses have found distinct patterns of structural brain alterations in individuals with depression depending on the stages of life (106,107). Similarly, studies on schizophrenia have reported more extensive GMV reductions in male-dominated samples compared to those with a more balanced gender distribution (108).

Another key heterogeneity factor stems from the variability in MRI devices and methodologies. Differences in field strength, head coils, or the software used to process the images (e.g., FSL or SPM) can significantly influence findings (109). While using harmonized methods to pre-process the images and mixed/random-effects models helps mitigate these discrepancies, certain sources of heterogeneity are more challenging to control.

Clinical characteristics, such as the age of onset, illness duration, symptom severity, and cognitive performance, are often highly variable and can impact neuroimaging findings. For example, neuro-progressive models of schizophrenia suggest that brain deterioration occurs with the clinical evolution of the disease, with more pronounced brain alterations seen in individuals with longer illness duration (110). Additionally, specific brain alterations associated with schizophrenia, such as GMV reduction in the PFC, have been found to correlate negatively with the severity of negative symptoms (111). Structural and functional brain alterations in the dorsolateral PFC and ACC are commonly associated with cognitive deficits across psychiatric disorders (112).

Differences in genetic haplotypes associated with mental disorders are another source of heterogeneity. For example, a systematic review reported that individuals with BD who carry the brain-derived neurotrophic factor (BDNF) Val66Met allele may have smaller hippocampi volumes (37). Medication use further complicates the picture, as pharmacological treatment can significantly alter or normalize the structure and function of brain regions (113). In one meta-analysis on patients with ADHD, samples with a higher proportion of medicated patients showed a less pronounced GMV reduction in the right caudate compared to non-medicated samples (114). Another critical source of heterogeneity is the presence of co-occurring mental disorders. For example, patients with PTSD and comorbid MDD exhibit more severe hippocampal volume reductions and larger alterations in the DMN connectivity than patients with PTSD alone (115). While some of these sources of heterogeneity can be addressed using secondary analysis like meta-regression, which assesses the impact of covariates on the samples' group-level results, other factors remain challenging to control entirely.

Thus, several sources of heterogeneity can influence the neural correlates of mental disorders. In this thesis, I will focus on three factors: genetic haplotypes, the presence of comorbid cognitive impairments, and the presence of co-occurring mental disorders. Figure 5 illustrates the potential influence of these factors on neuroimaging findings. Please note that the image is entirely hypothetical.

Figure 5. Hypothetical impact of sources of heterogeneity on neuroimaging findings

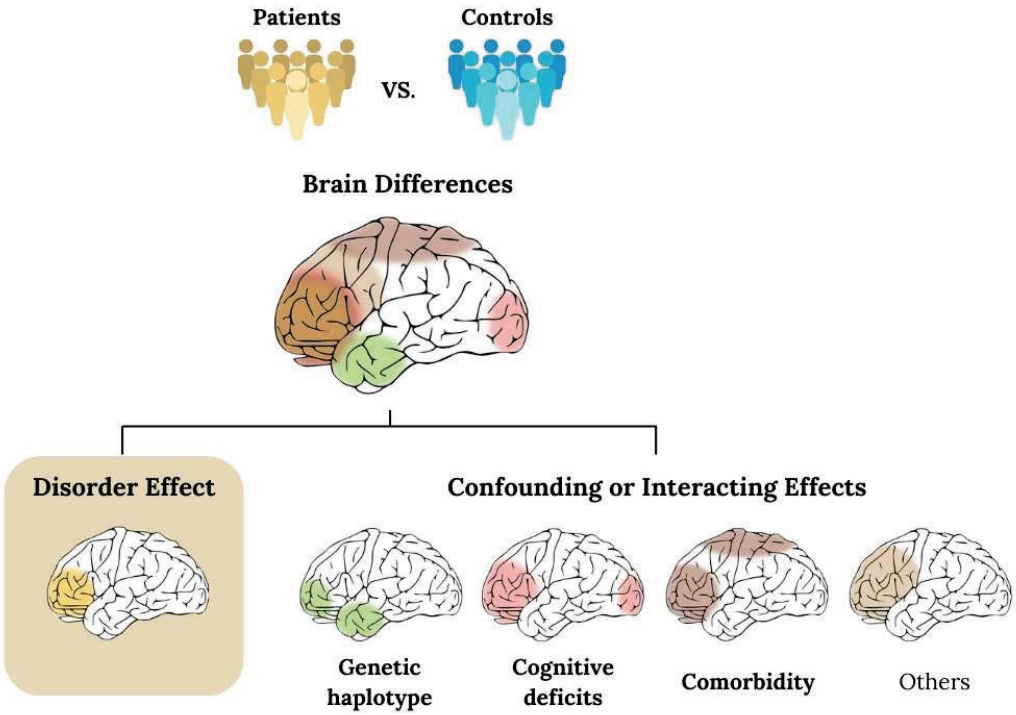


Figure created by the doctoral student. Please note that the image is entirely hypothetical and does not represent actual observed effects.

4.1.1. Genetic haplotypes

Genetic variations play a crucial role in shaping brain structure and function, significantly contributing to the heterogeneity observed in neuroimaging findings among individuals with mental disorders. Studies have shown that genetic polymorphisms in neurotransmitter systems, such as those affecting serotonin and dopamine, can alter brain structure and connectivity. These changes contribute to the variability in neuroimaging outcomes among individuals with similar psychiatric diagnoses (37,116,117). Furthermore, genetic predispositions can influence the expression of psychiatric symptoms and their corresponding neural correlates, resulting in a wide range of neurobiological profiles among patients with the same clinical diagnosis (118). This means that two patients diagnosed with the same disorder may present very different neuroimaging findings due to the underlying genetic differences. For example, higher interindividual variability in both functional connectivity and structural patterns has been observed in schizophrenia. This variability has been linked to polygenic risk scores,

representing the cumulative effect of many genetic variants. Despite similar clinical presentations, these scores reflect the diverse underlying neurobiological pathways (119,120).

Moreover, the impact of genetic variations extends beyond neurotransmitter systems. They also involve genes that affect brain development, neural plasticity, and synaptic function, all critical for normal brain functioning and resilience to mental disorders. The interaction between these genetic factors and environmental influences, such as stress or trauma, can further amplify the variability in neuroimaging findings. This complex interplay suggests that the neurobiological underpinnings of mental disorders are highly individualized, reflecting a mosaic of genetic, environmental, and developmental factors.

Large-scale genetic studies, such as those conducted by the ENIGMA consortium, have further underscored the complexity of the genetic underpinnings of mental disorders and their impact on brain imaging results. These collaborative efforts have identified numerous genetic loci associated with variations in brain structure and function in conditions such as schizophrenia, BD, and MDD (99). These findings suggest that mental disorders are polygenic, involving multiple genetic variants that contribute to subtle changes in brain anatomy and connectivity. The interplay between these genetic factors and environmental influences likely contributes to some of the variability in neuroimaging findings observed in psychiatric research, as individuals with similar genetic risk factors may exhibit different brain alterations depending on their unique experiences and environmental exposures. Additionally, the complex interactions between multiple genetic variants and their cumulative effects on the brain make it challenging to identify distinct neuroimaging patterns for specific disorders.

Importantly, these genetic differences may have two effects on studies investigating the neural correlates of mental disorders. First, they may modulate these neural correlates; for example, among individuals with polymorphism A, patients may show a pattern of differences from controls that is distinct from the pattern observed among individuals with polymorphism B (a statistical interaction). Second, these genetic differences may not modulate the neural correlates of the disorder directly; however, if they are associated with the disorder, they may act as confounding factors. For instance, if patients predominantly have polymorphism A while controls predominantly have polymorphism B, a simple comparison between patients and controls may show brain differences that are attributable to the genetic polymorphism rather than the disorder itself.

4.1.2. Comorbid cognitive impairments

The presence of cognitive impairments within the studied population can significantly contribute to the heterogeneity observed in neuroimaging findings for mental disorders. These impairments are common across a range of diagnoses, particularly in schizophrenia, BD, and MDD, and they often persist during asymptomatic periods (112,121). Increasing evidence suggests that these deficits may predispose individuals to develop these disorders, serving as an early marker of subsequent illness, helping maintain the disorder, and predicting the likelihood of recovery. Indeed, cognitive functioning in some mental disorders predicts long-term illness course independently of symptoms or diagnosis of the illness (112). Cognitive impairments can also vary widely in nature and severity among individuals with the same diagnosis, with some patients being globally impaired while others remain relatively spared in selective domains (122).

Both functional and structural neuroimaging research has consistently shown a strong association between cognitive impairments and brain alterations in psychiatry (66,123). Cognitive impairments are often associated with reduced engagement in stimulating activities, which further impacts brain plasticity and contributes to neuroimaging alterations (124). These impairments have been connected to structural atrophy in critical regions such as the PFC and hippocampus (112), essential for activating task-relevant areas and deactivating those from the DMN. Such alterations in the PFC and hippocampus have been associated with slower processing speed, reduced concentration, and impaired decision-making, particularly in patients with depression and schizophrenia (125,126). Those findings suggest that cognitive impairments modulate the neural correlates of mental disorders. This means that patients with cognitive impairments may exhibit brain alterations compared with healthy controls that are distinct from those observed in patients without such impairments, highlighting the need to consider cognitive status in neuroimaging studies (123).

Although cognitive impairments may influence the neural correlates of mental disorders, they should not probably be considered mere confounding factors, as they are often integral components of certain mental disorders. For instance, comorbid cognitive impairments are part of the clinical symptomatology in conditions like schizophrenia and BD, making it questionable to treat them as external variables to be controlled.

4.1.3. Co-occurring mental disorders

Another significant source of heterogeneity in neuroimaging findings in mental disorders is the presence of co-occurring mental disorders, which is often overlooked in the studies. The co-occurrence of two or more disorders in the same individual is common in psychiatric populations. Approximately half of the individuals with a mental disorder meet the diagnostic criteria for at least one other disorder simultaneously (127). For example, in a meta-analysis of OCD, 75% of the studies included patients with co-occurring mental disorders, such as MDD (up to 40%) or anxiety disorders (up to 80%) (75). Most of these co-occurring disorders could be labeled as 'comorbid' (implying a link between the disorders), although not all of them necessarily have such a link. For simplicity, this thesis uses the terms 'co-occurring' and 'comorbid' interchangeably. This high prevalence of comorbidities, combined with the limited methodologies to account for their effects adequately, significantly influences neuroimaging outcomes, contributing to the complexity of understanding the neural underpinnings of mental disorders (128).

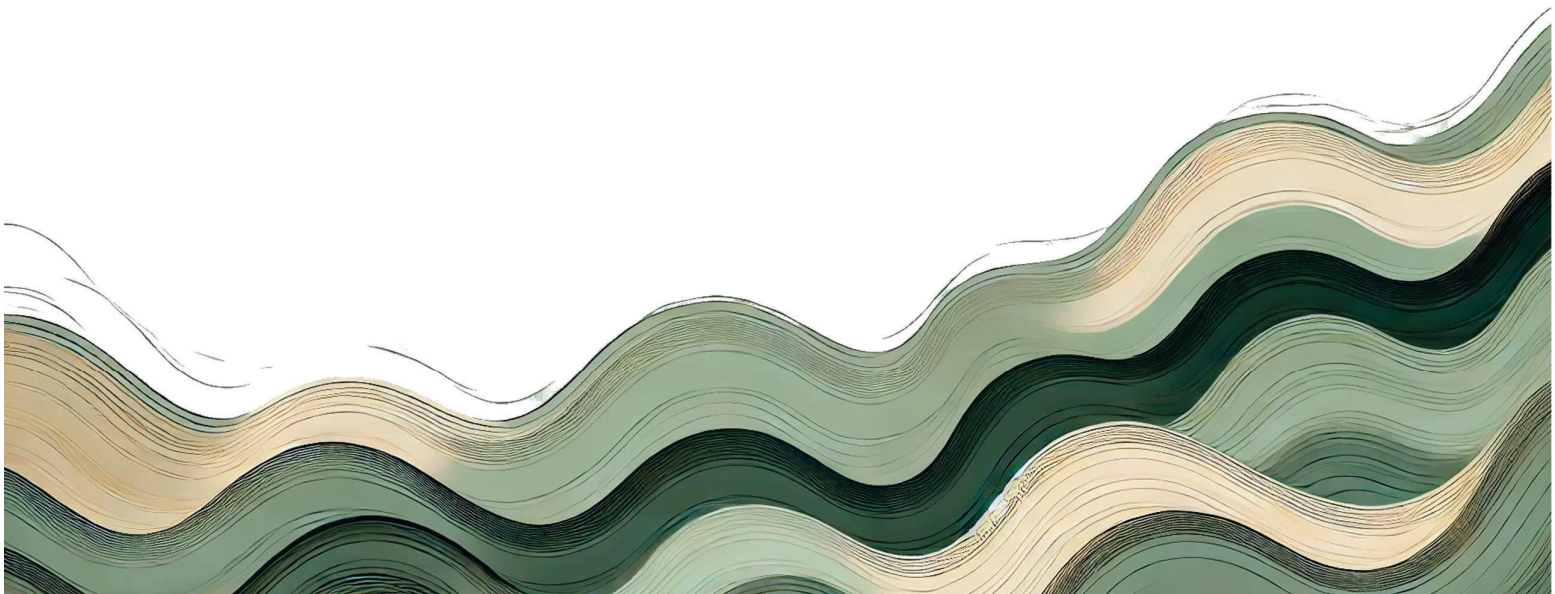
Comorbid disorders can lead to overlapping yet distinct patterns of brain alterations, complicating the interpretation of neuroimaging data and our understanding of the underlying neurobiological mechanisms. For instance, individuals with MDD frequently have comorbid anxiety disorders, which can lead to a complex combination of brain alterations. MDD is typically associated with reduced volume and activity in the PFC and hippocampus, whereas anxiety disorders often involve hyperactivity in the amygdala and altered connectivity in fear-processing circuits (56,58). When these conditions co-occur, the neuroimaging findings can reflect a complex amalgamation of both sets of alterations, complicating the identification of specific neural mechanisms for each disorder separately.

Numerous neuroimaging studies have attempted to address the impact of comorbidity in different ways. Some studies have decided to exclude patients with comorbid disorders to pursue diagnostic purity. However, this approach can lead to non-representative patient groups, consequently limiting findings' generalizability (129). Other studies have decided to include these patients, which may provide more representative patient groups but lead to non-disorder-specific findings influenced by the comorbid disorders. Although some studies that included those patients have attempted to assess the impact of the comorbidities through secondary analyses, robust methods to adequately account for these effects are still lacking. Given the high rates of comorbidity in psychiatric populations, it is crucial to account for these

overlapping conditions to identify more precise biomarkers. This challenge highlights the need for more personalized approaches in psychiatry, considering the full spectrum of an individual's mental health profile, including not one but several disorders.

The presence of co-occurring mental disorders can also have two effects when investigating the neural correlates of a specific disorder. First, they may modulate these correlates; for example, patients with disorder A and co-occurring disorder B may exhibit brain alterations that differ from those observed in patients without comorbidities when compared to controls (a statistical interaction). Second, co-occurring mental disorders can act as confounding factors; when investigating the neural correlates of disorder A, if patients with disorder A also have co-occurring disorder B, a simple comparison between patients and controls may reveal brain differences that are partially attributable to disorder B, potentially leading to less specific findings. Therefore, the presence of co-occurring mental disorders complicates both the interpretation and the precision of identifying the true neural correlates of the primary disorder under investigation.

Hypotheses

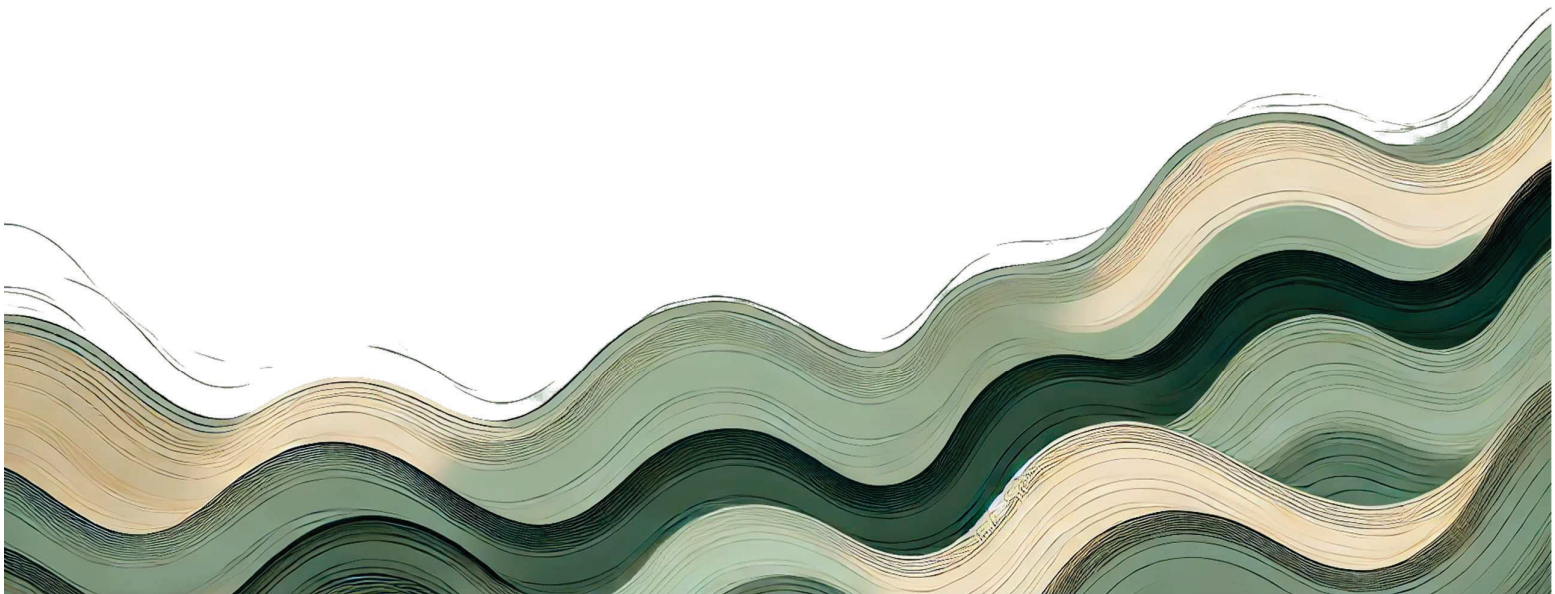


- **Hypothesis A**: The neural correlates of mental disorders depend on the presence of genetic haplotypes, comorbid cognitive impairment, and co-occurring mental disorders:
    - ***H1.*** *The neural correlates of mental disorders depend on the presence of genetic haplotypes.*
    - ***H2.*** *The neural correlates of mental disorders depend on the presence of* comorbid *cognitive impairments.*
    - ***H3.*** *The neural correlates of mental disorders depend on the presence of co-occurring mental disorders.*

- **Hypothesis B**: There are genetic haplotypes and co-occurring mental disorders that confound the analysis of the neural correlates of mental disorders:
    - ***H4.*** *There are genetic haplotypes associated with mental disorders that have relevant neural correlates (thus confounding the analysis of the neural correlates of the mental disorders).*
    - ***H5.*** *There are co-occurring mental disorders that confound the analysis of the neural correlates of mental disorders, making the results more diffuse and unspecific.*

Note: There are no hypotheses regarding confounding effects of comorbid cognitive impairments because the latter might be considered part of some disorders.

Objectives

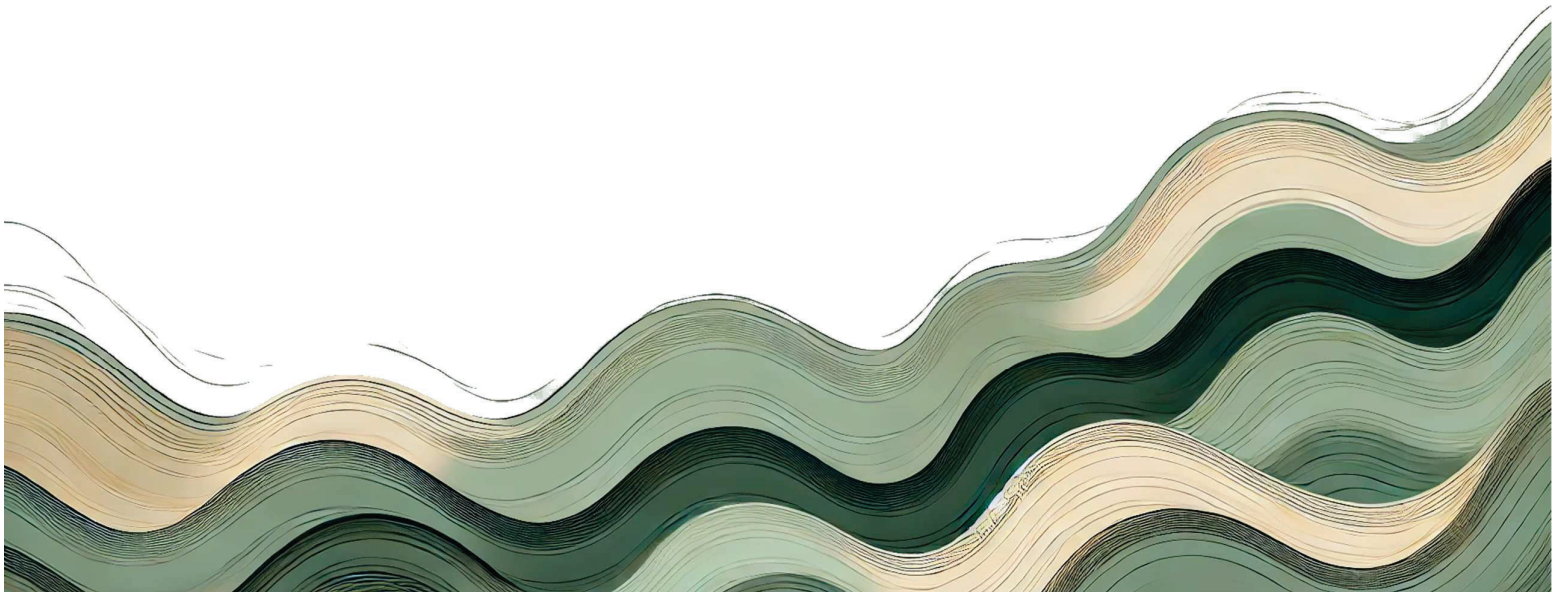


- **Objective A**: To assess whether the neural correlates of mental disorders may depend on genetic haplotypes, comorbid cognitive impairment, or co-occurring mental disorders:
    - ***O1****: To assess whether the neural correlates of a mental disorder may depend on the presence of a genetic haplotype.*
    - ***O2****: To assess whether the neural correlates of a mental disorder may depend on the presence of cognitive impairments.*
    - ***O3****: To assess whether the neural correlates of mental disorders depend on the presence of co-occurring mental disorders.*

- **Objective B**: To control the potential confounding effects of genetic haplotypes and co-occurring mental disorders in the analysis of the mental correlates of mental disorders:
    - ***O4****: To assess whether haplotypes associated with mental disorders may have relevant neural correlates when considering both the effects of the mental disorders and the genetic haplotypes.*
    - ***O5****: To assess whether the analysis of the neural correlates of mental disorders yields more focal and specific results when covarying with co-occurring disorders.*

- **Objective C**: To create an anatomical atlas of mental disorders for future studies:
    - ***O6****. To create an atlas mapping both disorder-specific and transdiagnostic gray matter volume alteration statistically associated with major mental disorders, accounting for the confounding effect of co-occurring disorders.*

Material, methods, and results



Study I

Brain structural and functional substrates of *ADGRL3* (*latrophilin 3*) haplotype in attention-deficit/ hyperactivity disorder

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Brain structural and functional substrates of *ADGRL3* (*latrophilin 3*) haplotype in attention-deficit/hyperactivity disorder

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Previous studies have shown that the gene encoding the adhesion G protein-coupled receptor L3 (*ADGRL3*; formerly *latrophilin 3*, *LPHN3*) is associated with Attention-Deficit/Hyperactivity Disorder (ADHD). Conversely, no studies have investigated the anatomical or functional brain substrates of *ADGRL3* risk variants. We examined here whether individuals with different *ADGRL3* haplotypes, including both patients with ADHD and healthy controls, showed differences in brain anatomy and function. We recruited and genotyped adult patients with combined type ADHD and healthy controls to achieve a sample balanced for age, sex, premorbid IQ, and three *ADGRL3* haplotype groups (risk, protective, and others). The final sample (n = 128) underwent structural and functional brain imaging (voxel-based morphometry and n-back working memory fMRI). We analyzed the brain structural and functional effects of ADHD, haplotypes, and their interaction, covarying for age, sex, and medication. Individuals (patients or controls) with the protective haplotype showed strong, widespread hypo-activation in the frontal cortex extending to inferior temporal and fusiform gyri. Individuals (patients or controls) with the risk haplotype also showed hypo-activation, more focused in the right temporal cortex. Patients showed parietal hyper-activation. Disorder-haplotype interactions, as well as structural findings, were not statistically significant. To sum up, both protective and risk *ADGRL3* haplotypes are associated with substantial brain hypo-activation during working memory tasks, stressing this gene's relevance in cognitive brain function. Conversely, we did not find brain effects of the interactions between adult ADHD and *ADGRL3* haplotypes.

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	All participants	ADHD status		Haplotype		
		Patients	Healthy controls	Protective	Risk	Other
All haplotypes						
Group size	128	64	64	42	51	35
Age (mean ± SD)	36.2 ± 11.9	36.2 ± 12.0	36.2 ± 11.8	36.0 ± 10.8	37.1 ± 12.3	35.3 ± 12.6
Sex (% males)	57.0%	65.6%	48.4%	57.1%	60.8%	51.4%
TAP score (mean ± SD)	22.9 ± 4.9	22.6 ± 5.1	23.1 ± 4.7	22.9 ± 5.0	23.0 ± 5.0	22.7 ± 4.7
Homo/heterozygosis	–	–	–	9/33	16/35	–

Table 1. Description of the sample. TAP: "*Test de Acentuación de Palabras*" (an indicator of premorbid IQ).

Attention-deficit/hyperactivity disorder (ADHD) is one of the most frequent behavioral psychiatric disorders in childhood; it affects ~ 5–6% of children and adolescents and has impairing symptoms that persist in more than 50% of adults[1]. The disorder is characterized by pervasive inattention and/or hyperactivity and impulsivity, associated with social and/or educational/occupational impairments[2]. Some patients have inattention predominantly (e.g., they make careless mistakes, are forgetful, etcetera). Other patients have hyperactivity and impulsivity mainly (e.g., they get up often when seated, talk out of turn, etcetera). Still, most patients have a "combined type" ADHD involving inattentive and hyperactive-impulsive symptoms.

Previous studies have reported several environmental factors that may increase the risk of ADHD, such as maternal pre-pregnancy overweight, preeclampsia, hypertensive disorders, acetaminophen exposure or smoking during pregnancy, childhood eczema or asthma, or vitamin D deficiency[3]. However, family, twin, and adoption studies have repeatedly demonstrated the substantial influence of genetic factors, with heritability estimated to be around 76%[4,5].

Meta-analyses of candidate genes and genome-wide association studies (GWAS) have identified several genes and loci associated with ADHD[6–9]. One leading candidate gene is the *BAIAP2* (brain-specific angiogenesis inhibitor 1-associated protein 2), which has shown a consistent association with ADHD across studies[8] and meta-analytic statistical significance even after Bonferroni correction. Besides, a recent meta-analysis has highlighted another candidate gene repetitively associated with ADHD, the *ADGRL3* (adhesion G protein-coupled receptor L3; formerly *LPHN3*, latrophilin 3)[9–12].

Magnetic resonance imaging (MRI) studies have described several structural and functional brain abnormalities in patients with ADHD, including decreased gray matter volume in the motor area, prefrontal cortex, and age-dependent volume in basal ganglia[13–16]. Studies have also identified reduced brain response to cognitive tasks in the same brain regions, although the evidence is still weak and needs further investigation[15–20].

Given the association between *ADGRL3* haplotype and ADHD, and the consistency of structural and functional brain studies, we aimed to investigate the relationship between *ADGRL3* haplotypes and the brain abnormalities to characterize the brain structural and functional differences between ADHD patients and controls depending on their *ADGRL3* haplotype. To this end, we recruited, genotyped, and MRI-scanned 64 patients with combined type ADHD and 64 healthy controls, balanced for age, sex, premorbid IQ, and *ADGRL3* haplotypes. We exploratorily hypothesized that beyond the brain structural and functional effects of ADHD, there could be effects of the haplotypes and even effects of the interaction between ADHD and the haplotypes. The latter would mean that the brain correlates of ADHD depend on the haplotype. This finding would be interesting to understand the disease better and pave the way for a haplotype-based personalization of non-invasive brain stimulation therapy[21].

Results

Participants. The final sample included 128 participants (64 patients and 64 controls), of which 42 (21 patients and 21 controls) were homo- or heterozygous for the protective haplotype, and 51 (28 patients and 23 controls) were homo- or heterozygous for the risk haplotype. As shown in Table 1, there were no substantial differences between patients and controls or between haplotype groups on age (mean: patients 36, controls 36, protective haplotype 36, risk haplotype 37, and other haplotypes 35 years; SD around 12 years), sex (patients 66%, controls 48%, protective haplotype 57%, risk haplotype 61%, other haplotypes 51% males), and premorbid IQ (TAP score mean: patients 23, controls 23, protective haplotype 23, risk haplotype 23, other haplotypes 23; SD around 5). The ratio of homozygosis vs. heterozygosis of the risk haplotype was higher in patients with ADHD than in healthy controls (patients 14 homozygous and 14 heterozygous, healthy controls: 2 homozygous and 21 heterozygous, chi-square p-value = 0.004).

Structural findings. We did not observe any statistically significant ADHD or *ADGRL3* haplotype effects after correction for multiple comparisons.

However, for the sake of exhaustivity, we report here (but not further discuss) the findings at uncorrected $p < 0.001$ level (Fig. 1 and Table 2). First, individuals (patients or controls) with the protective haplotype showed decreased gray matter in the right supramarginal gyrus compared to individuals without the protective haplotype (see details in Table 2). Second, individuals (patients or controls) with the risk haplotype showed increased gray matter in several frontotemporal regions and decreased gray matter in inferior temporal/fusiform gyrus compared to individuals without the risk haplotype. Third, patients with ADHD showed increased gray matter

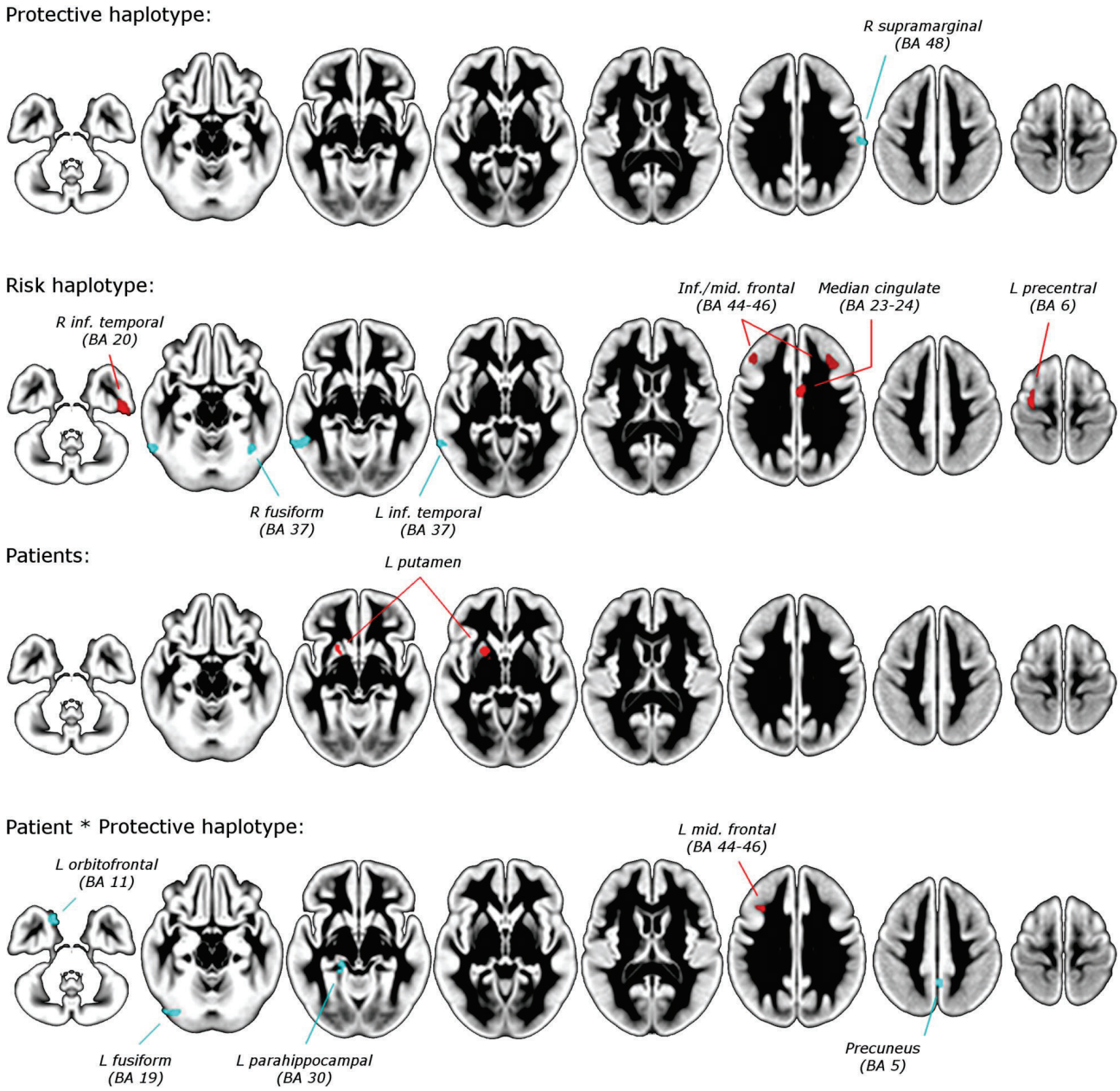

Figure 1. Brain increases and decreases of gray matter volume depending on *ADGRL3* haplotypes and the attention-deficit/hyperactivity disorder (ADHD) status, using uncorrected p-value < 0.001. Top: Volumetric differences in individuals (patients or controls) with the protective haplotype. Middle/top: Volumetric differences in individuals (patients or controls) with the risk haplotype. Middle/bottom: Volumetric differences in patients with ADHD relative to healthy subjects. Bottom: Volumetric interaction between ADHD status and protective haplotype. Areas in red indicate significantly more gray matter in individuals with the haplotype or patients or a positive interaction between the disorder and the haplotype; blue areas indicate substantially less gray matter in individuals with the haplotype or negative interaction between the disorder and the haplotype. Differences were not statistically significant after correction for multiple comparisons.

in the left putamen as compared to healthy controls. Finally, we observed interactions between the protective haplotype and ADHD status in the left middle frontal gyrus, orbitofrontal, fusiform, parahippocampal gyri, and precuneus. The interaction in the left middle frontal gyrus was positive: we observed a trend-level increase in individuals with protective haplotype, a trend-level increase in patients, and an extra increase in patients with protective haplotype. The interactions in the other regions were negative: we did not observe any overall effect of protective haplotype or disorder, but a decrease in patients with protective haplotype.

Functional findings. The performance of the different groups in the n-back task was mostly similar. We only observed a marginal increase of d' in individuals with the protective haplotype in the 2-back task ($t = 2.04$, uncorrected p-value = 0.043).

		Peak MNI	Peak t-value	Cluster size	Cluster breakdown
Gray matter decreases in individuals with protective haplotype[a,b]					
Modulated	R supramarginal	60, -20, 24	4.116	116	R supramarginal (112)
Gray matter increases in individuals with risk haplotype[a,b]					
Unmodulated	Median cingulate	4, − 2, 32	4.285	99	Median cingulate (67)
	L precentral	− 30, − 14, 58	4.331	81	L precentral (72)
Modulated	R inf. temporal	52, − 18, − 38	4.668	197	R inf. temporal (123)
	R mid. frontal	38, 24, 30	3.563	76	R mid. frontal (15)
	L inf. frontal	− 42, 30, 28	3.734	72	L inf. frontal (33) L mid. frontal (29)
Gray matter decreases in individuals with risk haplotype[a,b]					
Modulated	L inf. temporal	− 56, − 52, − 12	4.004	269	L inf. temporal (165) L mid. temporal (89)
	R fusiform	40, − 58, − 20	3.549	100	R fusiform (54) R cerebellum (39)
Gray matter increases in patients					
Unmodulated:	L putamen	− 18, 8, − 4	3.613	61	L putamen (13)
Modulated:	L putamen	− 18, 6, − 2	3.678	53	L putamen (10)
Interaction: gray matter increases in patients with protective haplotype[b,c]					
Unmodulated	L mid. frontal	− 32, 22, 32	4.545	50	L mid. frontal (9)
Interaction: gray matter decreases in patients with protective haplotype[b,d]					
Unmodulated	L orbitofrontal	− 16, 16, − 24	3.787	98	L orbitofrontal (29) L sup. temporal (22) L mid. temporal (16)
	L fusiform	− 34, − 78, − 16	3.956	71	L fusiform (39)
	L parahippocampal	− 18, − 32, − 10	3.920	54	L parahippocampal (3)
Modulated	Precuneus	2, − 50, 50	3.478	90	Precuneus (90)

Table 2. Effects of ADHD and *ADGRL3* haplotypes on gray matter volume (Contrasts Patients < controls, Protective > other haplotypes, and Patients with Risk > or < Controls with other haplotypes, did not returned significant results). *Inf.* Inferior, *L* left, *mid.* Middle, *R* right, *sup.* superior. [a]In the absence of disorder-haplotype interactions. [b]We compared risk and protective haplotype to other haplotypes. [c]Trend-level increase in individuals with protective haplotype, trend-level increase in patients, and extra increase in patients with protective haplotype. [d]No overall effects of protective haplotype or disorder, but decrease in patients with protective haplotype.

The fMRI study's main finding was a widespread hypo-activation in the 1-back vs. baseline contrast in individuals (patients or controls) with the protective haplotype (compared to individuals without the protective haplotype; Table 3 and Fig. 2). This hypo-activation especially included the inferior, superior, and middle frontal gyri, the inferior and middle temporal gyri, the anterior and median cingulate cortices, and to a lesser extent, the fusiform gyrus, the cuneus/precuneus, the supplementary motor area, the inferior and middle occipital gyri, the cerebellum, the supramarginal gyrus, the insula, the thalamus, the caudate, the parahippocampal gyrus, the putamen, and several other regions (see details in Table 3). The 2-back vs. baseline comparison showed hypo-activation, although this was less statistically significant and more circumscribed to the frontal gyri.

Individuals (patients or controls) with the risk haplotype also showed hypo-activation compared to individuals without risk haplotype, but it was substantially less extensive in the 1-back vs. baseline contrast. It only comprised the caudate, the olfactory and anterior cortices, and the rectus gyri. In the 2-back vs. baseline contrast, it was more extensive. It included the middle, superior, and inferior frontal gyri, the middle and superior temporal gyri, and to a lesser extent, the supramarginal gyrus, the caudate, the anterior cingulate cortex, and several other regions.

Finally, patients with ADHD showed hyper-activation of the inferior parietal, the angular, and the superior occipital gyri in the 2-back vs. baseline contrast compared to healthy controls.

We did not find any statistically significant effect for the other contrasts or interactions between ADHD status and *ADGRL3* haplotypes.

Discussion

This study explored brain structural and functional differences between *ADGRL3* haplotypes, between patients with ADHD and controls, and their interactions. The main findings were the widespread strong effects of *ADGRL3* haplotypes on the brain response to work the memory task. Conversely, contrary to our hypothesis, we did not find the brain effects of the interactions between *ADGRL3* haplotypes and adult ADHD.

Specifically, individuals (patients or controls) who were homo- or heterozygous for the protective *ADGRL3* haplotype showed extensive hypo-activation compared to individuals without the protective haplotype. Surprisingly, individuals (patients or controls) who were homo- or heterozygous for the risk haplotype also showed

		Peak MNI	Peak z-value	Cluster size	Cluster p-value	Cluster breakdown
Hypo-activation in individuals with protective haplotype[a,b]						
1-back:	Frontal/cingulate	− 4, − 20, 18	5.03	10,064	< 0.001	L sup. frontal (1011) L inf. frontal (798) R sup. frontal (599) L mid. frontal (556) Ant. cingulate (547) Median cingulate (519) R mid. frontal (459) L supplementary motor area (294) R supplementary motor area (281) L insula (248) R caudate (133) R precentral (128) L putamen (124) L thalamus (100) R thalamus (97) L caudate (61) R putamen (58) R insula (41) L sup. temporal (39) R inf. frontal (27) L gyrus rectus (16)
	R temporal/fusiform	14, − 88, − 18	4.24	4382	< 0.001	R inf. temporal (526) R fusiform (381) R mid. temporal (356) R cerebellum (320) Cuneus (255) Precuneus (223) R mid. occipital (149) R parahippocampal (129) R inf. occipital (127) R lingual (89) R sup. occipital (87) R angular (87) R sup. parietal (70) L calcarine (44) L sup. occipital (38) R calcarine (31) L sup. parietal (11)
	R inf. frontal	58, 16, 14	4.47	1356	< 0.001	R inf. frontal (1100) R insula (21) R sup. temporal (13) R Rolandic operculum (12) R precentral (10)
	L inf. temporal	− 52, − 46, − 18	4.53	901	0.007	L inf. temporal (507) L fusiform (153) L cerebellum (111) L mid. temporal (24) L inf. occipital (19)
	L fusiform	− 26, − 32, − 20	3.86	871	0.009	L fusiform (164) L mid. temporal (75) L parahippocampal (65) L hippocampus (61) L inf. temporal (18) L insula (13) L cerebellum (13) L putamen (10)
	R supramarginal	60, − 38, 34	4.28	853	0.011	R supramarginal (386) R inf. parietal (179) R sup. temporal (62)
2-back:	R inf. frontal	52, 50, 16	3.87	843	0.008	R inf. frontal (567) R mid. frontal (52) R sup. frontal (39) R sup. temporal (39)
	L inf. frontal	− 8, 2, − 10	3.83	710	0.021	L inf. frontal (150) L putamen (45) L insula (27) L sup. temporal (12)
Hypo-activation in individuals with risk haplotype[a,b]						
1-back:	L caudate	− 6, 18, 6	3.87	1.063	0.002	L caudate (115) Ant. cingulate (54) L olfactory (38) R caudate (34) R olfactory (29) R gyrus rectus (22) L gyrus rectus (18)

Continued

		Peak MNI	Peak z-value	Cluster size	Cluster p-value	Cluster breakdown
2-back:	R temporal/supramarginal	52, − 32, 6	4.11	3881	< 0.001	R mid. temporal (408) R supramarginal (303) R sup. temporal (231) Ant. cingulate (124) R inf. frontal (99) R calcarine (83) R caudate (76) L caudate (67) R postcentral (60) R sup. frontal (57) R inf. parietal (47) R inf. temporal (43) R lingual (38) L olfactory (35) R amygdala (34) R olfactory (31) R mid. frontal (24) R insula (16) R Heschl (16) R Rolandic operculum (15) R hippocampus (12) Precuneus (10)
	L mid. frontal	− 18, 24, 50	3.9	837	0.008	L mid. frontal (412) L sup. frontal (163) L supplementary motor area (15)
	R lingual	16, − 32, 0	3.98	646	0.033	R lingual (92) R hippocampus (66) R thalamus (57) R cerebellum (44) Vermis (10)
Hyper-activation in patients						
2-back:	R angular/occipital	38, − 74, 52	4.31	901	0.005	R angular (296) R sup. occipital (223) R mid. occipital (27) R inf. parietal (18)
	L inf. parietal	− 52, − 52, 46	3.39	708	0.021	L inf. parietal (323) L angular (93) L sup. parietal (52)

Table 3. Effects of ADHD and *ADGRL3* haplotypes on the brain response during n-back task (Contrasts Patients < controls, Risk > other haplotypes, and interactions, did not returned significant results). *Ant.* Anterior, *Inf.* Inferior, *L* left, *mid.* Middle, *R* right, *sup.* superior. [a]In the absence of disorder-haplotype interactions. [b]We compared risk and protective haplotype to other haplotypes.

hypo-activation compared to individuals without the risk haplotype. We must acknowledge that we do not know the functional meaning of these hypo-activations or whether they may relate or not to the protective and risk effects of these haplotypes.

Intriguingly, previous meta-analyses have shown widespread hypo-activation in patients with ADHD[17], whereas we found them to show hyper-activation. On the other hand, hypoactivation patterns in individuals with risk ADGRL3 haplotype compared to individuals with the protective haplotype were significantly higher and more extensive in the 2-back versus baseline contrast, that is, when the difficulty of the task increased. Hypoactivation patterns have been regularly reported in studies using working memory tasks in children and adolescents with ADHD, but not consistently in adult patients with the disorder. Considering the above, a potential explanation for these opposite observations could be that the hypo-activation reported in previous ADHD studies is indeed due to the more frequency of ADGRL3 risk haplotype in the patients rather than to ADHD-related executive cognitive failures. However, other explanations are possible because activation may depend on a variety of factors. For example, individuals who do not attend the task will have little or no activation, and both the disorder and the *ADGRL3* haplotype may probably affect the attention to the task. Besides, some authors have associated activation with task accuracy but also longer reaction time[22,23]. Even methylphenidate may play a role[24], although its involvement in working memory networks is unclear[25]. With these considerations in mind, one could hypothesize that hypo-activation in individuals with the protective haplotype and hypo-activation in patients with ADHD have different origins. For example, individuals with the protective haplotype might require weaker brain activation to attend, whereas individuals with a "tendency" to ADHD might have difficulty to activate. Under these hypotheses, individuals with a tendency to ADHD but protective haplotype would seldom develop the disorder because their lower activation requirement would cancel out their difficulty to activate. Of course, such speculations are only hypotheses. We encourage future studies to investigate them.

We failed to detect statistically significant interactions between adult ADHD and *ADGRL3* haplotypes. We found some interactions between the effects of *ADGRL3* haplotypes and disorder on brain morphometry. Still, readers should take them with caution because they did not survive the correction for multiple testing. In this regard, a recent meta-analysis has found that *ADGRL3* haplotypes confer a relevant risk in pediatric ADHD, but results were less significant in adult ADHD[9]. The meta-analysis and our study investigated different phenomena,

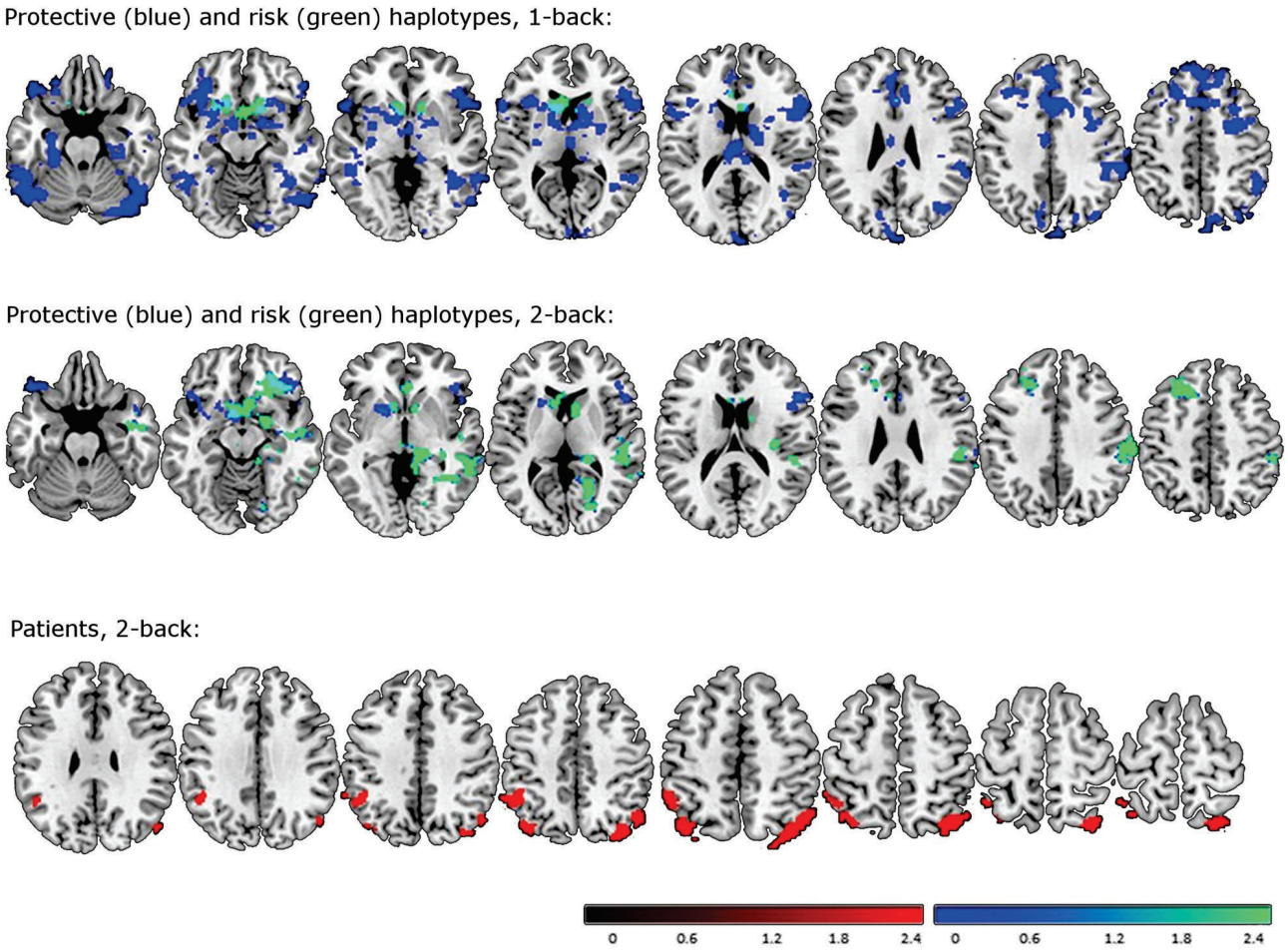

Figure 2. Brain hyper- and hypo-activation depending on *ADGRL3* haplotypes and the attention-deficit/hyperactivity disorder (ADHD) status during the N-back task. Top: Hypo-activation in individuals (patients or controls) with the protective haplotype (blue) and with the risk haplotype (green) during the performance of the 1-back task vs. baseline. The light-blue color shows overlap regions in both groups. Middle: Hypo-activation in individuals (patients or controls) with the protective haplotype (blue) and with the risk haplotype (green) during the performance of the 2-back task vs. baseline. The light-blue color shows overlap regions in both groups. Bottom: Hyper-activation in patients with ADHD relative to healthy control during the 2-back vs. baseline task. Color bars indicate z-values from the group-level analysis.

as the former reviewed studies of the association between the haplotypes and ADHD, and the latter investigates their brain correlates. However, there is a possibility that the weaker association between *ADGRL3* haplotypes and ADHD in adults may explain why we did not found evidence of any brain effect of the interactions in our study.

Even if we failed to detect interactions between the haplotype and the disorder, we still found an impressive result: *ADGRL3* protective and risk haplotypes significantly impact the brain response to a working memory task. Interestingly, the *ADGRL3* haplotype with a larger effect was the protective one, while the risk haplotype effect was weaker.

Structural effects were not statistically significant after correction for multiple comparisons. However, this lack of statistical significance is not surprising in ADHD literature, where some studies have reported frontostriatal abnormalities that may change with age and/or treatment, while others have failed to detect them[13,15,19,20,26,27]. In agreement with previous literature, we found more robust evidence of functional brain abnormalities than structural brain abnormalities in ADHD.

This study has several limitations. First, despite our efforts to achieve a finely balanced sample, the ratio of homozygous vs. heterozygous for the protective and risk haplotypes was higher in patients with ADHD than in controls. This imbalance means that we might have potentially erroneously attributed differences between the haplotypes' homozygotic and heterozygotic effects to the ADHD status or its interaction with haplotypes. However, this possibility seems unlikely to have had a significant consequence because our study's main findings were indeed the haplotypes' effects. Second, even if the global sample is moderately large for a neuroimaging study, it may still involve a limited statistical power to detect weaker effects. This little power may have affected, for example, the comparison of patients vs. controls, given the weak findings reported in previous meta-analyses[13,17]. It might also be the case for interactions between the haplotypes and the disorder. However, we were still able to detect hypo-activations that were very statistically significant, or in other words, very unlikely due to chance.

Third, our sample included adults, and a recent meta-analysis reported that the effects of *ADGRL3* haplotypes depend on age[9]. Finally, we scanned the individuals in a 1.5 T device, and the functional sequence had a thickness of 7 mm with a 0.7 mm gap. We started the study with this configuration years ago. When higher resolutions were available, we decided not to change them to scan all the study participants with the same parameters. These suboptimal MRI settings may also have limited, to some degree, the statistical power of the study. Again, this potentially lower statistical power did not prevent us from detecting extensive effects of *ADGRL3* haplotypes.

To sum up, in this study, we failed to detect interactions between adult ADHD and *ADGRL3* haplotypes. Still, we found that both protective and risk of *ADGRL3* haplotypes are associated with a critical brain hypo-activation during a working memory task, a result that stresses the relevance of this gene in cognitive brain function and warrants further study.

Materials and methods

Participants. We recruited patients with combined type ADHD and healthy controls from Vall d'Hebron University Hospital and Benito Menni CASM. We genotyped them to obtain a sample of patients and controls balanced for age, sex, premorbid IQ, and the three *ADGRL3* haplotype groups ("risk," "protective," and "others," see below). Given that haplotype frequencies differed between patients and controls, this approach involved genotyping many more individuals than those we finally included in the MRI study.

Experienced psychiatrists established the diagnosis of ADHD based on the Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revised (DSM-IV-TR)[2] and confirmed with the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID)[28,29], the Wender Utah Rating Scale (WURS)[30], the ADHD Rating Scale[31], and the Conners Adult ADHD Rating Scale (CAARS)[32]. Exclusion criteria were: (a) age younger than 18 or older than 65 years, (b) left-handedness, (c) history of brain trauma, neurological disease or systemic disease with potential brain affection (e.g., congenital hypothyroidism), (d) substance use disorder (abuse/dependence) of drugs including cocaine, heroin, synthetic drugs or alcohol, (e) IQ < 70 estimated from WAIS-III vocabulary and block design subtests, and (f) comorbid major psychiatric or personality disorders. The psychiatrist assessed the latter using the Structured Clinical Interview for Axis I (SCID-I)[33] and Axis II (SCID-II)[34], respectively.

We recruited the healthy controls from non-medical staff, their relatives and acquaintances, and independent sources in the community. They met the same exclusion criteria as the ADHD group. We also excluded them if they: (a) took any psychotropic medication other than non-regular use of benzodiazepines or other similar drugs for insomnia, or (b) had a first-degree relative who had experienced symptoms consistent with a major psychiatric disorder and/or had received in- or outpatient psychiatric care.

The final sample of brain imaging participants was balanced for age, sex, premorbid IQ, and *ADGRL3* haplotype. We estimated premorbid IQ with the "*Test de Acentuación de Palabras*" (TAP), a test requiring pronunciation of Spanish words with accents removed[35], analog to the National Adult Reading Test (NART)[36]. The reason to use this test is that *individuals preserve* the pronunciation of words learned before the disorder's onset. Thus a pronunciation test may be useful to estimate the premorbid IQ[37]. We acknowledge that this estimation is more advantageous for cognitive conditions such as dementia than for ADHD. However, we considered it would still be helpful here to avoid mixing any effects of the disorder on the IQ.

The Clinical Research Ethics Committees of both Germanes Hospitalàries (for FIDMAG/Hospital Benito Menni) and Hospital Universitari Vall d'Hebron (Barcelona, Spain) approved the study. We performed all methods following the relevant guidelines and the Declaration of Helsinki and regulations, and we obtained written informed consent from all subjects before inclusion into the study.

DNA isolation and genotyping. We isolated genomic DNA from peripheral blood lymphocytes using the salting-out procedure[38] or saliva using the Oragene DNA Self-Collection Kit (DNA Genotek, Kanata, Ontario, Canada). DNA concentrations were determined using the Pico-Green dsDNA Quantitation Kit (Molecular Probes, Eugene, OR).

We carried out genotyping using standard PCR methods, and amplification products were tested by electrophoresis on a 1.5% agarose gel and ethidium bromide staining. We amplified the SNPs rs1868790, rs6813183, and rs12503398 using independent PCR runs. Genomic DNA was amplified for three-marker haplotype with primers Fw 5′-CTTCATTTTGTACTTTATTGAAATGTG-3′ and Rv 5′-TTCCATAGGGCAACTGATCATA-3′ for the SNP rs1868790; Fw 5′-CTCAAACCATGTTTATTCTAGACCT-3′ and Rv 5′-CAAATTATTTTCTGACCC TCTATTCTT-3′ for the SNP rs6813183; and Fw 5′-GGGTTCCAAACTTCTGATGC-3′ and Rv 5′-CCCCTCCAT GAAATTCCTTT-3′ and the rs12503398. PCR reactions were carried out in a final volume of 25 µl, containing 50 ng of genomic DNA, 10 pM of each primer, 2.5 µl of PCR amplification Buffer (Invitrogen, Breda, The Netherlands), 2 mM of dNTPs, 0.5 mM MgCl, and 1U of TaqDNA polymerase (Roche). Amplification conditions consisted of an initial denaturation at 94 °C for 1 min followed by 35 cycles of denaturation at 94 °C for 1 min, annealing at 56 °C for rs1868790 and 60.3 °C for rs6813183 and rs12503398 for 1 min, and extension at 72 °C for 1 min, with a final extension step at 72 °C for 10 min. After purification of PCR products (EZNA Cycle Pure kit, OMEGA), we sequenced both strands using a Big Dye Termination system in a directly determined automated sequencing on an ABI 3130XL sequencer according to the protocol of the manufacturer. All sequencing results were analyzed using bioinformatics tools from the BioEdit Sequence Alignment Editor. *ADGRL3* haplotypes were estimated using the PHASE software[39].

In a previous study[40], we had found that the allelic combination with the highest association with ADHD combined type was rs1868790-rs6813183-rs12503398. Specifically, there was an over-representation of the combination T-C-A (patients: 22.9%; healthy controls: 12.8%), and thus we considered that individuals with this combination had the risk haplotype. Conversely, there was an under-representation of the combination A-G-G

(patients: 13.1%; healthy controls: 17.4%), and thus we considered that individuals with this combination had the protective haplotype.

Brain structural data. We scanned all participants in the same 1.5 T GE Signa scanner (General Electric Medical Systems, Milwaukee, WI, USA) at Sant Joan de Déu Hospital in Barcelona (Spain).

Participants underwent structural scanning with the following high-resolution T1 sequence: 180 axial slices, 1 mm slice thickness with no gap, 512×512 matrix size, $0.5 \times 0.5 \times 1$ mm^3 voxel resolution, 4 ms echo time, 2000 ms repetition time, 15° flip angle.

We visually inspected the raw structural images to check motion or other artifacts, removed the non-brain matter with the brain extraction tool (BET)[41], and segmented the brains into gray matter and other tissues with the FMRIB software library (FSL)[42]. We had to discard twenty scans due to motion artifacts or inaccurate brain extractions or segmentations.

Gray matter segments were then normalized to MNI space with FSL as follows: (a) affine registration of the native-space gray matter images to a common stereotactic space (Montreal Neurological Institute template, MNI); (b) creation of a first template using the registered gray matter images; (c) non-linear registration of the native-space gray matter images to the first template; (d) creation of a second template using the registered gray matter images; (e) non-linear registration of the native-space gray matter images to the second template. Modulated and non-modulated images were Gaussian-smoothed with a $\sigma = 4$ mm (FWHM = 9.4 mm) kernel, which has shown to yield increased sensitivity as compared to narrower kernels[43].

We used both modulated and non-modulated images because we have previously shown that non-linear registration can capture gross differences such as gross brain shape abnormalities, but not more subtle differences such as fine cortical thinning[43]. Thus, unmodulated images may detect the mesoscopic differences not captured by non-linear registration better. In such a case, the modulation would only introduce macroscopic noise, ultimately reducing statistical power[43]. Conversely, modulated images may better detect macroscopic differences captured by non-linear registration, as a significant part of these differences might be removed during the non-linear registration but re-introduced with modulation[44].

Brain functional data. We acquired the functional scans with the following gradient-echo echo-planar imaging (EPI) sequence depicting the blood oxygenation level-dependent (BOLD) contrast: 266 volumes, TR = 2000 ms, TE = 20 ms, FOV = 20, flip angle = 70°, number of axial planes = 16, thickness = 7 mm, section skip = 0.7 mm, in-plane resolution = 3×3 mm.

Within the scanner, participants performed a sequential-letter version of the n-back task[45]. We chose this task, which captures the active part of working memory, because impairment of working memory is one of the most robust findings in ADHD, especially in adulthood[46]. The computer presented two levels of memory load (1-back and 2-back) in a blocked design. Each block consisted of 24 letters shown every 2 s (1 s on, 1 s off), and all blocks contained five repetitions (1-back or 2-back depending on the block) located randomly within the blocks. Individuals had to indicate repetitions by pressing a button. The software presented four 1-back and four 2-back blocks in an interleaved way, with a baseline stimulus (an asterisk flashing with the same frequency as the letters) presented for 16 s between n-back blocks. The computer showed green characters in 1-back blocks and red characters in the 2-back blocks to identify which task the participant should perform. All participants first underwent a training session outside the scanner. We measured performance using the signal detection theory index of sensitivity, d'[47]. Higher values of d' indicate a better ability to discriminate between targets and distractors.

We analyzed functional images with FEAT (fMRI Expert Analysis Tool), also included in FSL[48]. For each participant, we discarded the first ten volumes to avoid T1 saturation effects, corrected for movement using MCFLIRT[49], brain-extracted using BET[41], spatially smoothed using a Gaussian kernel of FWHM 5 mm, normalized to the grand-mean intensity, and filtered with a high-pass temporal Gaussian-weighted least-squares straight-line fitting (sigma = 65 s). We had to discard fourteen scans due to lack of behavioral performance (defined as negative d' values in the 1-back and/or 2-back tasks), image artifacts, or excessive movement (defined as estimated maximum absolute movement > 3.0 mm or average movement > 0.3 mm).

We fitted within-individual general linear models, including the 1- and 2-back blocks, their temporal derivatives, and six motion parameters using FILM with local autocorrelation correction[50]. These models generated individual activation maps for the 1- and 2-back vs. baseline contrast. Individual statistical images were then co-registered to MNI space using FLIRT[49,51].

Statistical analysis. To assess the effects of the disorder, the impact of the *ADGRL3* haplotype and their interaction on the gray matter or BOLD response, we created a linear model with the following main binary regressors: ADHD status (patient vs. control), protective haplotype (presence vs. absence), risk haplotype (presence vs. absence), the interaction between ADHD status and protective haplotype, and the interaction between ADHD status and risk haplotype.

Beyond these regressors, we also included age, sex, and cumulative stimulant dose, given their brain structure and function relationships. With the inclusion of age, sex, and medication in the model, we both prevented their potential confounding effects (e.g., in the interactions) and decreased the residuals' variance, thus increasing statistical power.

Structural images were analyzed using 'threshold-free cluster enhancement' (TFCE)[52,53] due to its increased sensitivity compared to voxel- or cluster-based statistics[43]. We assessed statistical significance with the permutation test included in FSL and thresholded the maps using a familywise error rate < 0.05 (i.e., p corrected for

multiple comparisons). With an exploratory aim, we also report results thresholded using a more liberal uncorrected $p < 0.001$, which has increased false-positive rate but minimizes false-negative results[54].

We analyzed behavioral responses to the n-back task with R, and functional images were analyzed using the FMRIB's Local Analysis of Mixed Effects (FLAME) stage 1[55,56]. Z statistic images were thresholded using clusters determined by voxel $Z > 2.3$ and a cluster parametric $p < 0.05$ corrected for multiple comparisons[57].

Data availability

Data are available upon request to the Research Ethics Committee (CEI).

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Competing interests

The authors declare no competing interests.

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Study II

Aberrant resting-state functional connectivity underlies cognitive and functional impairments in remitted patients with bipolar disorder

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Aberrant resting-state functional connectivity underlies cognitive and functional impairments in remitted patients with bipolar disorder

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Abstract

Background: Bipolar disorder (BD) is commonly associated with cognitive impairments, that directly contribute to patients' functional disability. However, there is no effective treatment targeting cognition in BD. A key reason for the lack of pro-cognitive interventions is the limited insight into the brain correlates of cognitive impairments in these patients. This is the first study investigating the resting-state neural underpinnings of cognitive impairments in different neurocognitive subgroups of patients with BD.

Method: Patients with BD in full or partial remission and healthy controls (final sample of $n = 144$ and $n = 50$, respectively) underwent neuropsychological assessment and resting-state functional magnetic resonance imaging. We classified the patients into cognitively impaired ($n = 83$) and cognitively normal ($n = 61$) subgroups using hierarchical cluster analysis of the four cognitive domains. We used independent component analysis (ICA) to investigate the

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differences between the neurocognitive subgroups and healthy controls in resting-state functional connectivity (rsFC) in the default mode network (DMN), executive central network (ECN), and frontoparietal network (FPN).

Results: Cognitively impaired patients displayed greater positive rsFC within the DMN and less negative rsFC within the ECN than healthy controls. Across cognitively impaired patients, lower positive connectivity within DMN and lower negative rsFC within ECN correlated with worse global cognitive performance.

Conclusion: Cognitive impairments in BD seem to be associated with a *hyper*-connectivity within the DMN, which may explain the failure to suppress task-irrelevant DMN activity during the cognitive performance, and blunted anticorrelation in the ECN. Thus, aberrant connectivity within the DMN and ECN may serve as brain targets for pro-cognitive interventions.

KEYWORDS

bipolar disorder, cognitive impairments, functional connectivity, psychological functioning, resting-state fMRI

1 | INTRODUCTION

Cognitive impairments are a core feature of bipolar disorder (BD), mostly affecting verbal memory, working memory, and executive functions.[1,2] These impairments often prevail during asymptomatic periods, contributing to functional disability, including socio-occupational difficulties and poor quality of life.[1,3,4] Therefore, there is an important need to develop novel treatments targeting cognition to promote functional recovery.[5] However, there is still no effective treatment with enduring effects on cognitive impairment in BD.[6,7] A possible reason for this lack of pro-cognitive interventions is the limited knowledge of the neurobiological abnormalities underlying cognitive impairments,[8,9] and thus which specific neurocircuitry dysfunction should be targeted by pro-cognitive interventions.[10]

The International Society for Bipolar Disorders (ISBD) Targeting Cognition Task Force recently highlighted the need for investigating neural correlates by neuroimaging of potential pro-cognitive efficacy in candidate treatments.[10,11] Converging evidence suggests that cognitive impairments arise from disrupted neuroplasticity mechanisms and associated functional and structural changes in cognition-relevant neurocircuits.[12] Recent systematic reviews of functional magnetic resonance imaging (fMRI) correlates of cognitive impairment in mood disorders highlighted aberrant working memory-related activity in the medial and dorsal prefrontal cortex (dPFC).[11,13,14] The dPFC is involved in active maintenance

Significant outcomes

- Cognitively impaired patients displayed greater positive functional connectivity within the DMN than healthy controls.
- Cognitively impaired patients displayed less negative functional connectivity within the ECN than healthy controls.
- Aberrant functional connectivity within DMN and ECN was weakly associated with poorer cognitive performance.

Limitations

- The cross-sectional design limits causal inferences regarding the differences in network connectivity in the neuronal mechanisms of cognitive impairments.
- The a priori selection of studied cognitive networks may have biased the results.
- The lack of statistical difference between the neurocognitive groups (CI and CN) may hamper the utility of rs-fMRI biomarkers in treatment trials.
- The patients received pharmacological treatment at the time of the scanning, which may have influenced the differences found in network connectivity.

and manipulation of working memory-relevant stimuli[15,16] and belongs to the executive central network (ECN). This network is strongly involved in several cognition processes that require externally directed attention, including working memory and task-set switching,[17] Another consistent finding is *hyper*-activity within the default mode network (DMN) in working memory-related activity.[13,14,18] Indeed, the *hyper*-activity in the DMN may exacerbate cognitive impairments by disrupting task-relevant activity in prefrontal regions involved in cortical control during goal-directed behavior.[13] Despite the emerging evidence for aberrant activity in cortical control regions and DMN *hyper*-activity representing putative neurocircuitry targets for new pro-cognitive treatments in mood disorders, no study has yet investigated the role of DMN resting-state functional connectivity (rsFC) in patients' cognitive impairments. In addition to DMN and ECN, previous studies reported that the frontoparietal network (FPN) covers several areas engaged in cognitively challenging tasks.[19] Further, aberrant activity in some core regions of the FPN during cognitive interference and increased functional connectivity between FPN and insula had been reported in BD. Based on this evidence, we chose a priori to investigate the rsFC abnormalities underlying cognitive impairments within and between these three neural networks that all seem to play a role in cognitive impairments in BD.

Studies of rsFC in patients with BD have found that abnormal communication in large-scale functional networks, such as DMN, may underlie the pathophysiology of BD.[20,21] However, these abnormalities varied depending on whether mood was controlled or not.[22,23] Abnormal rsFC in the DMN has often been reported in BD patients compared to healthy controls (HC) during acute episodic states but not in remission,[24,25] but with inconsistent findings.[26] To date, no prior study has investigated rsFC differences in cognitive networks in subgroups of patients with BD with or without clinically relevant cognitive impairment and HC. Therefore, the present study aims to investigate the resting-state neural underpinnings of cognitive impairments of cognitive-related functional networks in distinct neurocognitive groups of remitted BD. Based on evidence from task-based fMRI for working memory related to *hypo*-activity in the dPFC couple with DMN *hyper*-activity,[14] we hypothesize that cognitively impaired (CI) patients display (i) *hyper*-connectivity within the DMN and (ii) aberrant connectivity in the ECN and FPN relative to those who are cognitively normal (CN) and HC, and (iii) that these abnormalities are associated with global cognitive impairments and functional disability.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The study included rs-fMRI, clinical and neurocognitive data from 153 patients with BD in full or partial remission and 52 HC. The data were combined from two cohorts: 79 patients from the Prefrontal Target Engagement as a biomarker model for Cognitive improvement (PRETEC-EPO: NCT03315897,[27] PRETEC-ABC: NCT03295305[28]); and 74 patients and 52 HC from the Bipolar Illness Onset study (BIO: NCT02888262,[29]). The two studies employed corresponding inclusion criteria and neurocognitive tests. They also employed the same MRI scanner, scanner sequence, and acquisition method and used the same ratings of mood and functioning. The studies were approved by the Danish Research Ethics Committee for the Capital Region of Denmark (PRETEC-EPO: NCT03315897, https://clinicaltrials.gov/ct2/show/NCT03315897; PRETEC-ABC: NCT03295305, https://clinicaltrials.gov/ct2/show/NCT03295305 BIO: NCT02888262, https://clinicaltrials.gov/ct2/show/NCT02888262).

Patients were recruited from the Mental Health Services, Capital Region of Denmark, and through consultant psychiatrists in Copenhagen. A total of 10% were recruited through relevant websites. Eligible patients were between 18 and 65 years of age and had an ICD-10 diagnosis of BD verified with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).[30] Furthermore, patients were in full or partial remission, with full remission defined as scores of ≤7 on the Hamilton Depression Rating Scale 17-items (HDRS-17)[31] and the Young Mania Rating Scale (YMRS),[32] whereas partial remission was defined as scores >7 and ≤14 on the same scales. 52 HC, aged 18 and 65, were recruited from the Blood Bank at Rigshospitalet, Copenhagen; they had no personal or first-degree relative history of treatment-required psychiatric disorder or neurological illness as indicated by SCAN interviews. Exclusion criteria for all participants included a history of severe brain injury, alcohol or substance abuse, diagnosis of dyslexia, pregnancy, or severe somatic illness. Neurocognitive assessment processing of the participants is shown in the Supplement.

We performed a hierarchical cluster analysis (HCA) to classify homogeneous clusters of patients based on the four cognitive domains. Squared Euclidean distance and Ward's method were used as agglomeration procedures to evaluate case similarities. We visually inspected the dendrogram to determine the optimal number of subgroups and conducted discriminant function analysis (DFA) to validate the retained clusters. Finally, we conducted an analysis of variance (ANOVA) to assess differences between neurocognitive subgroups of patients and HC in neurocognitive

performance across cognitive domains and Fisher's Least Significant Difference (LSD) post-hoc test to explore pairwise differences between groups.

2.2 | Statistical analysis of clinical, demographic and neurocognitive data

We used the Statistical Package for the Social Sciences (SPSS), version 25 (IBM Corporation, Armonk, NY) to conduct the statistical analysis. Differences in demographic and clinical characteristics between BD patients' neurocognitive subgroups and HC were assessed with independent samples t-test, Pearson's chi-squared (χ^2) and nonparametric Mann–Whitney U. We applied FDR to correct for multiple comparisons. Threshold for the level of significance was set at *FDR* $p < 0.05$.

2.3 | rs-fMRI acquisition and pre-processing

Functional MRI data acquisition protocol is shown in the Supplement. Resting-state-fMRI data were pre-processed and analyzed using FSL (FMRIB's Software Library v6.0.4[33]) (www.fsl.fmrib.ox.ac.uk/fsl). Pre-processing involved motion correction using rigid-body transformations (MCFLIRT, FSL), high-pass temporal filtering cut-off of 100 s period, non-brain tissue removal, linear registration to the individual T1-weighted image, and spatial smoothing using a 5 mm full-width-half-maximum gaussian kernel. We excluded those participants whose head motion exceeded an average relative framewise movement of 0.25 obtained by MCFLIRT. Then, to further denoise the functional data, we used single-session Independent Component Analysis (ICA) to decompose it into 20 spatially independent components. The resulting components were manually labeled as signals or noise (i.e., head movement, respiratory, cardiac, or scanner noise) in 24 participants and validated in 12 independent participants.[34] These manually labeled components were used to train FIX, a tool for automatically classifying artifacts versus signals.[35,36] FIX identified the resting-state network (RSN) activity in the functional data and regressed the noise from the full dataset. Finally, we applied non-linear registration to align the cleaned single-subject data to the standard MNI (Montreal Neurologic Institute) space at 2 mm isotropic voxel size.

2.4 | rs-fMRI statistical analysis

We used Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) to conduct group-level ICA by multi-session temporal concatenation, identifying the common RSNs across the group. The ICA dimensionality was set to 20 components.[19,37] For a better interpretation, we validated the resulting components with the publicly available RSNs (http://fsl.fmrib.ox.ac.uk/analysis/brainmap+rsns/) derived from the BrainMap database.[38] For that, we used automatic spatial correlation analysis (FSL's *fslcc* function) to correlate our components with the selected RSNs based on our a priori hypothesis (see Introduction) (DMN, ECN and FPN).[19] In the selected networks template, FPN was separated into two different networks belonging to right and left hemisphere, as it presented a strong lateralization. Therefore, we decided to study both FPN-right and FPN-left separately. We chose the component with the highest correlation coefficient to represent every network. The remaining components were not considered for further analyses. As an exploratory analysis, we investigated the group differences in the rest of the RSNs (visual, auditory, somatomotor and cerebellar).

After the selection of ICA components, we used FSL's dual regression[39] and non-parametric permutation inference (FSL's *randomize*,[40]) to investigate differences in within-RSN connectivity for all three groups of comparison (HC, CI, and CN). Dual regression has two steps; both are multivariate regressions conducted separately for each subject. In the first step, the dependent variables were the fMRI images of the subject (i.e., a 2D matrix of voxels × time points), the independent variables were the ICAs images (i.e., a 2D matrix of voxels × ICAs) and the fitted coefficients were a 2D matrix of ICAs × time points (i.e., the time series of the different ICAs). In other words, we modeled the subject fMRI images as the multiplication of the ICAs' time series and the ICAs' images. In the second step, the dependent variables were again the fMRI images of the subject (though transposed, i.e., a 2D matrix of timepoints × voxels), the independent variables were the obtained ICAs' time series (again transposed, i.e., a 2D matrix of timepoints × ICAs), and the fitted coefficients were a 2D matrix of ICAs × voxels (i.e., a subject-specific set of ICAs maps). The latter ICAs maps indicated the voxels' connectivity with the group-level ICA component representing an RSN, simultaneously controlling for influence from other ICA components.[41] Then, we applied voxelwise F-tests to assess differences in these ICAs maps between groups, using *randomize* with 5000 permutations to correct for multiple testing. Post hoc pairwise analyses (*t*-tests) were conducted for the RSN showing statistically significant effects of groups. For the post hoc pairwise t-test, we assessed cluster significance at $p < 0.05$ (threshold-free cluster enhancement (TFCE) corrected[42]) and a cluster size of $k > 100$ voxels. The significance threshold was further corrected by the number of independent components (IC).

Between-RSN rsFC was calculated using a partial correlation between each pair of the selected 4 ICA components for all three groups using the FSLNETs package (MATLAB script, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets). The partial correlation method aims to estimate more accurately the "direct" connections between networks than the full correlation method.[43] We assessed significance at $p < 0.05$, Family Wise Error (FWE) corrected for multiple comparisons.

2.5 | Correlation analysis with cognition, functioning, mood and medication

We extracted the mean rsFC strength from the significant results obtained in the group differences to explore the associations with the total global cognition score and FAST total score within CI group only to avoid bias in the findings due to the differences between subgroups in cognitive, clinical and demographic variables. Further, we investigated the association between rsFC and demographic and clinical variables that differed between groups and between patients in full or partial remission. As an exploratory post hoc analysis, we studied the correlation between the cognitive domains (processing speed, sustained attention, verbal learning, and working memory and executive functioning). To compute these associations, we used a partial Pearson's correlation coefficient controlled for any demographic or clinical variable shown to be significantly different between the neurocognitive subgroups. Analyses were carried out in SPSS, with FDR correction for multiple comparisons. Finally, we also investigated the association between the cognition scores and the whole voxelwise RSN map, using FSL across all BD patients.

3 | RESULTS

3.1 | Demographic and clinical characteristics of participants

Of the initial sample of 205 scanned participants, 11 were excluded because they did not complete the resting-sate scan ($n = 4$), lacked full-brain coverage ($n = 11$) or displayed high head-motion ($n = 6$), yielding a total of 194 participants for FC analysis. Therefore, the final sample comprised $n = 144$ patients and $n = 50$ age- and sex-matched HC. Results obtained from HCA and the visual inspection of the dendrogram (Figure S1) indicated that patients could be grouped into two neurocognitive subgroups with a large enough sample size for each group for further analysis: cognitively normal (CN), as compared to HC with 61 patients (42%) and cognitively impaired (CI) with 83 (58%) patients. As expected, CI patients showed significant worse performance in global cognition ($p < 0.001$) and all individual cognitive domains compared to CN patients and HC (Table 1), and CN patients showed no significant difference in cognitive performance compared to HC. Comparing these two neurocognitive subgroups and HC revealed significant group differences in age and functioning (Table 1): CI patients were older than CN patients ($p_{age} = 0.001$, $p_{FAST} = 0.001$) and HC ($p_{age} = 0.039$, $p_{FAST} < 0.001$). CN patients also showed functional impairment compared with HC ($p < 0.001$). Finally, CI patients had fewer years of education than HC ($p < 0.001$).

We found no differences in the distribution of BD type, number of mood episodes, subsyndromal mood symptoms, or total number of medications in CI versus CN patients (Table 1). However, CI patients had a significantly longer course of illness than CN ($p = 0.001$) and received antipsychotic ($p = 0.002$) and anticonvulsant ($p = 0.028$) treatment more frequently than CN patients, while CN patients more often received treatment with lithium than CI patients ($p = 0.041$).

3.2 | rs-fMRI analysis

First, we selected the ICA components with the highest correlation with our four networks of interest (Figure S2). The DMN comprised the bilateral anterior PFC (aPFC) and ventromedial PFC (vmPFC), caudate, frontal inferior orbital gyrus, precuneus, anterior cingulate cortex (ACC), middle cingulate cortex (MDD), posterior cingulate cortex (PCC), temporal pole, precentral and postcentral gyrus, and angular gyrus ($r = 0.53$). The ECN comprised the bilateral dPFC, ACC, MCC, supramarginal gyrus, precuneus, putamen, insula, fusiform gyrus ($r = 0.51$). The right-FPN comprised the right PFC, right postcentral and precentral gyrus, right insula right superior occipital cortex and right middle temporal gyrus right ($r = 0.63$). The left-FPN comprised the left PFC, left precentral gyrus, left caudate, left supramarginal gyrus and left middle temporal gyrus right ($r = 0.71$). Note that some of the regions can overlap with several networks.

Analyses of within-network connectivity showed a significant difference among groups within the DMN and ECN (Table 2). Post hoc analyses with Bonferroni corrected for 2 networks, showed a greater positive connectivity within the DMN (Figure 1A) and less negative connectivity within the ECN in CI patients compared to HC (Figure 2A). Significant rsFC within the DMN was localized in seven clusters: (i) bilateral precuneus, (ii) left ACC and left superior frontal gyrus (SFG), (iii) left

TABLE 1 Comparison of cognitive performance, demographic and clinical variables in healthy controls and bipolar patient subgroups: cognitively impaired and cognitively normal.

	CI (83)	CN (61)	HC (50)	F or X2	*p*-value	CI versus CN	CI versus HC	CN versus HC
Demographics								
Age M (SD)	36.02 (11.35)	30.51 (7.81)	31.54 (9.96)	6.211	**0.002**	**0.004**	**0.039**	1
Sex *n* (%) females	53 (64)	45 (74)	32 (63)	2.19	0.333	0.210	1.000	0.226
Years of education M (SD)[a]	13.84 (2.85)	14.96 (3.03)	16.10 (2.24)	10.59	**< 0.001**	0.055	**< 0.001**	0.097
Verbal IQ M (SD)[a]	110.80 (6.15)	112.80 (5.40)	112.68 (5.11)	3.10	0.047	0.088	0.155	1
Cognitive domain								
Processing speed	−1.63 (1.03)	0.78 (0.58)	0 (1)	94.07	**< 0.001**	**< 0.001**	**< 0.001**	1
Sustained attention	−1.14 (1.09)	−0.01 (0.62)	0 (1)	36.43	**< 0.001**	**< 0.001**	**< 0.001**	1
Verbal learning and memory	−1.30 (1.28)	−0.20 (1.06)	0 (1)	27.60	**< 0.001**	**< 0.001**	**< 0.001**	1
Working memory and executive function	−0.94 (0.69)	−0.01 (0.50)	0 (1)	56.38	**< 0.001**	**< 0.001**	**< 0.001**	1
Global cognition	−1.27 (0.72)	−0.37 (0.40)	0 (1)	104.29	**< 0.001**	**< 0.001**	**< 0.001**	1
Functioning								
FAST total score. M (SD)	23.11 (12.57)	16.31 (11.30)	1.24 (1.78)	69.01	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Clinical characteristics								
HDRS-17. M (SD)	5.40 (3.65)	5.16 (4.22)	-	-	-	0.788	-	-
YMRS. M (SD)	2.29 (2.78)	2.72 (3.11)	-	-	-	0.360	-	-
BD-type II. *n* (%)	51 (61)	43 (70)	-	-	-	0.295	-	-
Illness duration in years. M (SD) [b]	15.04 (11.01)	9.57 (7.47)	-	-	-	**0.001**	-	-
Mood episodes categorized								
No. of depressive episodes. *n* (%)[b]						0.816		
0 episodes	1 (1)	0 (0)	-	-	-		-	-
1–10 episodes	55 (67)	41 (69)	-	-	-		-	-
11–20 episodes	15 (18)	13 (22)	-	-	-		-	-
>20 episodes	11 (13)	5 (9)	-	-	-		-	-
No. of hypomanic episodes. *n* (%)[c]						0.407		
0 episodes	12 (15)	5 (8)	-	-	-		-	-
1–10 episodes	53 (66)	35 (59)	-	-	-		-	-
11–20 episodes	7 (9)	12 (20)	-	-	-		-	-
>20 episodes	8 (10)	7 (12)	-	-	-		-	-
No. of manic episodes. *n* (%)[a]						0.238		
0 episodes	54 (66)	46 (75)	-	-	-		-	-
1–10 episodes	27 (33)	15 (25)	-	-	-		-	-
11–20 episodes	0 (0)	0 (0)	-	-	-		-	-
>20 episodes	1 (1)	0 (0)	-	-	-		-	-
No. of mixed episodes. *n* (%)[b]						0.518		
0 episodes	65 (81)	47 (77)	-	-	-		-	-
1–10 episodes	11 (14)	12 (20)	-	-	-		-	-
11–20 episodes	2 (2)	1 (2)	-	-	-		-	-

(Continues)

TABLE 1 (Continued)

	CI (83)	CN (61)	HC (50)	F or X2	*p*-value	CI versus CN	CI versus HC	CN versus HC
>20 episodes	2 (2)	1 (2)	-	-	-		-	-
Medication status								
Any type *n* (%)[a]								
Antidepressants *n* (%)[a]	20 (24)	17 (28)	-	-	-	0.566	-	-
Antipsychotics *n* (%)[a]	35 (42)	10 (16)	-	-	-	**0.002**	-	-
Anticonvulsants *n* (%)[a]	51 (61)	25 (41)	-	-	-	**0.028**	-	-
Lithium *n* (%)[a]	31 (37)	33 (54)	-	-	-	**0.041**	-	-
Total number of medication classes. *n* (%)						0.741		
0	12 (15)	11 (18)	-	-	-		-	-
1	1 (39)	23 (38)	-	-	-		-	-
2	30 (36)	18 (29)	-	-	-		-	-
3	12 (14)	6 (10)	-	-	-		-	-
4	5 (5)	2 (3)	-	-	-		-	-

Note: Significant *p*-values are formatted in bold.

Abbreviations: BD, bipolar disorder; CI, cognitively impaired; CN, cognitively normal; FAST, functioning assessment short test; HC, healthy controls; HDRS-17, hamilton depression rating scale 17-item version; M, mean; SD, standard deviation; YMRS, young mania rating scale.

[a]Missing data for 1 subject.

[b]Missing data for 3 subjects.

[c]Missing data for 4 subjects.

caudate, (iv) left superior parietal lobule, (v) right SFG, (vi) left precentral and postcentral gyrus, and (vii) bilateral cuneal cortex. Significant rsFC within the ECN was localized in five clusters: (i) left planum temporale and supramarginal gyrus, (ii) right planum polare and superior temporal gyrus, (iii) left precuneus, (iv) left planum polare, and (v) bilateral PCC. We found no significant difference between the two neurocognitive groups or between CN patients and HC. Exploratory analysis with other RSNs did not show any statistically significant result.

Between-network connectivity analyses showed that CN patients presented a *hyper*-connectivity between the ECN and right FPN compared to HC ($p < 0.026$) and between ECN and left FPN compared to CI patients ($p < 0.026$). CI patients showed a *hyper*-connectivity between DMN and ECN ($p = 0.010$) compared to HC. None of the results survived FWE correction for multiple comparisons.

3.3 | Correlation analysis with cognition, functioning, mood, and medication

Across the CI patients, *higher* connectivity in the bilateral precuneus correlated with poorer global cognitive performance ($p < 0.04$, Table 3, Figure 1B). Further, *lower* connectivity in an ECN cluster (right planum polare) also correlated with poorer global cognition ($p < 0.02$, Table 3, Figure 2B). However, neither of these associations survived correction for multiple comparisons. Further, higher connectivity in a DMN cluster (left ACC), correlated with poorer functioning measured with the FAST ($p < 0.03$, Table 3, Figure 1B). This association also did not survive correction for multiple comparisons. Additional exploratory post hoc analyses showed positive associations between connectivity in the DMN cluster located in the precuneus and working memory and executive functioning ($p < 0.02$). Further association analyses with demographic and clinical variables that differed between groups showed that the hyper-connectivity observed in a ECN cluster (planum temporale) correlated positively with higher age ($p < 0.001$) and longer illness duration ($p < 0.04$); and negatively with more severe subsyndromal depression ($p < 0.03$) and with the treatment with anticonvulsants ($p < 0.037$). The hyper-connectivity observed in the right planum polare cluster of the ECN correlated negatively with higher age ($p < 0.045$), and positively with the treatment with anticonvulsants ($p < 0.047$). Finally, greater positive connectivity in the precuneus cluster of the DMN was observed in patients treated with lithium ($p < 0.03$) and in partial remission

TABLE 2 Peak cluster showing higher resting-state functional connectivity within the default mode network and executive control network ($p < 0.025$, cluster-corrected and IC corrected) between the cognitively impaired patients and healthy controls.

Regions	*p*-value	No. of voxels (cluster size)	Peak MNI coordinates		
			X	Y	Z
DMN					
B Precuneus	0.002	1233	−4	−56	62
Left ACC/Left SFG	0.002	803	−8	6	42
Left caudate	0.006	600	−16	−20	20
Left superior parietal lobule	0.008	462	−30	−56	38
Right SFG	0.008	305	22	2	54
Left precentral/postcentral gyrus	0.016	127	−62	−4	16
B cuneal cortex	0.011	124	−2	−84	40
ECN					
Left planum temporale/left supramarginal gyrus	0.005	721	−52	−36	14
Right planum polare/Right STG	0.010	311	50	−2	−8
Left precuneus	0.013	252	−8	−54	66
Left planum polare	0.009	118	−44	−14	−4
B PCC	0.015	114	−6	−38	32

Abbreviations: ACC, anterior cingulate cortex; B, bilateral; DMN, default mode network; ECN, executive central network; L, left; MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex; R, right; SFG, superior frontal gyrus; STG, superior temporal gyrus.

($p < 0.045$). Only the association between age and the planum temporal survived correction for multiple comparisons. Results for the cognitive association with each RSN are presented in the Supplemental Material.

4 | DISCUSSION

This is the first resting-state fMRI study to specifically investigate the neuronal correlates of cognitive impairments in a large sample of remitted patients with BD. We used a cluster-analytic approach to classify patients into subgroups according to the level of their cognitive impairments rather than by diagnostic group, leading to two groups: cognitively impaired (CI; 56%, $n = 83$) and cognitively normal (CN; 44%, $n = 61$). In support of our main hypothesis, CI patients showed greater positive rsFC within the DMN compared to HC. This *hyper*-connectivity was mainly located in the bilateral precuneus, left ACC, bilateral SFG, left caudate, and left superior temporal lobule. In support of our secondary hypothesis, CI patients also showed a less negative rsFC within the ECN compared to HC, located in the left planum temporale, bilateral planum polare, left precuneus, and bilateral PCC. In contrast, we found no significant difference in rsFC between the two neurocognitive groups or between CN and HC. Notably, lower positive connectivity in the precuneus cluster of DMN; and lower negative connectivity in the right planum polare cluster of ECN were weakly associated with poorer cognitive performance in CI patients, specifically in the working memory and executive function domain. Greater positive connectivity in the left ACC cluster of DMN was associated with worse psychosocial functioning. Exploratory associations with demographic and clinical variables showed that the connectivity within the ECN clusters of the right planum polare and planum temporale correlated with age, illness duration, subsyndromal depression symptoms and the treatment with anticonvulsants. Further, the observed connectivity in the precuneus cluster of DMN was associated with the treatment with lithium and partial remission of patients. However, the correlations between the rsFC differences and the demographic and clinical variables did not survive correction for multiple comparisons, so the differences found in rsFC could not be explained by these variables.

Our finding that CI patients displayed *hyper*-connectivity within the DMN relative to HC is consistent with a previous meta-analysis,[26] in which a shift from *hypo*-connectivity within the DMN in the acute phase to *hyper*-connectivity in remission was observed. However, those results contrast with a systematic review, in which normalization within DMN connectivity during remission was observed.[25] A plausible explanation for these differences is that all studies included in this meta-analysis

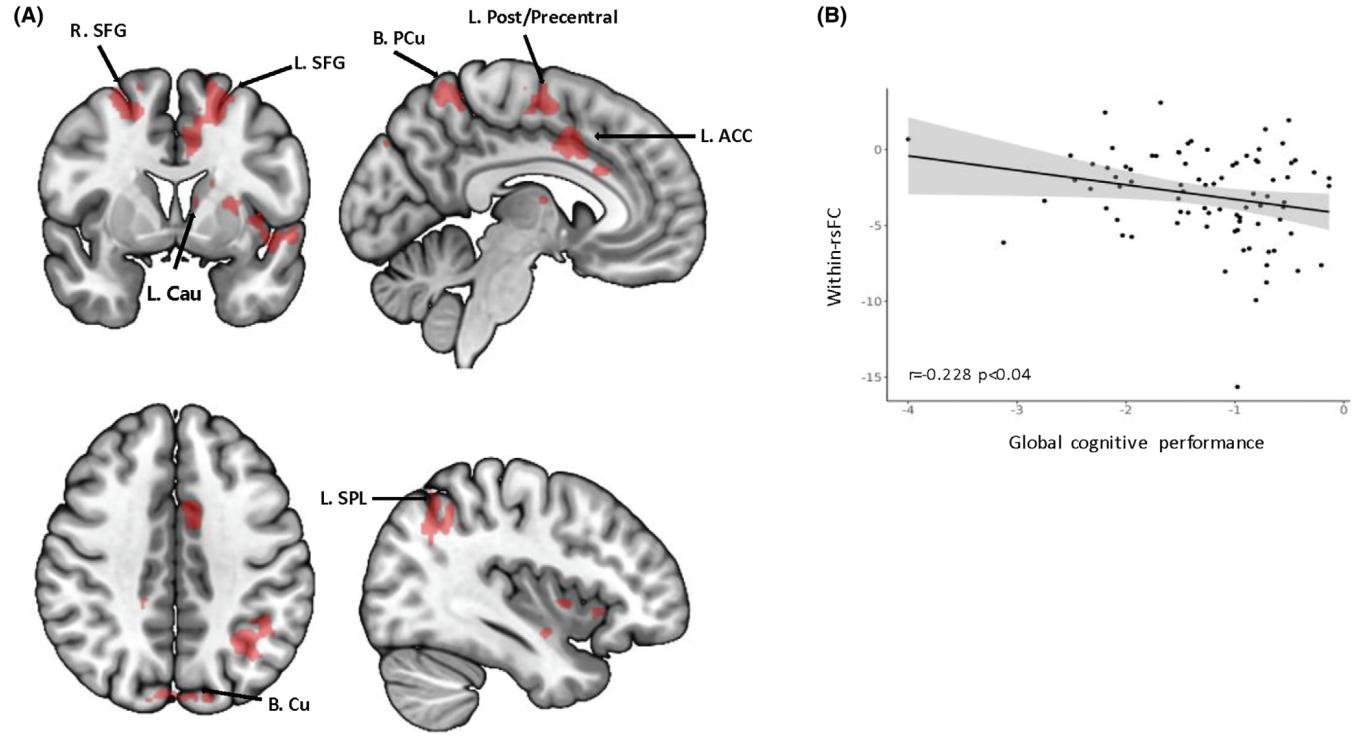

FIGURE 1 Group differences in resting-state functional connectivity (rsFC) within the default mode network (DMN) and their association with cognitive performance and functioning across all subjects. (A) Statistical map showing a significant greater rsFC in seven cluster within the DMN in cognitive impaired patients compared to healthy controls ($p < 0.025$, cluster and component corrected). (B) Correlation analysis with 95% confidence interval of the linear fit between the within rsFC in the bilateral precuneus and z-standardized global cognitive scores across CI participants. ACC, anterior cingulate cortex; B, bilateral; Cau, caudate; CN, cognitively normal; CI, cognitively impaired; Cu, cuneus cortex; HC, healthy controls; L, left; PCu, precuneus; R, right; rsFC, resting-state functional connectivity; SFG, superior frontal gyrus; SPL, superior parietal lobule.

investigated BD patients as a homogeneous sample independent of their cognitive status. Indeed, we found no difference in between CN patients and HC, suggesting that depending on the percentage of CI patients in the whole sample of remitted BD patients, it will be more or less likely to obtain a significant difference in rsFC, respectively. Thus, this study strongly supports the need to investigate neural correlates in BD patients grouped according to their cognitive profile to investigate neural correlates of cognitive impairments. These results are in line with prior studies of task-based fMRI in mood disorders.[14,18,44] A *hyper*-connected DMN during rest may explain the failure to suppress DMN activity during working memory processes in CI patients.[14,18] In addition, greater rsFC within the DMN had been suggested as a potential biomarker for major depressive disorder (MDD),[45] implicated in functions such as self-referential thinking,[46] ruminative thought processing,[47] and memory retrieval.[48] A rs-fMRI study of the association between network rsFC and cognitive performance in MDD reported an association between greater positive connectivity within the DMN and worse cognitive performance,[49] especially in working memory and executive functioning. Aberrant rsFC within the ECN in CI patients compared to HC may be related to the previous observation of reduced activity in dlPFC, as region belonging to the ECN, in patients with BD exhibiting impaired cognitive task performance relative to CN patients and HC.[14,18] Specifically, dlPFC, as well as ECN, is involved in active manipulation of working-memory relevant stimuli.[15,16,50] However, the significant ECN clusters did not contain the dlPFC area. Hence, the role of dlPFC resting-state connectivity in the ECN underlying cognitive impairments in mood disorders needs to be further investigated.

The findings have several implications. First, they suggest that lower positive rsFC within DMN, as well as a less negative rsFC within ECN, in regions such as precuneus and right planunm polare, represent neural correlates of cognitive impairments in BD. Thus, neurocircuitry rsFC abnormalities constitute promising targets for pro-cognitive interventions, which – if replicated – may aid go-no/go decisions in treatment development strategies.[51] Emerging evidence indicates

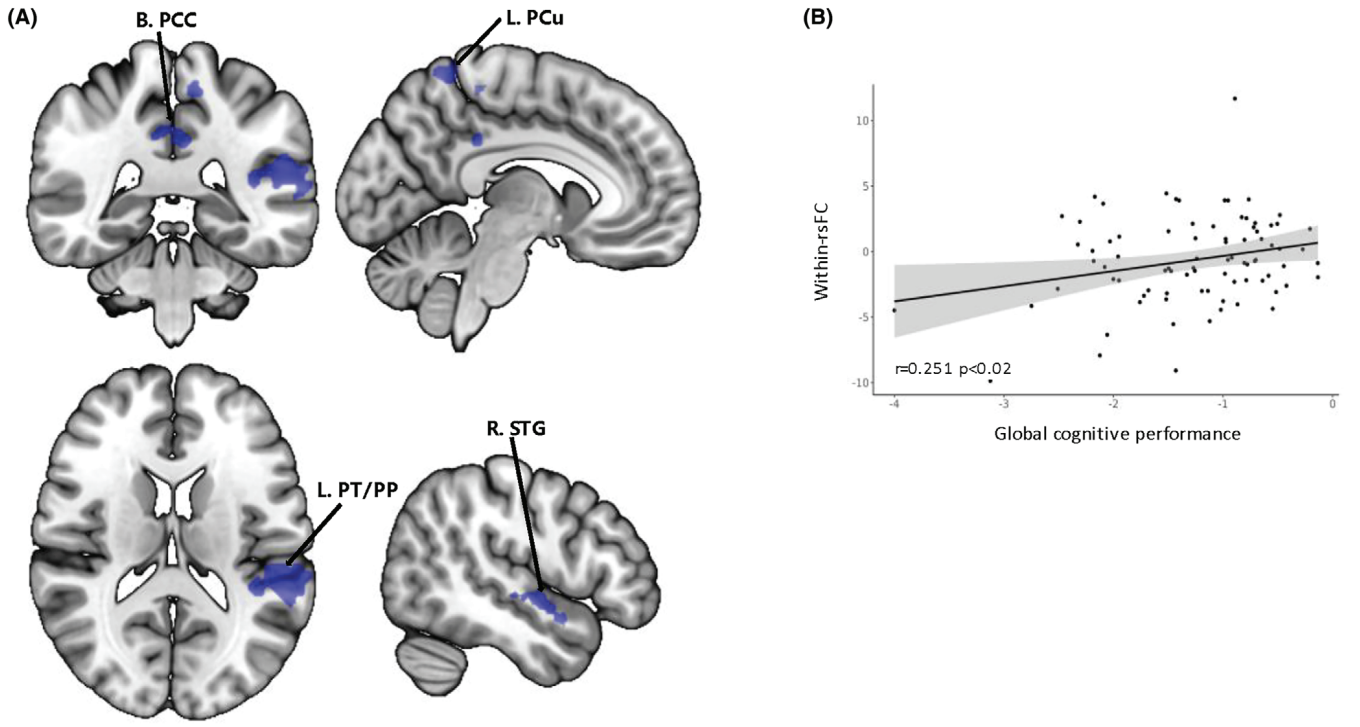

FIGURE 2 Group differences in resting-state functional connectivity (rsFC) within the executive central network (ECN) and their association with cognitive performance and functioning. (A) Statistical map showing a significant less negative rsFC in five cluster within the ECN in cognitive impaired patients compared to healthy controls ($p < 0.025$, cluster and component corrected). (B) Correlation analysis with 95% confidence interval of the linear fit between the within rsFC in the right planum polare and z-standardized global cognitive scores across CI participants. B, bilateral; CN, cognitively normal; CI, cognitively impaired; HC, healthy controls; L, Left; PCC, posterior cingulate cortex; PCu, precuneus, PP, planum polare; PT, planum temporale; R, right; rsFC, resting-state functional connectivity; STG, superior temporal gyrus.

that particularly the aberrant connectivity within DMN may be extended to CI patients with *other* neuropsychiatric conditions, such as unipolar disorder or schizophrenia.[13,49] Second, from a theoretical perspective, it is interesting that rsFC abnormalities were seen both within and between DMN and ECN in partially overlapping parietal and PCC areas. These rsFC abnormalities may arise from disruption of structural connectivity due to white matter deficits that have been observed in CI relative to CN patients with mood disorders and HC.[52,53] Interestingly, an MRI study exploring the corpus callosum (CC) in children and adolescents with BD found a lower circularity of the splenium of the CC in a sample of pediatric patients with BD relative to HC, suggesting that such white matter abnormalities may occur early in the course of BD.[54] Indeed, this lends support to the hypothesis of an abnormal neurodevelopmental trajectory in BD.[55]

A strength of this study was the large dataset of clinically well-characterized BD patients ($n = 144$) investigated with MRI, which enabled a large sample size for the neurocognitive subgroups ($n = 61$ and $n = 83$). Further, patients were in full or partial remission, which enabled the investigation of neural correlates of cognitive impairments without confounding mood-dependent effects. However, there are a few limitations. Firstly, the cross-sectional design impedes causal inferences of neuronal mechanisms of cognitive impairments. We also acknowledge that the priori selection of cognitive networks may lead to a bias in the presented results since cognitive impairments could also be affected by other networks that are not directly involved in cognition. The lack of statistical difference between the neurocognitive groups (CI and CN) was another limitation because this impedes the utility of rs-fMRI biomarkers in treatment trials. Nevertheless, the difference between CI and HC (with the CN exhibiting rsFC in-between the other groups) still suggests that illness-related alterations in rsFC are associated with cognitive impairment in BD. Furthermore, medications may have influenced the network connectivity differences between groups. However, the association analyses between the medication with the observed differences within networks did not survive correction for multiple comparisons. This suggested that the medication could not explain the findings. A final limitation was that we did not collect data on psychotic

TABLE 3 Correlation analyses between clusters with significant functional connectivity within networks and global cognition across all subjects and controlling for age.

		Global cognition	
	Regions	**R**	***p***
DMN			
	B Precuneus	−0.224	**0.04**
	L ACC/L SFG	−0.102	0.36
	L caudate	−0.015	0.89
	L SPL	−0.149	0.18
	R SFG	−0.056	0.61
	L precentral/postcentral gyrus	−0.163	0.48
	B cuneal cortex	−0.041	0.14
ECN			
	L PT/L supramarginal gyrus	0.041	0.714
	R PP/R STG	0.251	**0.022**
	L precuneus	−0.124	0.264
	L PP	−0.122	0.269
	B PCC	0.061	0.580

Note: Significant *p*-values are formatted in bold; Neither correlation survived FDR correction.

Abbreviations: ACC, anterior cingulate cortex; B, bilateral; DMN, default mode network; ECN, executive central network; FAST, functioning assessment short test; L, Left; PCC, posterior cingulate cortex; PP, planum polare; PT, planum temporale; R, right; SFG, superior frontal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus.

symptom history, which could have influenced the obtained findings.

The insights from this first rs-fMRI study into the neurobiological underpinnings of cognitive impairments in BD can have implications for treatment development strategies targeting cognition and functioning. Based on this evidence and the ISBD Targeting Cognition Task Force guidelines, we recommend that future cognition intervention trials include rs-fMRI to investigate treatment effects on rsFC within DMN and ECN as potential efficacy markers, which may support go/no-go decisions in the development of candidate treatments targeting cognition.

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CONFLICT OF INTEREST STATEMENT

Kamilla W. Miskowiak reports receiving consultancy fees from Lundbeck, Gideon Richter, Angelini, and Janssen-Cilag in the past four years. Lars V. Kessing has within the past four years been a consultant for Lundbeck and Teva. Eduard Vieta has received a grant and served as a consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, Sunovion, Takeda, all of them unrelated to the current work. GMK has received honoraria as a speaker for Sage Therapeutics and H. Lundbeck, and as an advisor for Onsero and Sanos. Lydia Fortea, Alexander T. Ysbæk-Nielsen, Julian Macoveanu, Jeff Zarp Petersen, Patrick M. Fisher, Joaquim Radua report no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13615.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The studies were approved by the Danish Research Ethics Committee for the Capital Region of Denmark (PRETEC-EPO: H-16043370; PRETEC-ABC: H-16043480; BIO: H-7-2014-007).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Material & Methods

Neurocognitive assessment and processing

Cognition was assessed with a comprehensive test battery which included: Trial Making Test Part A & B (TMT-A; TMT-B) (1), Rapid Visual Information Processing (RVP), and Spatial Working Memory (SWM) from CANTAB (Cambridge Cognition Ltd.), Rey Auditory Verbal Learning Test (RAVLT) (2), the coding and digit span forward subtests from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (3), Verbal Fluency (letters 'S' and 'D') (4), and the Letter-Number Sequencing subtest from the Wechsler Adult Intelligence Scale (WAIS-III) (5). Verbal intelligence was estimated using Danish Adult Reading Task (DART) (6). Participant functioning was assessed in six domains (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time) using Functional Assessment Short Test (FAST) (7), which has proven useful in measuring its relationship to cognition in clinical and neuroimaging studies (8,9). Most participants (*n* = 201; 98%) underwent MRI scan and neuropsychological testing 0–3 days apart (same day = 85; 1 day = 50; 2 days = 34; and 3 days = 32).

We transformed raw scores from the neuropsychological test to *z*-scores based on the mean and standard deviation from the HC group. These *z*-scores were then averaged and grouped into four cognitive domains: processing speed, sustained attention, verbal learning and memory, and working memory and executive functions. Finally, a global composite score was calculated by averaging the *z*-scores of the four cognitive domains. We performed a hierarchical cluster analysis (HCA) to classify homogeneous clusters of patients based on the four cognitive domains. We used Squared Euclidean distance and Ward's method as agglomeration procedures to evaluate case similarities. We visually inspected the dendrogram to determine the optimal number of subgroups and conducted discriminant function analysis (DFA) to validate the retained clusters.

rs-fMRI acquisition protocol

Functional MRI data were acquired at Copenhagen University Hospital, Rigshospitalet, using a 3 Tesla Siemens Prisma scanner (Siemens Trio, Erlangen, Germany) with a 64-channel head-neck coil. We acquired blood-oxygen-level-dependent (BOLD) fMRI during resting-state with a T2*-weighted gradient echo spiral echo-planar (EPI) sequence with an echo time (TE) of 30 ms, repetition time (TR) of 2 s, and flip angle of 90°. A total of 300 volumes were acquired, each consisting of 32 slices with a slice thickness of 3 mm with 25% gaps in-between and a field of view (FOV) of 230 × 230 mm using a 64 × 64 grid. To register the BOLD images to the MNI standard space (see below), we also acquired T1-weighted structural images (TR = 1900 ms; TE = 2.58 ms; flip angle = 9°; distance factor = 50%; FOV = 230 × 230 mm; slice thickness = 0.9 mm). Furthermore, we acquired a standard B0 field map sequence with the same FOV and resolution as the fMRI sequence (TR = 400 ms; TE = 7.38 ms; flip angle = 60°) and used it for geometric distortions correction of the BOLD images. We ascertained image quality by visual inspection of all individual participant images. Here, we excluded 5 participants: four did not complete the full resting-state scan, and one lacked full-brain coverage.

Results

Correlation analysis with cognition

The exploratory correlation analysis across all BD patients between global cognitive scores and the three studied resting state networks (RSNs), i.e., the default mode network (DMN), the executive central network (ECN), the right frontoparietal network (FPN), and left FPN revealed no significant regions. Additional correlation analysis testing the correlation of distinct cognitive domains revealed a positive association between the left frontal medial cortex and left frontal pole within the DMN and verbal learning and memory. In addition, the right supramarginal gyrus within the right FPN showed a negative association with processing speed. Finally, the left middle frontal gyrus and left frontal pole within the FPN showed a positive association with verbal learning and memory. However, neither of those associations survived correction for multiple comparisons.

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Figure S1. Dendrogram obtained by the Hierarchical Cluster Analysis of 144 patients with bipolar disorder

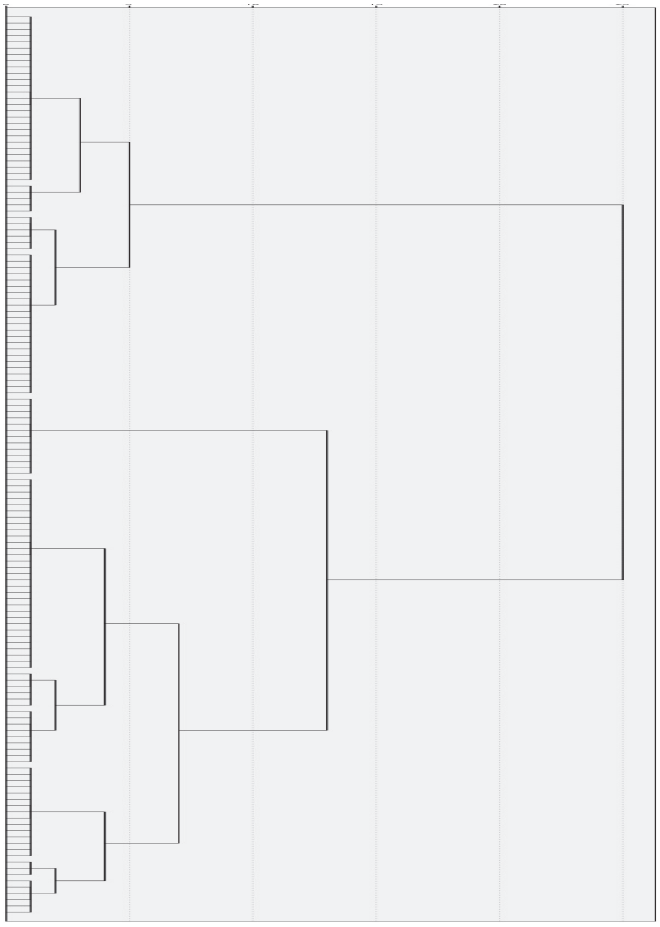
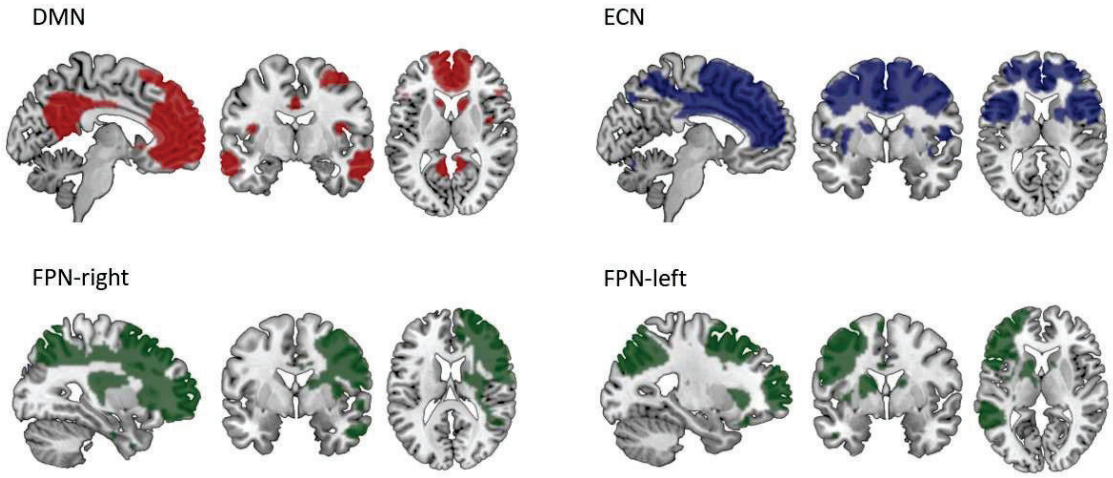


Figure S2. Selected component from ICA analysis with all subjects representing the four resting state networks (RSN) in interest.



Study III-I

Focusing on Comorbidity—A Novel Meta-Analytic Approach and Protocol to Disentangle the Specific Neuroanatomy of Co-occurring Mental Disorders

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Focusing on Comorbidity—A Novel Meta-Analytic Approach and Protocol to Disentangle the Specific Neuroanatomy of Co-occurring Mental Disorders

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Background: In mental health, comorbidities are the norm rather than the exception. However, current meta-analytic methods for summarizing the neural correlates of mental disorders do not consider comorbidities, reducing them to a source of noise and bias rather than benefitting from their valuable information.

Objectives: We describe and validate a novel neuroimaging meta-analytic approach that focuses on comorbidities. In addition, we present the protocol for a meta-analysis of all major mental disorders and their comorbidities.

Methods: The novel approach consists of a modification of Seed-based d Mapping—with Permutation of Subject Images (SDM-PSI) in which the linear models have no intercept. As in previous SDM meta-analyses, the dependent variable is the brain anatomical difference between patients and controls in a voxel. However, there is no primary disorder, and the independent variables are the percentages of patients with each disorder and each pair of potentially comorbid disorders. We use simulations to validate and provide an example of this novel approach, which correctly disentangled the abnormalities associated with each disorder and comorbidity. We then describe a protocol for conducting the new meta-analysis of all major mental disorders and their comorbidities. Specifically, we will include all voxel-based morphometry (VBM) studies of mental disorders for which a meta-analysis has already been published, including at least 10 studies. We will use the novel approach to analyze all included studies in two separate single linear models, one for children/adolescents and one for adults.

Discussion: The novel approach is a valid method to focus on comorbidities. The meta-analysis will yield a comprehensive atlas of the neuroanatomy of all major mental disorders and their comorbidities, which we hope might help develop potential diagnostic and therapeutic tools.

Keywords: meta-analysis, magnetic resonance imaging (MRI), seed-based d mapping (SDM), gray matter (GM), mental disorder, comorbidity, medication

INTRODUCTION

Authors have reported potential brain anatomical abnormalities for different mental disorders since the 1980s (1). At present, the neuroscientific community has enough data (thousands of studies) to create an atlas of these abnormalities, but this is not yet a reality due to the heterogeneity in the findings across studies investigating the same disorder. For instance, a meta-analysis of structural brain alterations of social anxiety disorder (SAD) found that studies presented contradictory findings, such as increases and decreases in gray matter (GM) volume in the hippocampus and other brain regions (2). Similarly, whereas several meta-analyses had reported significant SAD-related abnormalities in GM in the amygdala-hippocampal, prefrontal, and parietal regions (3–5), an ENIGMA study only found a significant larger GM volume in the right putamen (6). Another example could be the case of obsessive-compulsive disorder (OCD) neuroanatomical findings, where although the abnormalities of the corticostriatal-thalamocortical circuits have been consistently reported (7–9), recent evidence has been accumulating to other regions outside these circuits with less agreement among meta- and mega-analysis reports (7, 10, 11). Moreover, the exact direction of increases and decreases in GM volume in certain areas, such as the orbitofrontal cortex (OFC), has been unclear (12). For example, some reports show reduced GM in bilateral (13) or right (14) OFC, whereas there are also studies reporting increased bilateral (15) or left (16) OFC.

The found heterogeneity may be partly related to the use of magnetic resonance imaging (MRI) devices with varying field strengths (17) and head coils (18) or to the techniques or software used to process the images (18, 19). In addition, several clinical parameters might moderate the findings, such as the age at disease onset and the duration of disease (20, 21),

the current age (22), symptom heterogeneity (23), the gender distribution (24), the medication status (25, 26), or clinical stage (27). For example, in a meta-analysis of attention-deficit hyperactivity disorder (ADHD) (28), we found that samples with more medicated patients showed less decreased GM volume in the right caudate.

Another relevant but little explored source of heterogeneity may be the varying presence of comorbidities, which are the rule in psychiatry (29). About half of people with mental disorders have more than one comorbid mental disorder (30, 31). Some authors claim that "there are no patients without comorbidity" (32). We must acknowledge that some studies exclude individuals with specific comorbid mental disorders. Still, this exclusion is frequently limited to very few entities such as psychosis and substance use disorders. Similarly, we must acknowledge that some comorbidities are conceptually impossible, e.g., a patient with bipolar disorder (BD) cannot be diagnosed with comorbid major depressive disorder (MDD), but again, the list of impossible comorbidities is limited. Therefore, most patients included in a study of a given mental disorder might also have other mental disorders. For example, in a meta-analysis of neuroimaging studies in OCD, patients had comorbid depression or anxiety disorders in 65% of the studies. The percentage of patients with comorbid disorders reached 50% (for depression) and 85% (for anxiety disorders) in some included studies (33). This common presence of abnormalities from other mental disorders might thus confound the results of case-control studies.

Relevantly, previous studies have found that some brain abnormalities associated with different mental disorders are non-specific. For example, in several meta-analyses, we observed similar decreases of GM volume in the anterior cingulate/medial frontal cortex in disorders as different as psychosis, anxiety disorders (AD), ADHD, and autism spectrum disorders (ASD) (33–37). Similarly, an ENIGMA study reported a high similarity of brain structural abnormalities between MDD, BD, OCD, and schizophrenia (38, 39). We fully acknowledge that some of these non-specific abnormalities may be transdiagnostic, i.e., associated with two or more mental disorders. However, there is also the possibility that some others are related to the confounding effects of comorbidities.

This study aims to describe and validate a novel neuroimaging meta-analytic approach that focuses on comorbidities and presents the protocol for a meta-analysis of all major mental disorders and their potential comorbidities. We exemplify this protocol for voxel-based morphometry (VBM) studies investigating GM volume differences between patients with mental disorders and healthy controls. However, it could be similarly applied to any neuroimaging modality compatible with SDM (e.g., functional MRI or diffusion tensor imaging). Specifically, we will meta-analyze brain abnormalities from different disorders with different comorbidities, with a single meta-linear model (though separately for children/adolescents and adults). This analysis will yield an MRI-based atlas that dissects the specific brain anatomical abnormalities of each mental disorder and comorbidity. In complementary analyses and depending on data availability reported in the studies, we will explore the potentially confounding or moderating effects of age, sex, medication, age of onset, duration of illness, and symptom severity.

METHODS AND ANALYSIS

The Novel Approach

The new approach is conceptually novel, but it involves only a minor modification of the "seed-based d mapping-permutation of subject images" (SDM-PSI) (www.sdmproject.com) (11, 40–42), an already validated and widely used brain imaging meta-analytic method (43–51). The main advantage of this method is that it directly tests whether there are differences between patients and controls, rather than conducting indirect tests such as whether peaks tend to converge in some regions more than in others (52).

It first creates maps of the lower and upper bounds of possible effect sizes for each study based on the available statistical information and the anisotropic covariance between adjacent voxels (53). Second, it uses maximum likelihood estimation techniques to impute several effect sizes maps for each study, assuming that the effect size follows a truncated normal distribution within the lower and upper bounds. Third, it fits a random-effects meta-analytic linear model separately for each voxel. Fourth, it combines the meta-analytic maps resulting from the different imputations using Rubin's rules. Finally, it conducts a permutation test to yield threshold-free cluster enhancement (TFCE)-based (54) familywise error rates (FWER, i.e., corrected *p*-values).

In this paper, we will first describe the new concept, then report the small methodological changes, and finally report a validation of the approach using simulations.

Description

Commonly, the primary (random-effects meta-analytic) linear model of a meta-analysis is just a (weighted) mean:

$$Y_i = \beta + \varepsilon_i$$

where Y_i is the effect size of the ith study, β is the meta-analytic effect size, and ε_i is the residual for the i^{th} study. It is important to remember that this model is conducted separately for each voxel.

In some previous meta-analyses, we attempted to control for comorbidity via meta-regression (covariation) by the percentage of patients with a comorbid disorder:

$$Y_i = \beta_A + \beta_{AB-A} X_{i,AB} + \varepsilon_i$$

where the intercept β_A is the effect size for patients with only disorder A, the coefficient β_{AB-A} is the difference between patients with both disorders and patients with only the disorder A, and $X_{i,AB}$ is the proportion of patients with both disorders in the i^{th} study.

However, these attempts had two relevant limitations. First, β_{AB-A} (the difference between patients with both disorder A and disorder B and patients with only disorder A) mixed the effects of disorder B and the effects of the comorbidity AB. Thus, we could not know which part of β_{AB-A} was shared by any patient with disorder B (with or without disorder A) and which part

of β_{AB-A} was specific to those patients with both disorder A and disorder B. For instance, imagine that patients with only disorder A show decreased amygdala, patients with only disorder B show decreased cerebellum, and patients with both disorder A and disorder B show decreased amygdala, cerebellum, and prefrontal cortex. The decrease in the cerebellum is shared by any patient with disorder B, and the reduction in the prefrontal cortex is specific to those with both disorder A and disorder B, but β_{AB-A} would mix both abnormalities. Second, we could only include studies on disorder A in which a variable proportion of patients had disorder B. Conversely, we could not include studies on disorder B in which a variable proportion of patients had the disorder A, with the subsequent loss in precision.

Here, we propose to use the following model to study two disorders A and B:

$$Y_i = \beta_A X_{iA} + \beta_B X_{iB} + \beta_{AB} X_{iAB} + \varepsilon_i$$

where β_A is the effect size for patients with only disorder A, X_{iA} is the proportion of patients with disorder A in the i^{th} study, β_B is the effect size for patients with only disorder B, X_{iB} is the proportion of patients with disorder B in the i^{th} study, β_{AB} is the effect size of the comorbidity AB, and X_{iAB} is the proportion of patients with both disorders in the i^{th} study.

This model overcomes the limitations of the previous attempts because it separates the effects of disorder B and the effects of the comorbidity AB and can accept both studies on disorder A and studies on disorder B because it treats all disorders equally. Indeed, we can extend the model to as many disorders and comorbidities as wished. Still, considering the complexity of the analysis and the likely poor reporting of co-occurring comorbidities, we will only consider pairs of comorbid mental disorders that are possible (e.g., anxiety and MDD) and have been studied by at least ten studies.

Validation

To validate the novel approach, we simulated 64 studies on disorder A, 64 on disorder B, and 64 on disorder C, with varying levels of comorbidity, and then meta-analyzed them using the novel approach. The reason to simulate 64 studies for each disorder is that we simulated eight levels of comorbidity (including no comorbidity) for each of the two comorbid disorders, e.g., for disorder A, we simulated eight levels of comorbid disorder B X 8 levels of comorbid disorder C.

Specifically, we first simulated for each study that a varying proportion of the patients had one of the other disorders or both. We then created the subjects' gray matter maps as white noise following a standard normal distribution. Still, for each patient, we added or subtracted 0.5 in four brain regions depending on the disorders he/she had and the rules in **Figure 1**. We thus created abnormalities with a medium effect size (Cohen's d around 0.5). Finally, we conducted the voxelwise *t*-test between patients and controls to derive the study t-map.

To meta-analyze the studies' t-maps with the novel SDM-PSI approach (with default values and defining statistical significance as TFCE permutation-based FWER < 0.05), we modeled:

$$Y_i = \beta_A X_{iA} + \beta_B X_{iB} + \beta_C X_{iC} + \beta_{AB} X_{iAB} + \beta_{AC} X_{iAC} + \beta_{BC} X_{iBC}$$

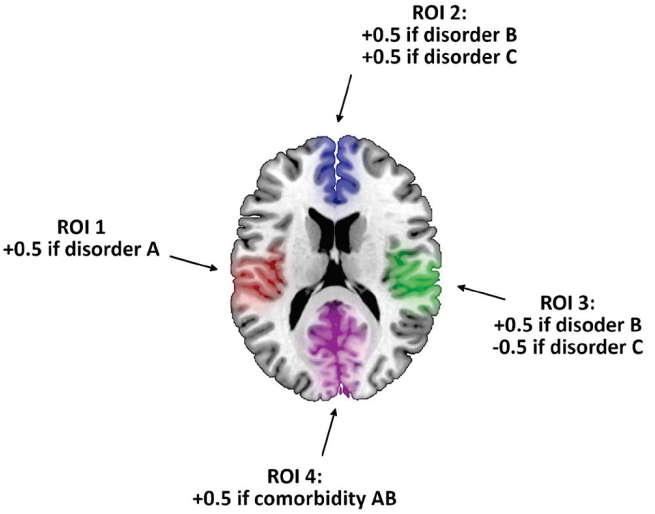

FIGURE 1 | Rules for creating the gray matter maps of a simulated patient. After creating a map using white noise, we added or subtracted 0.5 in the colored brain regions of interest (ROI) depending on the disorders he/she had.

For example, imagine that disorder A was OCD, disorder B was MDD, and disorder C referred to anxiety disorders. Studies on OCD would be coded as $X_{iA} = 1$, $X_{iAB} =$ [proportion of patients with comorbid MDD], and $X_{iAC} =$ [proportion of patients with comorbid anxiety disorders]. Studies on MDD would be coded as $X_{iB} = 1$, $X_{iAB} =$ [proportion of patients with comorbid OCD], and $X_{iBC} =$ [proportion of patients with comorbid anxiety disorders]. Finally, studies on anxiety disorders would be coded as $X_{iC} = 1$, $X_{iAC} =$ [proportion of patients with comorbid OCD], and $X_{iBC} =$ [proportion of patients with comorbid MDD]. Although studies seldom report the proportion of patients with multiple comorbidities (e.g., in studies on OCD, the proportion of patients with both comorbid MDD and anxiety disorders), our new approach could easily account for them if reported. Meta-analysts should add a regressor for each reported combination of comorbid mental disorders.

For comparison purposes, we also conducted three meta-regressions using the previous SDM-PSI approach (again, with default values and defining statistical significance as TFCE permutation-based FWER < 0.05):

$$Y_i = \beta_A + \beta_{AB-A} X_{iAB} + \beta_{AC-A} X_{iAC}$$
$$Y_i = \beta_B + \beta_{AB-B} X_{iAB} + \beta_{BC-B} X_{iBC}$$
$$Y_i = \beta_C + \beta_{AC-C} X_{iAC} + \beta_{BC-C} X_{iBC}$$

Results of the Validation

The novel SDM-PSI approach detected all the simulated abnormalities with the correct effect size and did not yield any falsely positive findings (**Table 1**, left column; and **Figure 2**).

The previous SDM-PSI reported a list of findings very similar to the simulated factual data (**Table 1**, right columns; and **Figure 3**). However, the results showed the two main limitations we had expected. First, they mixed the abnormalities of the

TABLE 1 | Results of the novel approach validation.

	Simulated factual data	Novel SDM-PSI approach	Previous SDM-PSI approach		
			Main disorder is A	Main disorder is B	Main disorder is C
Disorder A	ROI 1, g +0.5	β_A = ROI 1, g +0.5	β_A = ROI 1, g +0.5 ROI 2, g +0.4 ROI 4, g +0.2	β_{AB-B} = ROI 1, +0.5 ROI 4, +0.5	β_{AC-C} = ROI 1, g +0.5
Comorbidity AB	ROI 4, g +0.5	β_{AB} = ROI 4, g +0.5	β_{AB-A} = ROI 4, g +0.5 ROI 2, g +0.4 ROI 3, g +0.5		(Not studied)
Disorder B	ROI 2, g +0.5 ROI 3, g +0.5	β_B = ROI 2, g +0.5 ROI 3, g +0.5		β_B = ROI 2, g +0.7 ROI 3, g +0.3	β_{BC-C} = ROI 2, g +0.4 ROI 3, g +0.5
Comorbidity BC	(None)	β_{BC} = (None)	(Not studied)	β_{BC-B} = ROI 2, g +0.5 ROI 3, g −0.5	
Disorder C	ROI 2, g +0.5 ROI 3, g −0.5	β_C = ROI 2, g +0.5 ROI 3, g −0.5	β_{AC-A} = ROI 2, g +0.5 ROI 3, g −0.5		β_C = ROI 2, g +0.7 ROI 3, g −0.3
Comorbidity AC	(None)	β_{AC} = (None)		(Not studied)	(See Disorder A)

"g", average Hedges' g of the voxels within the cluster of statistical significance; ROI, region of interest.

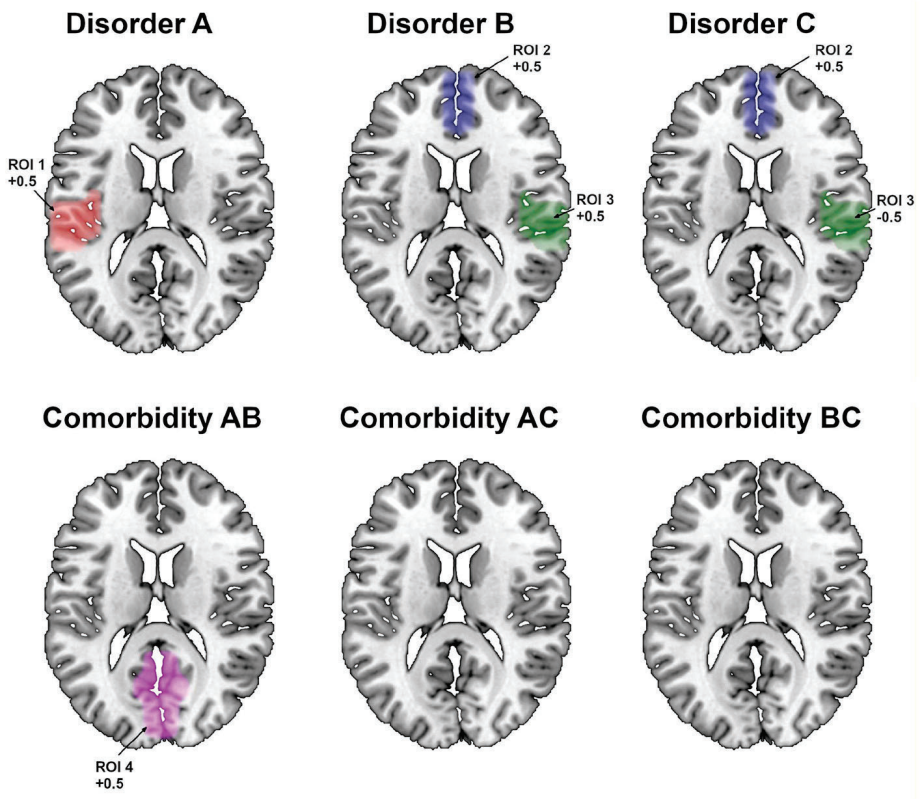

FIGURE 2 | Regions showing statistically significant effects using the novel SDM-PSI approach. ROI, region of interest.

comorbid disorder and the comorbidity. For instance, in the meta-regression using studies on disorder A, the coefficient β_{AB-A} mixes the anomalies simulated for disorder B and comorbidity AB. We acknowledge that this limitation could be potentially overcome by looking at the meta-regression using studies on disorder B. However, this strategy would be confusing in this example because we would still not know whether abnormality in the region of interest (ROI) 4 is due to disorder A or comorbidity AB. The second limitation was a slight loss of accuracy, as shown by that some Hedges' g are slightly different from 0.5, and there are a few falsely positive results.

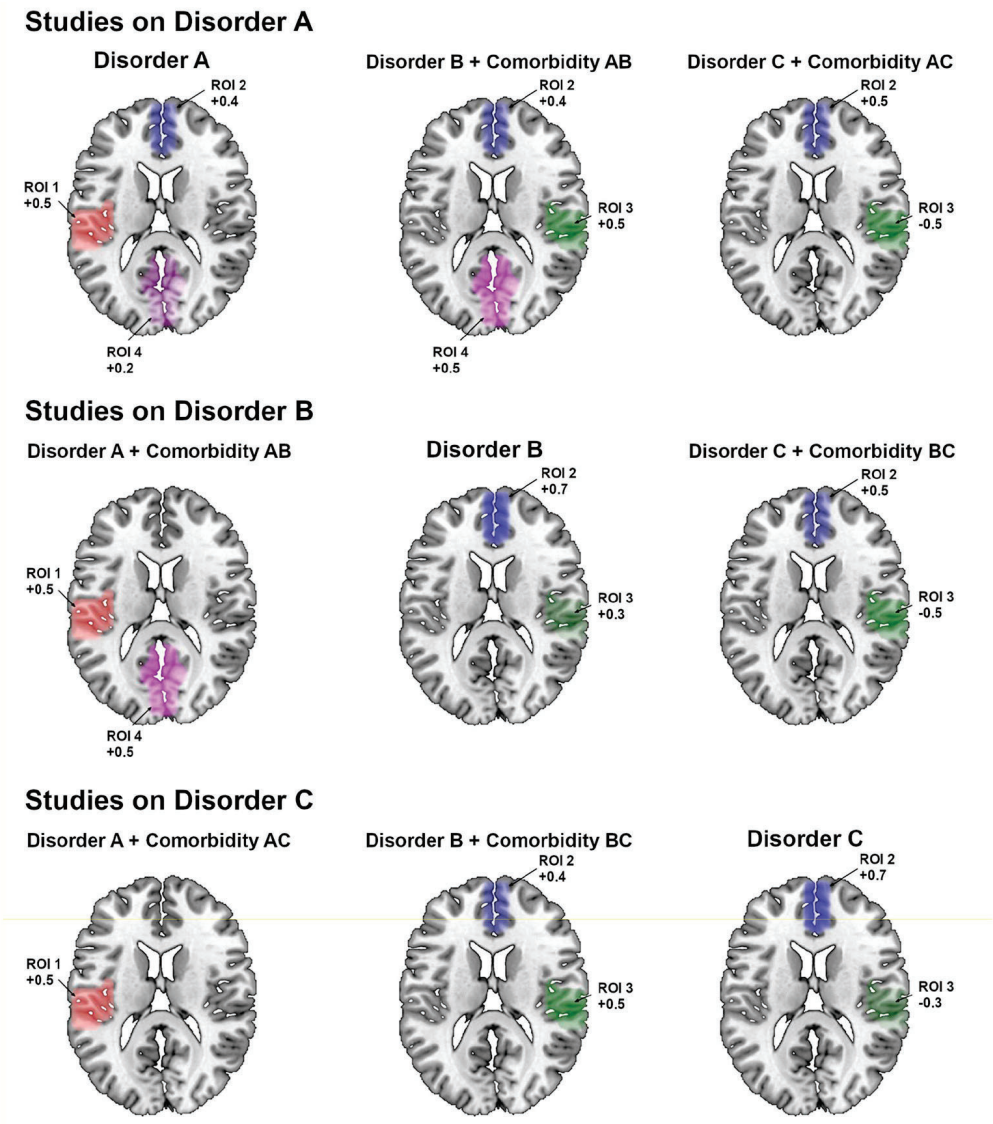

FIGURE 3 | Regions showing statistically significant effects using the previous SDM-PSI approach (separate results for meta-analysis of studies on disorder A, meta-analysis of studies on disorder B, and meta-analysis of studies on disorder C). ROI, region of interest.

Therefore, while the novel SDM-PSI approach does not invalidate the previous version, it better disentangles the specific abnormalities of comorbid disorders.

Results were similar when we created the simulated data with double error, thus expecting Cohen's d around 0.25 (**Table 2**). That said, one can expect poorer estimations with smaller effect sizes or in meta-analyses with few studies. Thus, we would not recommend the new approach when the number of studies for each regressor is too small for the expected effect sizes.

Protocol for the -Meta-Analysis

We pre-registered this protocol to PROSPERO (CRD42021245098).

Design

Meta-regression of case-control VBM studies of GM volume abnormalities in all major mental disorders. The dependent variable will be the brain anatomical differences between patients and controls in a voxel. The independent variables will be the percentages of patients with each mental disorder and each pair of potentially comorbid mental disorders.

Systematic Search

With few exceptions (see below), we will include all whole-brain VBM studies in any mental disorder listed in the mental, behavioral, or neurodevelopmental disorders classification of ICD-11 (International Classification of Diseases 11th Revision). Note that we will use ICD-11 to select the major disorders to

TABLE 2 | Results of the novel approach validation after creating the simulated data with double error.

	Simulated factual data	Novel SDM-PSI approach	Previous SDM-PSI approach		
			Main disorder is A	Main disorder is B	Main disorder is C
Disorder A	ROI 1, g +0.25	β_A = ROI 1, g +0.25	β_A = ROI 1, g +0.26 ROI 2, g +0.23 ROI 4, g +0.11	β_{AB-B} = ROI 1, +0.23 ROI 4, +0.27	β_{AC-C} = ROI 1, g +0.25
Comorbidity AB	ROI 4, g +0.25	β_{AB} = ROI 4, g +0.25	β_{AB-A} = ROI 4, g +0.23 ROI 2, g +0.22 ROI 3, g +0.24		(not studied)
Disorder B	ROI 2, g +0.25 ROI 3, g +0.25	β_B = ROI 2, g +0.23 ROI 3, g +0.26		β_B = ROI 2, g +0.35 ROI 3, g +0.15	β_{BC-C} = ROI 2, g +0.29 ROI 3, g +0.25
Comorbidity BC	(None)	β_{BC} = (None)	(Not studied)	β_{BC-B} = ROI 2, g +0.25 ROI 3, g −0.26	
Disorder C	ROI 2, g +0.25 ROI 3, g −0.25	β_C = ROI 2, g +0.24 ROI 3, g −0.24	β_{AC-A} = ROI 2, g +0.20 ROI 3, g −0.31		β_C = ROI 2, g +0.37 ROI 3, g −0.15
Comorbidity AC	(None)	β_{AC} = (None)		(not studied)	(see Disorder A)

"g", average Hedges' g of the voxels within the cluster of statistical significance; ROI, region of interest.

investigate. Still, as we clarify later, we will include studies using any standard clinical assessment beyond ICD (e.g., DSM). Our search will have two steps.

First Step: Search and Inclusion of Meta-Analyses

In the first step, we will search for the most recent SDM meta-analysis (if any) in the PubMed and Scopus databases for each mental disorder listed in ICD-11 classification (excluding nicotine use disorder, substance-induced specific disorders, neurocognitive disorders, and mental or behavioral disorders associated with pregnancy, childbirth, or the puerperium). The keywords will be the mental disorder (e.g., "major depression," "anxiety disorders," "bipolar disorders," etc.) AND ("meta-analysis") AND ("voxel-based morphometry" OR "VBM" OR "gray matter" OR "grey matter"). We will first screen all the results by the title/abstract and afterward by full-text reading.

The inclusion criterion will be meta-analyses of studies that employed VBM to investigate whole-brain GM volume differences between patients with the above disorders and healthy controls. The exclusion criterion will be meta-analyses from which we can include <10 studies even after adding new studies as described in the second step. We will select the most recent meta-analysis conducted with SDM if more than one meta-analysis meets our inclusion/exclusion criteria. Suppose the inclusion/exclusion criteria of a meta-analysis led to the exclusion of studies that we would include according to our second-step study inclusion/exclusion criteria (see next). In that case, we will look for these potentially includable studies (e.g., a meta-analysis may have excluded studies in children/adolescents while we will include them). Conversely, suppose the inclusion/exclusion criteria of a meta-analysis led to the inclusion of studies that we would exclude according to our second-step inclusion/exclusion criteria. In that case, we would exclude these studies (e.g., a meta-analysis may have included studies with fewer than 10 participants per group while we will exclude them). Suppose during our search, a new meta-analysis is published after we have included a meta-analysis for the same mental disorder. In that case, we will include both analyses (but we will include the duplicated studies only once.

Second Step: Search and Inclusion of Individual Studies

In the second step, we will search in PubMed and Scopus databases for the studies published since the search date of the selected meta-analysis. The keywords used in this search will be [Title/Abstract]: (selected mental disorder) and ("VBM" OR "morphometry" OR "voxel-based" OR "voxelwise" OR "gray matter" OR "grey matter"). We will first screen all the results by the title/abstract and then by full-text reading.

Inclusion criteria will be: (1) studies reporting whole-brain regional GM volume differences between individuals with the included mental disorders, diagnosed by standard clinical assessments (DSM or ICD), and matched healthy controls; (2) employing VBM to conduct the comparisons, (3) reporting the peaks of the clusters of statistically significant voxels or null findings, or availability of statistical parametric map; (4) using a constant statistical threshold throughout the whole gray matter; (5) published as peer-reviewed original articles in English in indexed journals. Exclusion criteria will be: (1) sample size smaller than 10 participants in either the patient or the control group; (2) no case-control comparisons; (3) disorders' subtypes with a known organic origin (e.g., pediatric autoimmune neuropsychiatric disorders associated with streptococci); (4) coordinates of the peaks of the clusters cannot be obtained after contacting the authors (unless maps are available, in which case we will not need the coordinates); (5) ROI or small volume

correction (SVC) analyses; (6) ANOVA analysis without whole-brain t-test *post hoc* analyses; (7) case reports, conferences abstracts, editorials, non-scientific letters, and research protocols; (8) duplicated datasets (we will only include the largest sample size); (9) studies that only analyze the correlation of GM volume with any other measure or that use GM volume features to predict diagnosis unless they specify an additional VBM case-control comparison in the abstract. Special cases will be: (1) longitudinal studies: we will only include the baseline comparison; (2) studies reporting different subgroup analyses: we will include the combined analysis of all subgroups if available. Otherwise, we will include them as different studies if they use different control groups and provide demographic and clinical data for both subgroups separately. If they share the control group, we will divide the control sample size between the number of subgroups.

Two researchers will conduct the systematic search independently, and we will resolve any discrepancies by consensus with a third researcher.

Data Collection

For each study separately, we will extract the sample sizes, demographic and clinical data, methodologic details, and the original statistical parametric map (when available) or the coordinates and *t*-values (or equivalent statistics when available) of the peaks of the clusters of statistically significant voxels (or null findings).

Demographic data will include age distribution (mean and standard deviation) and percentage of males and females.

Clinical data will consist of the percentages of patients with different mental disorders, the percentage of patients receiving each medication group (antipsychotics, antidepressants, anxiolytics -other than hypnotic-, mood stabilizers, and stimulants), the severity of the primary disorder assessed by standard measures [e.g., Hamilton Depression Rating Scale (HDRS) (55)], the age of onset or illness duration of the primary disorder (mean and standard deviation), and the different subtypes for the primary disorder as reported in the included meta-analyses (e.g., inattentive, hyperactive, or combined type for ADHD, type I or II for BD, etc.).

Methodological details will include the pre-processing analysis software (e.g., FSL, SPM) and their version, stereotactic space (e.g., MNI, Talairach space, or MNI coordinates converted to Talairach using the old Brett transform), and the statistical significance threshold (e.g., FWER < 0.05). For studies reporting peaks obtained using two or more whole-brain statistical significance levels (e.g., uncorrected $p < 0.001$ and corrected FWER $p < 0.05$), we will include all peaks obtained using the less conservative threshold. We will also record the information required for the quality assessment (see below).

Given the magnitude of data, we will store them in a database and a well-organized file system with automatic daily backups.

Quality Assessment

We will use the Newcastle-Ottawa Scale (NOS) for case-control studies to assess each study's quality (56). The NOS assesses three characteristics of the studies: the selection of the study groups, the comparability of the groups, and the ascertainment of the exposure for case-control studies. The "selection of the study groups" evaluates the adequate definition of case and control, as well as the representativity of the cases (e.g., selection of all eligible cases with the outcome of interest over a defined period, in a defined catchment area or hospital, etc.), and the controls (community controls or hospital controls). The "comparability of the groups" evaluates if researchers matched cases and controls and/or adjusted for confounders (e.g., age, sex, handedness). Here, statements of no differences between groups or non-statistically significant differences are insufficient for establishing comparability. Finally, we will not evaluate the "ascertainment of the exposure for case-control studies" because both groups underwent a structural MRI in our studies.

We will also assess how much demographic or clinical data each independent study reports.

Imputation of Missing Comorbidity Data

Not all studies report the percentage of patients with specific comorbid disorders. For instance, in the meta-analysis of OCD mentioned earlier, 12% of studies had not excluded comorbid MDD but did not report how many patients had this diagnosis. To impute these unreported data, we will assume they are missing at random. In other words, the proportion of patients with no information about comorbid MDD should follow a similar distribution than in studies reporting this information.

The proportion of patients with a comorbid disorder likely follows a zero-inflated distribution. For example, the percentage of patients with MDD might follow some statistical distribution, but this distribution probably has excess zeroes due to the studies that excluded patients with MDD. However, as fitting zero-inflated distributions with the small data available would be unfeasible, we will use a more straightforward, distribution-free approach. Specifically, the imputation will consist of assigning to each study not reporting the proportion of patients with comorbid MDD, the proportion from another random OCD study. Thus, for example, we may estimate that the missing proportion in a given study is the same as in the study by van den Heuvel et al. (57), or the same as in the study by Pujol et al. (58), or the same as in any other random study (including studies that excluded MDD).

We will repeat these imputations 50 times. We want to remark that his number is commonly considered more than adequate for multiple imputation (Rubin recommended 3 to 10 imputations (59). Additionally, we have checked that the histogram of the imputed proportions of patients with MDD is similar to the histogram of known proportions of patients with MDD after only ten imputations and nearly identical after twenty imputations.

These imputations will be conducted separately for each comorbid disorder. Thus, for instance, in studies with OCD, we will impute comorbid MDD and comorbid anxiety disorders separately.

Statistical Analyses

We will carry out the data pre-processing and the statistical analysis with the SDM-PSI 6.21 software (https://www.sdmproject.com/) (11, 40–42). We will conduct two independent analyses, one for adults and one for children/adolescents.

The pre-processing of statistical parametric maps is the straightforward conversion into images of effect sizes. For studies with only peak information available, the pre-processing consists of estimating the 3D images of the lower and higher bounds of potential effect sizes. The software will later impute the effect sizes multiple times within these bounds.

We will include all major mental disorders in one single linear model described earlier. Then, we will estimate the effects related to each disorder and comorbidity by testing different contrasts within the model. The steps will be those of standard SDM-PSI (11, 40–42) unless otherwise specified:

1. Estimation of the 3D images of maximum likely effect sizes for each model coefficient.
2. Multiple imputation of the study 3D images of effect size adding spatially realistic noise to the expected effect size according to the estimated distribution within the bounds. Following SDM-PSI default parameters, we will conduct this process 50 times, resulting in 50 imputed datasets covering the imputations' uncertainty.
3. Separately for each imputation dataset, random-effects meta-linear model. The dependent variable will be the effect size of the voxel. The independent variables will be the percentages of patients with each mental disorder and the percentages of patients with each pair of potentially comorbid disorders (as far as they involve at least ten studies). In case that at least studies reported the percentage of patients with more than three or more comorbid disorders (e.g., OCD, MDD, and anxiety), we will also include these percentages as an independent variable in the model.
4. Using Rubin's rules, combination of the meta-analytic 3D images of effect size from the different imputation datasets.

To assess the statistical significance, the software converts the 3D image of z-values into a 3D image of threshold-free cluster enhancement (TFCE) statistics and finds the p-value of the TFCE statistics using a Freedman-Lane-based permutation test (60). We will consider statistically significant those voxels with family-wise error-rate (FWER, i.e., corrected p-values) <0.05. For comprehensive reporting, we will also publish supplementary results using significance thresholds of FWER < 0.01, uncorrected $p < 0.001$, and uncorrected $p < 0.005$.

In the complementary analyses, we will add additional independent variables to the linear model to explore potential interactions with mean sample age and percentage of males and control the medication's possible confounding effects. Depending on our final dataset, we will try to assess the effects of the age of onset or illness duration and the severity of the primary disorder, as reported in the original studies. Furthermore, we will perform a subgroup analysis excluding those disorders for which we cannot safely collect whether they are comorbidities for other disorders (e.g., we expect that we will not have information on comorbid personality disorders in many studies).

We will use the I^2 statistic to quantify heterogeneity and conduct meta-regression by the standard error [similar to an Egger-test (41)] to detect potential publication bias. Conventionally, I^2 values above 50% are interpreted as an indication of significant heterogeneity (61).

DISCUSSION

This paper first presents and validates a neuroimaging meta-analytic approach that focuses on comorbidities in mental disorders. Then, using simulations, we show that the new method may detect all GM volume differences with the correct effect size and without falsely positive findings. Finally, we describe the protocol for a meta-analysis of all major mental disorders and their comorbidities, separately for adult and pediatric groups. We will also assess the potentially confounding effects of medication, age of onset or illness duration and the symptom severity of the primary disorder, and the moderator effects of sex on GM volume.

We broadly expect some findings according to previous literature, though a significant part of these findings might change due to the improvements of the new approach. For example, for chronic schizophrenia, previous meta-analyses have detected reduced GM volume in the bilateral insula/ superior temporal gyrus, dorsal, and rostral anterior cingulate cortex (ACC) / medial frontal gyrus, and the thalamus (62, 63). Similarly, for the first episode of psychosis, we expect a reduced GM volume in the right dorsal ACC and the right posterior insula/superior temporal gyrus (35, 62, 63). In OCD, previous meta-analyses have detected both increased GM volumes, mainly located in subcortical regions (e.g., bilateral putamen, left cerebellum, and left hippocampus), and decreased GM volumes, located primarily on prefrontal and cingulate areas (e.g., bilateral ACC/ventromedial prefrontal cortex, bilateral inferior frontal gyrus) (9, 33, 34). For BD and MDD, previous meta-analyses have detected a commonly reduced GM volume in the medial prefrontal system and ACC, regions strongly implicated in mood regulation (64). However, smaller hippocampus and parahippocampal gyrus volumes have been more reported in MDD (26, 37, 65–69). For ADHD, previous meta-analyses have reported a reduced GM volume in ventromedial orbitofrontal cortex/ventromedial prefrontal cortex/rostral ACC, and the right basal ganglia/anterior and posterior insula (34, 70). For ASD, previous meta-analyses have reported reduced GM volume in dorsal ACC/dorsomedial prefrontal cortex, left cerebellum, and increased GM volume in the left middle superior anterior lobe and middle frontal gyrus (33, 70). For anxiety disorders, previous meta-analyses have reported a reduced GM volume in the right ventral ACC and inferior frontal gyrus (71). These areas have been primarily reported in panic disorder, together with the prefrontal cortex (72, 73). However, some of these findings may have been influenced by comorbidity. Thus, we need to conduct the new meta-analysis to know which results remain, which do not, and which had not been detected due to the confounding effects of comorbidities.

We hope that this improved atlas of the anatomical localization of the brain abnormalities associated with each mental disorder will help improve our understanding of their physio-pathological processes. In addition, we hope that this atlas

could be the base for developing MRI-based diagnostic tools that help earlier diagnoses and, therefore, more targeted treatments. For instance, when complex psychotic symptoms hamper the assessment of other symptoms needed for the diagnosis, the "opinion" of an MRI-based diagnostic tool could provide timely extra information to establish an affective vs. non-affective diagnosis and thus a more focused treatment earlier. Or similarly, in depressed individuals at risk of manic shift, the "opinion" of an MRI-based diagnostic tool may help the clinician better evaluate the probability of bipolar vs. unipolar disorder and thus design a more personalized preventive strategy. Indeed, we have found elsewhere that diagnostic labels are among the variables that best predict the future recurrence of an episodic disorder.

Better knowledge about the disorder-specific abnormalities could also increase the efficacy of therapies to modify specific brain regions' activity [e.g., deep brain stimulation or non-invasive brain stimulations such as repetitive transcranial magnetic stimulation (74)]. Improved knowledge about the spatial distribution of these abnormalities may help localize the brain targets better. Indeed, previous studies have already shown how the efficacy of such therapies depends on the exact position of the brain target (75).

We acknowledge that the novel approach has several limitations. The first relates to the debatable nosology of current mental disorders, based on clinical consensus rather than known biological underpinnings. We know, for example, that major psychiatric disorders share some genetic risk factors, and there are high percentages of comorbidity and diagnostic change. However, this does not mean that there are no disorder-specific brain correlates. As noted above, diagnostic labels are among the best predictors of future outcomes, highlighting their clinical relevance. The second relates to the commonly poor reporting of some comorbid disorders in the literature and the subthreshold disorder-specific symptoms that we will not consider due to the complexity of the analysis and the expected large amount of missing data. For instance, studies may check for schizophrenia but not for personality disorders. For this reason, we will conduct subgroup analyses excluding the disorders under-reported as comorbidities. A third limitation is that, as stated earlier, some studies may not report the proportion of patients with specific comorbidities. Thus, we will have to use multiple imputation. We will use a simplistic imputation algorithm without considering whether the proportion of patients with a given comorbid disorder may depend on the age or symptom severity of the sample. We preferred this simple algorithm because we anticipate that we would not be able to collect the necessary data for robustly using more complex imputation algorithms. Another limitation is that, as in any other meta-analysis, a potential drawback may be the heterogeneity across studies. Considering comorbidity, age, sex, and medication, we aim to explain the heterogeneity more than previous meta-analyses, but we anticipate that there will still be unexplained heterogeneity. A significant source of heterogeneity may be due to differences in the MRI equipment (e.g., varying field strength or head coils) and acquisition parameters (76) and the VBM processing method employed by the different studies, such as software and version, normalization, statistical correction, or the size of the smoothing kernel (19). Another relevant source of heterogeneity may be different subject-specific artifacts such as head motion (77), body mass index (78), drops in signal-to-noise ratio due to susceptibility artifacts, the symptom severity of the disorders, or the different phases present in some disorders (e.g., the various episodes in BD) (79, 80). Also, we will only study those mental disorders for which a meta-analysis has already been published and examined by at least ten studies. Last but not least, we must highlight that even when, for simplicity, we talk about GM volume abnormalities, we should more appropriately refer to differences in T1-MRI signal, given that the acquired MRI data are not a direct measure of brain structure (81).

AUTHOR CONTRIBUTIONS

LF, AA-E, and JR conceived the study, modified the SDM-PSI software, and validated the novel approach. All authors participated in the redaction of the manuscript, including minor or major modifications of the protocol.

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Study III-II

Atlas of gray matter volume differences across psychiatric conditions: A systematic review with a novel meta-analysis that considers co-occurring disorders

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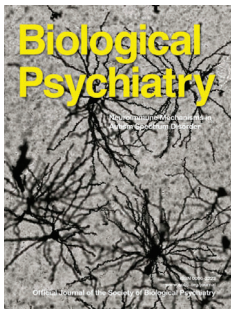

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Atlas of gray matter volume differences across psychiatric conditions: A systematic review with a novel meta-analysis that considers co-occurring disorders

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Short Title:

Atlas of GMV differences across mental disorders

Keywords:

meta-analysis; gray matter volume; psychiatric conditions; comorbidity; major depressive disorder; anxiety disorders.

ABSTRACT

Background:

Regional gray matter volume (GMV) differences between individuals with mental disorders and comparison subjects may be confounded by co-occurring disorders. To disentangle the disorder-specific GMV correlates, we conducted a large-scale multi-disorder meta-analysis using a novel approach that explicitly models co-occurring disorders.

Methods:

We systematically reviewed voxel-based morphometry studies indexed in PubMed and Scopus up to January 2023 comparing adults with major mental disorders (anorexia nervosa, schizophrenia-spectrum, anxiety, bipolar, major depressive, obsessive-compulsive, and post-traumatic stress disorders, plus attention-deficit/hyperactivity, autism spectrum, and borderline personality disorders) to comparison subjects. Two authors independently extracted data and assessed quality using the Newcastle-Ottawa Scale. We derived GMV correlates for each disorder using: a) a multi-disorder meta-analysis accounting for all co-occurring mental disorders simultaneously; b) separate standard meta-analyses for each disorder ignoring co-occurring disorders. We assessed the alterations' extent, intensity (effect size), and specificity (inter-disorder correlations and transdiagnostic alterations) for both approaches.

Results:

We included 433 studies (499 datasets) involving 19,718 patients and 16,441 comparison subjects (51% females, aged 20-67 years). We provide GMV correlate maps for each disorder using both approaches. The novel approach, which accounted for co-occurring disorders, produced GMV correlates that were more focal and disorder-specific (less correlated across disorders and fewer transdiagnostic abnormalities).

Conclusions:

This work offers the most comprehensive atlas of GMV correlates across major mental disorders. Modeling co-occurring disorders yielded more specific correlates, supporting this approach's validity. The atlas NIfTI maps are available online.

INTRODUCTION

Hundreds of studies have reported a plethora of brain features statistically associated with mental disorders (1–4). And even if neuroimaging has long refrained from uncovering pathognomonic anatomical markers, improved knowledge of the features statistically associated with the disorders would help advance brain-targeted research and interventions (5). However, this knowledge is still inconsistent, partly because of the demographic and clinical variation between studies (1,6,7) and partly because of the common but usually overlooked presence of co-occurring disorders.

Arguably, the frequent co-occurrence of mental disorders is one of the most significant contributors to the limited knowledge about the neural underpinnings of mental disorders (5). Indeed, approximately half of the individuals with a mental disorder meet the diagnostic criteria for at least one other disorder simultaneously (8). For example, in a meta-analysis of obsessive-compulsive disorder (OCD), 75% of the studies included patients with co-occurring mental disorders, such as major depressive disorder (MDD, up to 40%) or anxiety disorders (up to 80%) (9). Numerous studies have investigated common and distinct gray matter volume (GMV) features associated with mental disorders, employing various methods to address the issue of co-occurring disorders. Some meta-analyses decided to exclude these patients, including possible non-representative patient groups, and consequently limiting the generalizability of findings at the brain level (10). Other studies decided to include these patients, which provides more representative patient groups but may lead to non-disorder-specific findings influenced by the co-occurring disorders. Although they often tried to assess the impact of the co-occurring disorder in the main results by secondary analysis, there are no current robust methods to account for it adequately

The present study aimed to establish a new methodology to account for the presence of co-occurring mental disorders. Furthermore, it sought to provide an updated structural magnetic resonance imaging (MRI)-based atlas to map the common and distinct GMV alterations associated with each major mental disorder. For that, we systematically searched all voxel-based morphometry (VBM) studies comparing major psychiatric disorders and comparison subjects and conducted a novel meta-analysis of all mental disorders simultaneously, considering the percentage of individuals with each disorder. This methodology (11) differs from prior multi-disorder meta-analyses, which often carried out a separate meta-analysis for each disorder. Nevertheless, Goodking et al. (2018) (2) made a significant contribution by identifying a common neurobiological substrate of GMV alterations across several mental disorders, which remained significant after excluding studies with patients having co-occurring disorders. Finally, we conducted additional analyses to capture the magnitude and uniqueness of the GMV alterations associated with each mental disorder. We hypothesized that different disorders would show shared and specific alterations.

METHODS AND MATERIALS

We conducted this meta-analysis as per PRISMA guidelines (12,13) (see Supplement) and pre-registered and published the protocol (PROSPERO: CRD42021245098 and (11)). The present study focuses on non-

substance-related psychiatric disorders in adults. Two researchers independently conducted the systematic search, data extraction, and quality assessment (LF, MO, MDP, VO, AF, SM, YWY, and LDF) and resolved discrepancies with a third researcher (JR).

Systematic literature search and data extraction

Our systematic search strategy had two stages: identifying meta-analyses of case-control whole-brain VBM studies for each psychiatric disorder listed in the ICD-11 (14) and enriching our samples with additional eligible studies. We conducted both searches in PubMed and Scopus up to 31st December 2021 (see keywords and full search queries in the Supplement). We screened all results by title/abstract, followed by full-text review. We excluded substance use disorders because they add complexity to the model, as different substances have some common and distinct effects on the brain (15). Further studies should use this methodology to model and focus on the common and distinct effects of substances. Note that for schizophrenia, we also included other psychotic-related disorders (e.g., schizoaffective disorder). Further information about both stages of the search process, inclusion and exclusion criteria, and data extraction is presented in the Supplement.

Novel meta-analysis considering co-occurring disorders

To investigate the regional differences in GMV between each mental disorder and comparison subjects, we employed SDM-PSI version 6.23 (www.sdmproject.com) (16,17), recently adapted to enable investigation into all co-occurring mental disorders simultaneously (11). Briefly, the meta-analysis employed a linear model without an intercept, where the dependent variable was the brain anatomical difference between patients and comparison subjects in a voxel, and the independent variables were the percentages of patients diagnosed with each included disorder (whether as a primary or co-occurring disorder). For example, consider a study involving patients with MDD, of whom 30% also had an anxiety disorder and 10% had OCD. In this case, the meta-analysis would explain the brain anatomical differences between patients and comparison subjects by the effects of MDD, plus 30% of the effects of anxiety disorders, plus 10% of the effects of OCD. This modeling differs from previous works where all brain anatomical differences between patients and comparison subjects would exclusively be attributed to MDD. To perform the novel meta-analytical analyses, we excluded those studies that lacked complete information about co-occurring mental disorders. Details of the methods employed by SMD-PSI and the used SDM code are presented in the Supplement.

This linear model allowed us to derive the GMV correlates of each disorder and conduct an ANOVA (followed by post hoc t-tests) to detect differences across pairs of disorders. To prevent significant results with very small effect sizes (standardized mean difference, Hedges' $g<|0.2|$), we set a z threshold based on the mean of z-values corresponding to a $g=0.2$, ensuring that $z\geq3.09$ ($p<0.001$). We used Gaussian Random Fields to correct for multiple testing; we report findings at FWER<0.05. In the Supplement, we list findings at more lenient threshold (uncorrected $p<0.005$). Finally, we independently evaluated potential publication bias for each significant meta-analytic peak and calculated the percentage of variability that reflected the residual heterogeneity across studies (the I^2 statistic).

We also explored a linear model that accounts for interactions between disorders (Supplement).

Separate standard meta-analyses ignoring co-occurring disorders

To compare the novel approach with the commonly used method, we conducted separate meta-analyses for each primary mental disorder using the standard SDM-PSI methodology without considering co-occurring mental disorders.

Extent, intensity, and specificity of the GMV differences

We assessed the observed GMV alterations' extent, intensity (effect size), and specificity (inter-disorder correlations and transdiagnostic alterations) for both the novel meta-analysis that considers co-occurring disorders vs. the standard one that ignores them. From this analysis, we excluded ADHD and ASD due to their classification as neurodevelopmental disorders and BPD because it is a personality disorder. Detailed information is presented in the Supplement.

Data availability

We provide the meta-analytic images at https://neurovault.org/collections/17834/ under the CC-BY license to allow other groups to use our anatomical atlas. We also provided the meta-analytical maps obtained with the separate standard meta-analyses for each mental disorder without accounting for co-occurring disorders. SDM software can be downloaded at https://www.sdmproject.com/, and the new function to correlate brain images is freely available as the "nifti.pbcor" R package.

RESULTS

The literature search yielded a total of 499 datasets investigating 19,718 individuals with mental disorders and 16,441 comparison subjects (See Table 1 for demographics and Table S2-6 for co-occurring disorders). The included mental disorders were anorexia nervosa, anxiety, bipolar disorder (BD), MDD, OCD, post-traumatic stress disorder (PTSD), and schizophrenic disorders, plus attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), borderline personality disorder (BPD), internet gaming disorder. After excluding studies that lacked complete information about co-occurring disorders, we had 290 datasets (11,395 patients and 8,826 comparison subjects). For internet gaming disorder, only nine studies reported full information about co-occurring disorders, so we discarded it from the main analysis. We describe the systematic search results in the Supplement.

Results from the novel and standard meta-analyses

For anorexia, both meta-analyses found smaller GMV in the temporal lobe, precuneus, supplementary motor area, and middle cingulate, while the standard analysis also in the anterior cingulate (ACC) and cerebellum. For anxiety disorders, both identified smaller GMV in the temporal and occipital lobes; the novel analysis found smaller GMV in the thalamus and right striatum and larger GMV in the right cerebellum, while the standard analysis found smaller GMV in the middle cingulate and insula. For BD, both revealed smaller GMV

in the prefrontal cortex (PFC), orbitofrontal cortex, temporal lobes, insulas, cerebellum, and striatum. For MDD, both identified smaller GMV in the PFC, ACC, middle cingulate, bilateral insula, and cerebellum, and the novel analysis also in the thalamus, hippocampus and left striatum. For OCD, both found smaller GMV in the parietal lobe and larger GMV in the right cerebellum; the novel analysis found smaller GMV in the orbitofrontal cortex, and the standard analysis in the ACC and superior temporal gyrus. For PTSD, both identified smaller GMV in the left lingual gyrus, and the standard approach also in the superior frontal gyrus. For schizophrenia, both identified widespread smaller GMV across cortical and subcortical regions. Detailed information can be found in the Supplement (Table 2 and Fig. 2-3), including uncorrected results (Table S7) and standard meta-analyses (Table S8, Fig. S1).

In the ANOVA to detect GMV differences across disorders, we identified 14 cortical clusters (Table S9). Significant results from the post-hoc pairwise t-tests are presented in Table S10. Briefly, anorexia showed distinctly smaller GMV in the precuneus compared to other mental disorders. PTSD exhibited larger GMV compared to most other disorders in regions where, in the primary analyses, they showed reduced GMV relative to controls, while PTSD did not. Finally, OCD showed smaller GMV in the right inferior parietal gyrus compared to anxiety disorders and PTSD.

Results from the novel meta-analysis accounting for interactions are presented in the Supplement (Tables S12-13).

Extent, intensity, and specificity of the GMV differences

As shown in Fig. 4, schizophrenic disorders exhibited the highest percentage of voxels (20%), showing GMV differences with comparison subjects with a Hedges' g>0.2, followed by BD (12%), anorexia (8%), anxiety disorders (5%), and PTSD (4%). Anorexia exhibited the highest intensity of GMV differences (g=0.94), followed by PTSD (g=0.83). MDD and OCD showed differences in 3% of voxels with milder intensity (g<0.34). In the standard meta-analysis, we observed a higher percentage of voxels showing GMV differences in all the disorders except BD, while a similar intensity (or occasionally smaller, e.g., anorexia: g=0.69 vs. 0.94; BD: g=0.35 vs. 0.46).

The correlation analysis (Fig. 4) showed similarities in GMV differences between schizophrenic disorders and those from BD, MDD, OCD, and anxiety disorders (r=[0.39-0.56]), moderate similarities between BD and those from MDD, anxiety disorders, and OCD (r=[0.27-0.40]), and weakly similarities between MDD and anorexia (r=0.25). The standard meta-analysis revealed more significant correlations between all mental disorders.

In the transdiagnostic analysis, several clusters showed smaller GMV ($g \geq 0.2$) in at least three disorders, including the PFC, orbitofrontal cortex, ACC, middle cingulate, and temporal gyrus, including the insulas (Table 3, Fig. S2). This transdiagnostic map significantly correlated with alterations associated with schizophrenic disorders (r=0.99), BD (r=0.95), anxiety (r=0.65), MDD (r=0.52), anorexia (r=0.43), OCD

(r=0.38) and PTSD (r=0.65). The standard analysis showed more transdiagnostic regions, including the precuneus, fusiform gyrus, and parietal lobe (Table S11, Fig. S3).

Findings from the standard meta-analysis were similar when we repeated the analysis using only studies with complete information on co-occurring disorders (Table S12).

DISCUSSION

This work provides a comprehensive GMV neuroanatomical atlas of major mental disorders, accounting for co-occurring disorders. Here, we report the main GMV alterations associated with anorexia, anxiety disorders, BD, MDD, OCD, PTSD, and schizophrenic disorders (Table 2-S8, Fig. 2-S1), with further details provided in the Supplement. Alterations associated with ADHD, ASD, and BPD are reported in the Supplement. We discuss the results for each disorder below, including the extent and intensity of the alterations. We also discuss separately their specificity, based on the correlations between disorders and the extent of transdiagnostic alterations. Finally, we comment on the strengths and limitations of this work.

Importantly, GMV alterations derived from this novel meta-analysis were more focal (fewer voxels included) and disorder-specific (less correlated and shared among disorders) than when we conducted separate standard meta-analyses per each disorder (i.e., ignoring co-occurring disorders), even when we included the same studies. The presence of more focal and disorder-specific alterations supports the increased validity of the novel approach. Or, seen from the opposite side, the maps from the standard meta-analyses would mix alterations from different co-occurring disorders, resulting in more extensive alterations over-correlated across disorders with inflated transdiagnostic alterations.

Results from the novel and standard meta-analyses

Anorexia nervosa

Findings from both meta-analyses aligned with previous work (18–20), except for smaller GMV in ACC and cerebellum that was found in previous work and our standard meta-analyses, but not in our novel approach, likely to our adjustment for co-occurring disorders. Indeed, these regions have been associated with MDD, which is commonly co-occurring in anorexia (Table 2). Interestingly, smaller GMV in the precuneus was unique to anorexia. However, this finding should be interpreted cautiously due to significant study heterogeneity, which may be linked to individual variability in anorexia, particularly in weight recovery, warranting further investigation.

Anxiety disorders

Findings from both meta-analyses partially matched previous studies (1,21,22). A main difference is that previous research often reported larger GMV in the parietal and occipital lobes (21,22), primarily associated with SAD (23), whereas our analysis included all anxiety disorders. Another discrepancy was smaller GMV in the middle cingulate and insula, reported by the standard approach (1). In the interaction meta-analysis, we found smaller GMV in these regions for individuals with anxiety but without MDD or OCD, suggesting that

the neural correlates of anxiety disorders may vary based on the presence of co-occurring mental disorders. Notably, individuals with anxiety and MDD/OCD showed an effect size of g=0.3 in these regions, though not statistically significant, likely due to the small sample size.

Bipolar disorders

Findings from both meta-analyses are consistent with previous studies (6,23,24), supporting smaller GMV in the dorsal/ventral PFC and ACC as a common substrate of mood disorders (24).

Major depressive disorder

Findings from both meta-analyses aligned with previous studies (1,26), further supporting evidence for biomarkers in mood disorders (24). The novel meta-analysis also identified differences in several subcortical regions, contrasting with the standard approach and prior research, which often reported subcortical alterations only in the hippocampus (1,24,25). This discrepancy may arise from including patients with co-occurring disorders, usually excluded, as MDD has been found to cluster in distinct biotypes with different neural correlates (26). As a result, previous studies may have overlooked biotypes less likely to co-occur with other psychiatric disorders. Interestingly, controlling for the interaction with co-occurring anxiety disorders, these subcortical regions were no longer significant, suggesting that the neural correlates of MDD may vary depending on the presence of co-occurring mental disorders. Finally, the effect sizes of the GMV alterations were generally small ($g<0.25$), which may be attributed to the fact that MDD is primarily driven by brain functional irregularities rather than structural ones (3,27).

Obsessive-compulsive disorder

Findings from both meta-analyses partially aligned with previous studies (31–33), although the novel approach did not identify smaller GMV in the temporal gyrus, as reported in previous research and the standard analysis. This discrepancy may be due to the presence of co-occurring disorders (23% had MDD, and 17% anxiety disorders). Indeed, abnormalities in the temporal lobes have often been associated with these mental disorders (1,24) and are supported by our present findings. Interestingly, smaller GMV in the parietal gyrus was statistically different between OCD and other anxiety-related disorders (anxiety and PTSD).

Post-traumatic stress disorder

The main finding of the novel meta-analysis, supported by the standard approach, was consistent with previous studies (1,30). However, previous meta-analyses also reported alterations in regions from the frontolimbic circuit, such as the PFC and hippocampus (31,32), essential for threat processing and emotion regulation (33). We observed smaller GMV in the dorsal PFC in both meta-analyses (uncorrected $p<0.005$) but no significant differences in the hippocampus, possibly due to previous studies specifically targeting that region.

Schizophrenic disorders

Findings from both meta-analyses align with previous research and established models for schizophrenic disorders, as discussed in previous meta-analyses and ENIGMA findings (34,35). Interestingly, the findings also included the GMV decreases found to estimate relapse risk after a first episode of psychosis (right middle temporal, right inferior frontal/precentral, right middle frontal, bilateral rectus, and right Angular) (36).

Specificity of the GMV differences – correlations across disorders

Schizophrenic disorders showed the highest percentage of voxels with GMV alterations, affecting multiple brain networks. Additionally, the spatial pattern of GMV alterations of schizophrenic disorders was correlated with those of BD, MDD, OCD, and anxiety. These findings are consistent with those reported by the ENIGMA (4), which identified strong correlations among mood disorders, schizophrenic disorders, and OCD, involving regions like the insula, hippocampus, and fusiform gyrus, explaining 42% and 89% of the variance. Supporting these ENIGMA findings, the abnormality pattern of BD also correlated with MDD, OCD, and anxiety. The GMV abnormality pattern of MDD also correlated with anorexia, possibly due to the common depressive symptoms in these patients, without reaching the threshold of MDD. Surprisingly, the GMV abnormality pattern of PTSD did not correlate with any other mental disorder, showing significant differences with other mental disorders.

These findings contrast with those from the standard meta-analyses, where almost all mental disorders significantly correlated with each other. This discrepancy may rely on the high prevalence of co-occurring disorders not accounted for in the standard meta-analysis. For instance, in the standard analysis, the GMV abnormality pattern of MDD significantly correlated with those from anxiety (r=0.60) and OCD (r=0.47). Therefore, the observed similarities are likely due to the common co-occurrence of these disorders, where 28% of the individuals with anxiety and 23% of the individuals with OCD presented co-occurring MDD. This finding supports the need to adjust for co-occurring mental disorders when investigating specific brain alterations associated with each mental disorder. It also suggests that our method successfully mitigated this potential confounding effect.

Specificity of the GMV differences – extent of transdiagnostic alterations

Our study identified smaller GMV in the dorsal PFC, orbitofrontal cortex, dorsal ACC, middle cingulate, and insula across psychotic, mood, and anxiety disorders. This finding supports previous hypotheses of common neurobiological substrates across mental disorders (2–4), specifically the dorsal ACC and insula, highlighting that they are not due to the presence of co-occurring disorders. Previous studies have also reported smaller GMV in the PFC associated with mood disorders (24) and in the middle cingulate linked to mood, anxiety, and trauma-related disorders (1).

These regions are crucial for emotion regulation, social behavior, and cognitive and executive functions (39,40), commonly impaired across mental disorders. Therefore, these GMV alterations could be associated with cognitive impairments rather than diagnosis-specific symptoms (2,39). Although evidence

suggests that those common substrates are associated with the disorders rather than a risk state, we cannot rule out that our findings could stem from early life trauma. Notably, evidence showed that early life trauma is associated with an increased risk of developing specific disorders in adulthood, such as mood or psychotic disorders (40). Additionally, childhood maltreatment is associated with smaller GMV in several brain regions, including the ACC, even though they did not develop any mental disorder (41). Another potential explanation could be the shared genetic pattern across disorders. For instance, a study investigating the genetic architecture of 11 mental disorders (42) identified four factors explaining the genetic structure for (i) compulsive behaviors (anorexia, OCD), (ii) psychotic features (schizophrenic disorders, BD), (iii) neurodevelopmental disorders (ADHD, ASD), and (iv) internalizing disorders (anxiety, MDD). This genetic clustering partially differs from our neuroanatomical patterns (e.g., there are no overlapping structures between anorexia and OCD). Additionally, there is converging evidence of a shared genetic pattern across mood and psychotic disorders (MDD, BD, and schizophrenic disorders) (43). Our findings suggest that genetics and neuroanatomy can provide different and complementary information about the neurobiological underpinnings of mental disorders.

Strengths of this work

Despite multiple efforts to investigate disorder-specific and transdiagnostic structural alterations in mental disorders (1–4), prior studies often exclude patients with co-occurring disorders or investigate their potential effect via meta-regressions. Our work presents the first large-scale meta-analysis considering all mental disorders simultaneously in a single linear model, effectively accounting for co-occurring disorders and providing a more accurate disorder-specific spatial pattern of GMV alterations. We also investigated the similarities of GMV alterations across disorders, supporting findings by Opel (4). Finally, we presented new and complementary evidence regarding ACC and insula being a transdiagnostic biomarker, as suggested by Godking (2).

There are several applications of the current work. Firstly, we provide a new meta-analytical methodology, overcoming the previous limitation of not fully accounting for co-occurring mental disorders when investigating disorder-specific brain alterations. This methodology can be extended to other MRI modalities, including functional MRI and diffusion tension imaging, contributing to a deeper comprehension of the psycho-pathological processes underlying mental disorders. Additionally, the provided atlas of GMV alterations offers an improved localization of alterations in mental disorders, which may also enhance the efficacy of therapies targeting specific brain regions to improve symptom severity, such as deep brain stimulation or non-invasive brain stimulations (44).

Finally, the atlas could benefit future machine learning research, particularly in improving the diagnoses of mental disorders. We fully acknowledge the low accuracy of MRI-based machine learning tools (45,46), which is expected considering that the diagnostic labels are a pragmatic but conventional classification. For this reason, we should not think about diagnostic prediction but risk estimation,

acknowledging the uncertainty of the estimates. Similarly, we must remind here some rules for properly using machine learning in mental health research, such as pre-registering the analysis, starting with simpler algorithms, avoiding data leakage, considering implementation issues, or mitigating racial and gender biases (47). Taking all these considerations into account, we believe that this atlas may help create models that estimate the risk of different mental disorders, offering the clinician additional information that might help enhance diagnostic accuracy and, thus, a more focused treatment earlier.

Limitations

The current study has several limitations. Firstly, the included studies' cross-sectional nature impedes the causality inference; thus, findings must be interpreted as statistical associations. Additionally, there is a limitation concerning the debatable nosology of current mental disorders based on clinical consensus rather than known biological underpinnings (48). Further, the proportion of co-occurring disorders in our study did not reflect those in the general population (Table S6). However, our focus was not on the comorbidity patterns in the general population but on disentangling the specific neuroanatomy of co-occurring mental disorders. We also must consider limitations inherent to meta-analysis, such as results being based on summarized data (e.g., peak and effect sizes) rather than raw data (49). Similarly, we did not examine the effects of potential clinical and methodological moderators such as symptom severity, body mass index, or software used. We decided not to analyze the effects of these covariates to avoid adding complexity to the current paper and invite future studies to investigate them. Another limitation is that we only included those mental disorders for which a meta-analysis has already been published and examined by at least ten studies. Finally, we must highlight that even when, for simplicity, we talk about GMV differences, we should more appropriately refer to differences in T1-MRI signal, given that the acquired MRI data are not a direct measure of brain structure (50).

Conclusion

In summary, we present the first large-scale atlas of specific and transdiagnostic GMV alterations statistically associated with major psychiatric conditions, considering the confounding effect of co-occurring disorders. This innovative meta-analysis, which involved 19,718 patients and 16,441 comparison subjects, represents a significant contribution to our understanding of the shared and distinct neural substrates underlying mental disorders. This work adds to admirable initiatives, such as the Health's Brain Research Through Advanced Innovative Neurotechnology (BRAIN) (51), ENIGMA consortium (4) or Psychiatric Genetics Consortium (42), that enhance our knowledge of the physiopathology of mental disorders, paving the way for future diagnostic aid tools and precision-based interventions directed to specific brain targets. To allow other groups to use our anatomical atlas, we have uploaded the images at https://neurovault.org/collections/17834/ under the CC-BY license.

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FINANCIAL DISCLOSURES

MV has received research grants from Eli Lilly & Company and has served as a speaker for Abbott, Bristol–Myers Squibb, GlaxoSmithKline, Janssen–Cilag, and Lundbeck. KR received a grant from TAKEDA Pharmaceuticals for another study and consultation fees from SUPERNUS and Lundbeck. EV has received grants and served as a consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Abbvie, Aimentia, Angelini, Biogen, Biohaven, Boehringer Ingelheim, Casen-Recordati, Celon, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo Smith-Kline, Idorsia, Janssen, Lundbeck, Novartis, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris. Evia has participated as a co-investigator in a Janssen-Cilag, S.A., clinical trial and as a speaker for Novo Nordisk. JR has received CME honoraria from Inspira Networks for a machine learning course promoted by Adamed, outside the submitted work. All other authors report no biomedical financial interest or potential conflicts of interest.

Supplement Description:

Supplemental Methods, Results, Discussion, Figures S1-S14, Tables S1-S15

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Figure 1. Flowchart of the systematic literature searches for all mental disorders included.

Footnote: VBM: voxel-based morphometry

Figure 2. Atlas of gray matter volume alterations in mental disorders – maps of the main findings at family-wise error rate (FWER)<0.05 and k≥100 for anxiety disorder, anorexia nervosa, attention-deficit hyperactivity disorder, autism spectrum disorders, and bipolar disorder.

Region names indicated the location of the maximum peak of the significant clusters. Regions with larger GMV are displayed in yellow/red. Regions with smaller GMV are displayed in green/blue. The right side of the brain image represents the right hemisphere. The displayed slices correspond to z=-25, -15, 0, 15 30, 45. ADHD: attention-deficit hyperactivity disorder, ASD: autism spectrum disorders, B: bilateral, BD: bipolar disorder, IFG: inferior frontal gyrus, L: left, MFG: middle frontal gyrus, MOG: middle occipital gyrus, MTG: middle temporal gyrus, PHG: parahippocampal gyrus, R: right, SFG: superior frontal gyrus, SMA: supplementary motor area, SMA: supramarginal gyrus, SOG: superior occipital gyrus, STG: superior temporal gyrus, STR: striatum, THAL: thalamus.

Figure 3. Atlas of gray matter volume alterations in mental disorders – maps of the main findings at family-wise error rate (FWER)<0.05 and k≥100 for borderline personality disorder, major depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and schizophrenia-spectrum disorders.

Region names indicated the location of the maximum peak of the significant clusters. Regions with larger GMV are displayed in yellow/red. Regions with smaller GMV are displayed in green/blue. The right side of the brain image represents the right hemisphere. The displayed slices correspond to z=-25, -15, 0, 15 30, 45. B: bilateral, BPD: borderline personality disorder, IPG: inferior parietal gyrus, ITG: inferior temporal gyrus, L: left, MDD: major depressive disorder, MTG: middle temporal gyrus, OCD: obsessive-compulsive disorder, PTSD: post-traumatic stress disorder, R: right, SCH Dis.: schizophrenic disorders, STG: superior temporal gyrus.

Figure 4. Extent of gray matter volume differences between disorders and similarity of the differences across disorders

Footnote: GMV: gray matter volume, g: Hedges' g, ADHD: attention-deficit/hyperactive disorder, ASD: autism spectrum disorder, BD: bipolar disorder; BPD: borderline personality disorder, GMV: gray matter volume, IGD: internet gaming disorder, MDD: major depressive disorder, OCD: obsessive-compulsive disorder, PTSD: post-traumatic stress disorder, SCH Dis: schizophrenic disorders.

Table 1. Demographic and clinical characteristics of the included participants.

Mental Disorder	N	Females (%)	Age Mean	Age SD	Duration of illness mean (years)	Duration of illness SD (years)	Co-occurring disorders (%)	Medication (%)
Anorexia nervosa	484	91.9%	28.05	8.3	7.80	8	14% anxiety 10% MDD 8% OCD 2% PTSD	Total: 25.5% 21% AntiD 5% AP
Anxiety disorders	1844	59.3%	32.87	11.1	8.40	9	1% ADHD 20% MDD	Total: 24% 21.5% AntiD 10% AA
ADHD	788	42.5%	32.04	12.4	-	-	2% anorexia 12% anxiety 1% BD 2% BPD 14% MDD	Total: 29% 29% STM
ASD	493	11.8%	29.69	8.7	-	-	3% anxiety 3% ADHD 7% MDD 1% SSD	Total: 15% 11% AntiD 6% AA 5% AP
BD	3350	56.1%	36.82	12.9	12.07	10	4% anxiety 1% ADHD	Total: 86% 19% AntiD 12% AA 45% AP 65% MS
BPD	414	83.5%	30.89	8.9	-	-	7% anorexia 20% anxiety 38% MDD 3% OCD 21% PTSD	Total: 35% 21% AntiD 8% AA 17% AP 15% MS
Internet gaming disorder	312	5.8%	22.61	2.6	-	-	0%	0%
MDD	6897	61.7%	35.82	13.1	7.58	10	6% anxiety	Total: 49% 42% AntiD 5% AA 6% AP
OCD	1204	49%	32.26	9.8	10.11	9	13% anxiety 15% MDD	Total: 61% 56%AntiD 5% AP
PTSD	464	53.7%	34.51	11.7	7.3	8	3% anxiety 22% MDD	Total: 21% 20% AntiD
Schizophrenic disorders	5465	36.2%	33.12	11.2	9.37	10	0%	Total: 80% 80% AP

AA: anxiolytics, AntiD: antidepressants, ADHD: attention-deficit hyperactivity disorder, AP: antipsychotic, ASD: autism spectrum disorder, BD: bipolar disorder; BPD: borderline personality disorder, MDD: major depressive disorder, MS: mood stabilizer, OCD: obsessive-compulsive disorder, PTSD: post-traumatic stress disorder, SD: standard deviation, STM: stimulants.

Table 2. Atlas of gray matter volume alterations in mental disorders – location and statistics of the main differences with healthy controls. Significance was set at family wise error rate (FWER)<0.05.

	Peak				Clusters	
	MNI	**Hedges'g (95% CI)**	**Z-value**	**I2 p-bias**	**N voxels (P-value)**	**Breakdown**
Anorexia Nervosa (Z > |3.09|)						
Anorexia < Comparison subjects						
L supplementary motor area	-2,-10,60	-0.94 (-1.17, -0.71)	7.96	42% p=0.17	2639 (<0.001)	B SMA (1303) B MCC (685) B paracentral lobule (225)
R precuneus	6,-70,40	-0.94 (-1.16, -0.70)	7.95	52% p=0.99	990 (<0.001)	B precuneus (680) B cuneus cortex (103)
L middle temporal gyrus	-46,-2,-24	-0.67 (-0.89, -0.46)	6.09	13% p=0.97	872 (<0.001)	R MTG (281)
R middle temporal gyrus	58,-18,-16	-0.67 (-0.88, -0.45)	6.10	15% p=0.96	387 (0.012)	R middle/ITG (270)
Anxiety Disorders (Z > |3.09|)						
Anxiety < Comparison subjects						
R superior temporal gyrus	54,-22,12	-0.36 (-0.49, -0.24)	5.56	10% p=0.78	1924 (<0.001)	R STG (818) R RO (535) R heschl gyrus (148)
L supramarginal gyrus	-54,-42,24	-0.39 (-0.51, -0.27)	6.47	4% p=0.43	1312 (<0.001)	L STG (462) L SMG (415)
R striatum	22,14,-4	-0.38 (-0.51, -0.25)	5.83	24% p=0.09	420 (0.004)	R putamen (99) R stritatum (88)
R thalamus	18,-26,12	-0.45 (-0.57, -0.33)	7.47	8% p=0.55	282 (0.021)	R thalamus (154)
L middle occipital gyrus	-22,-90,20	-0.37 (-0.51, -0.24)	5.40	0% p=0.17	271 (0.026)	L superior/MOG (136)
Anxiety > CS						
R cerebellum	10,-74,-16	0.31 (0.18, 0.44)	4.57	2% p=0.83	262 (0.029)	R cerebellum (218)
Attention deficit/hyperactive disorder (Z > |3.09|)						
ADHD < Comparison subjects						
R supramarginal gyrus	54,-42,28	-0.33 (-0.48, -0.18)	4.40	12% p=0.40	333 (<0.001)	R SMG (221)
Autism spectrum disorder (Z > |3.09|)						
ASD < Comparison subjects						
R cerebellum	18,-66,-16	-0.47 (-0.65, -0.28)	4.98	60% p=0.15	389 (0.014)	R cerebellum (335)
B calcarine fissure*	6,-74,12	-0.49 (-0.68, -0.30)	5.05	39% p=0.74	396 (0.015)	B calcarine fissure (221)
Bipolar Disorder (Z > |3.97|						
BD < Comparison subjects						

L superior frontal gyrus, medial	2,34,36	-0.33 (-0.43, -0.23)	9.70	6% p=0.64	15652	B SFG, dorsal (5193) R MTG (2727) B MFG (1349) R IFG (1336) B ACC (919) R insula (838) R ITG (536) B MCC (526) B SMA (227) R amygdala (101)
L middle temporal gyrus	-46,-70,8	-0.27 (-0.36, -0.18)	7.41	1% p=0.86	3920	L postcentral gyrus (1012) L IPG (779) B SMG (483) L MTG (385) L angular gyrus (329) L precentral gyrus (283) L STG (253) L MOG (171)
R parahippocampal gyrus	18,-34,-12	-0.41 (-0.50, -0.33)	7.27	2% p=0.82	1603	R cerebellum (675) R fusiform gyrus (231) R PHG (180)
L superior temporal gyrus	-34,6,-24	-0.31 (-0.40, -0.23)	6.89	2% p=0.96	1457	L STG (359) L ITG (271) L insula (151) L MTG (147)
L fusiform gyrus	-26,-54,-16	-0.32 (-0.41, -0.23)	7.12	1% p=0.57	1474	L cerebellum (700) L fusiform gyrus (299) L lingual gyrus (176)
L gyrus rectus	-10,34,-28	-0.32 (-0.41, -0.23)	7.23	4% p=0.55	1219	B gyrus rectus (499) B SFG, orbital (306)
R caudate	2,10,8	-0.32 (-0.41, -0.24)	8.70	4% p=0.26	701	R caudate (124)
R cerebellum	6,-62,-28	-0.32 (-0.41, -0.23)	6.27	33% p=0.96	523	R cerebellum (379)
R middle occipital gyrus	38,-86,8	-0.38 (-0.47, -0.30)	7.30	35% p=0.06	445	R MOG (397)
R angular gyrus	42,-66,48	-0.29 (-0.38, -0.20)	6.48	3% p=0.20	475	R angular gyrus (286) R IPG (173)
L calcarine fissure	-10,-74,12	-0.32 (-0.40, -0.23)	5.91	1% p=0.44	291	B calcarine fissure (123)
BD > Comparison subjects						
L precuneus	-10,-46,64	0.30 (0.20, .39)	6.26	15% p=0.69	864	B paracentral lobe (356) L precuneus (307)
R superior frontal gyrus	22,26,48	0.30 (0.22, .39)	7.17	2% p=0.63	561	R MFG (362) R SFG (146)
L superior occipital gyrus	-10,-94,8	0.28 (0.18, .37)	5.95	0% p=0.56	336	L superior occipital gyrus (117)
Borderline Personality Disorder (Z > |3.09|)						
BPD vs. Comparison subjects						
No significant results						

Major depressive disorder (Z > |4.65|)						
MDD < Comparison subjects						
R cerebellum	6,-38,-12	-0.25 (-0.32, -0.19)	7.49	17% p=0.65	23891	B cerebellum (2800) B MCC (1816) R IFG (1815) B MFG (1811) B MTG (1419) B SMA (13549 B SFG, dorsal (1282) B ACC (1231) B precuneus (1204) R precentral gyrus (1158) B fusiform gyrus (910) B ITG (758) R postcentral gyrus (653) R STG (628) B lingual gyrus (540) R insula (503) B cuneus cortex (280) L calcarine fissure (213) R hippocampus (146)
L inferior temporal gyrus	-46,-14,-36	-0.22 (-0.28, -0.16)	7.11	2% p=0.34	7160	L insula (928) L STG (824) L IFG (489) B striatum (445) L ITG (360) L MFG (248) L fusiform gyrus (245) L putamen (237) L RO (181) L MTG (175) L PHG (169) L caudate (120)
L angular	-46,-66,36	-0.23 (-0.29, -0.16)	6.96	0% p=0.51	1222	L angular (638) L IPG (249) L superior parietal gyrus (147)
B gyrus rectus	2,58,-20	-0.23 (-0.30, -0.17)	6.99	3% p=0.72	795	B gyrus rectus (352) L SFG, orbital (214)
L inferior parietal gyrus	-42,-26,44	-0.18 (-0.25, -0.11)	5.15	1% p=0.95	566	L postcentral gyrus (390) L IPG (61)
Obsesive-compulsive disorder (Z > |3.09|)						
OCD < Comparison subjects						
R angular gyrus	54,-50,36	-0.33 (-0.45, -0.22)	5.70	2% p=0.84	723 (<0.001)	R angular gyrus (347) R IPG (206) R SMG (141)
B gyrus rectus	2,30,-28	-0.31 (-0.43, -0.20)	5.26	19% p=0.89	299 (0.024)	B gyrus rectus (153)
OCD > Comparison subjects						
R cerebellum	10,-34,-16	0.34 (0.22, 0.45)	5.69	25% p=0.78	1186 (<0.001)	R cerebellum (403) R fusiform gyrus (167)

Posttraumatic stress disorder (Z > |3.09|)						
PTSD < Comparison subjects						
L lingual gyrus	-10,-66,-4	-0.83 (-1.08, -0.57)	6.41	7% p=0.66	859 (<0.001)	L lingual gyrus (334) L fusiform gyrus (185) L cerebellum (144)
Schizophrenic disorders (Z > |6.12|)						
Schizophrenic disorders < CS						
L superior temporal gyrus	-58,-10,0	-0.48 (-0.57, -0.40)	10.80	4% p=0.88	30642 (<0.001)	B SFG (4623) B MCC (2513) L STG (1926) B ACC (1782) L IFG (1745) L insula (1496) B MFG (1187) L MTG (1051) B gyrus rectus (764) L RO (653) B SMA (498) L putamen (260) L PHG (239) L precentral gyrus (228) L postcentral gyrus (218) L heschl gyrus (184) L precuneus (149) L fusiform gyrus (145) L amygdala (131) L striatum (117)
R postcentral gyrus	62,-10,16	-0.46 (-0.55, -0.36)	9.47	22% p=0.72	10958 (<0.001)	R STG (2160) R IFG (1336) R insula (1016) R RO (981) R MTG (833) R precentral gyrus (743) R postcentral gyrus (713) R SMG (618) R heschl gyrus (185)
L middle temporal gyrus	-42,-66,20	-0.29 (-0.38, -0.20)	6.52	3% p=0.55	1864 (<0.001)	L MTG (497) L IPG (398) L angular gyrus (358) L ITG (325)
R middle occipital gyrus	46,-74,16	-0.23 (-0.32, -0.14)	4.99	5% p=0.74	1040 (0.006)	R MTG (597) R MOG (220) R angular gyrus (131)
R hippocampus	26,-18,-16	-0.25 (-0.34, -0.16)	5.30	0% p=0.78	816 (0.015)	R cerebellum (375) R fusiform gyrus (133) R hippocampus (111)
L lingual gyrus	-26,-46,-8	-0.23 (0-.32, -0.14)	5.09	0% p=0.93	601 (0.037)	L cerebellum (116) L lingual gyrus (110) L fusiform gyrus (105)

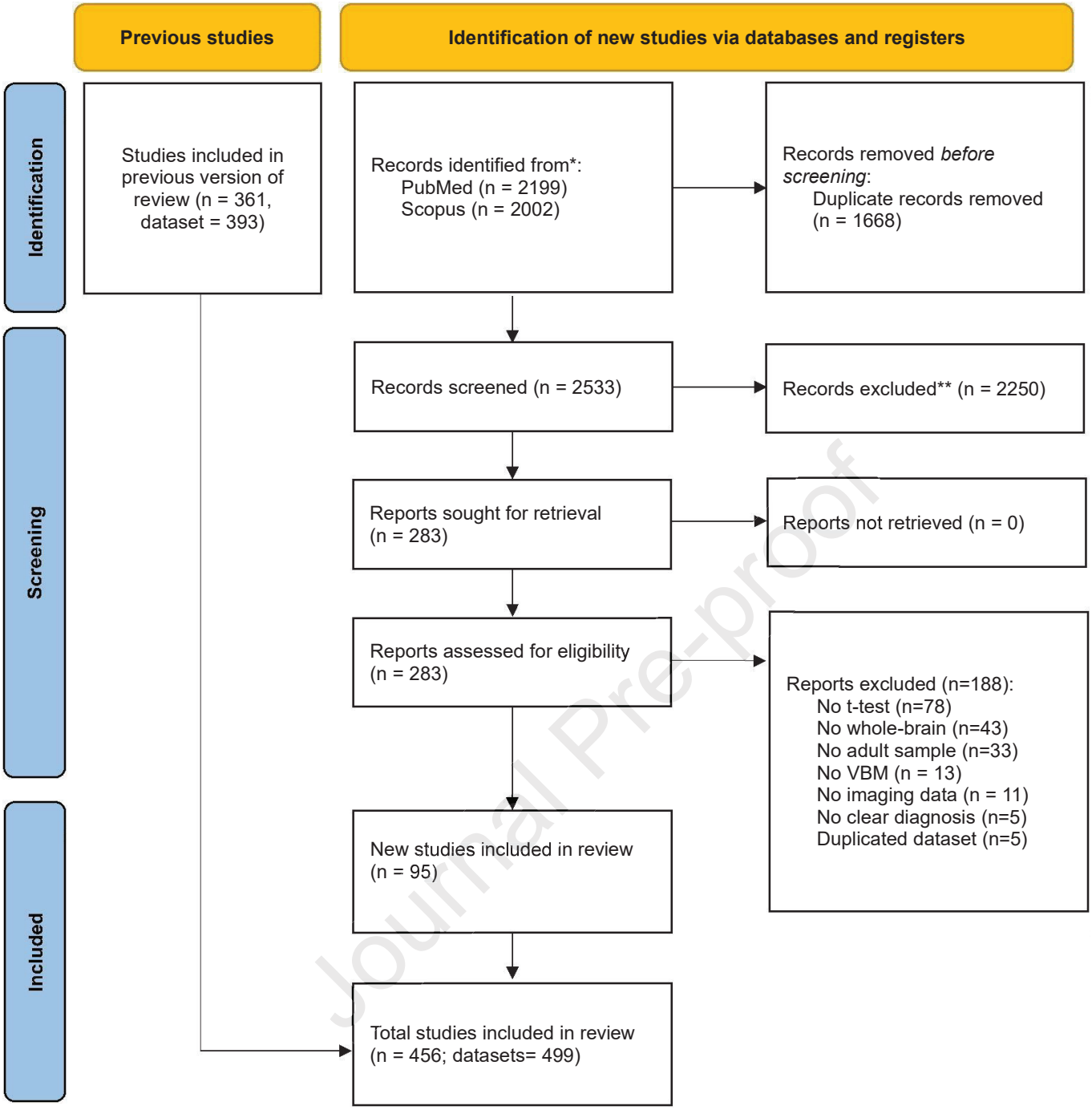
ADHD: attention-deficit hyperactivity disorder, ASD: autism spectrum disorders, BD: bipolar disorder, BPD: borderline personality disorder, MDD: major depressive disorder, OCD: obsessive-compulsive disorder, PTSD: post-traumatic stress disorder; ACC: anterior cingulate cortex, IFG: inferior frontal gyrus, IPG: nferior parietal gyrus, ITG: inferior temporal

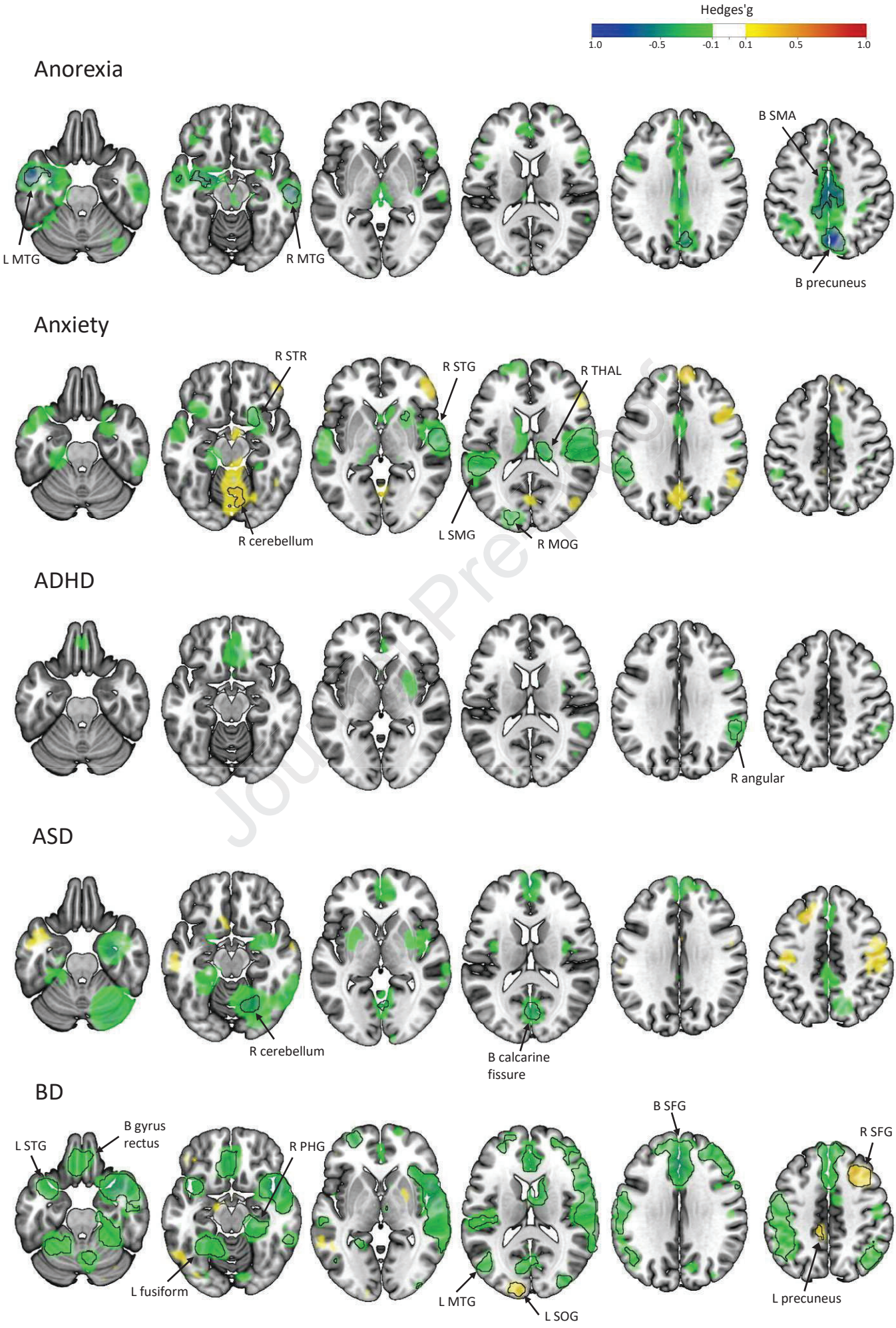
gyrus, MCC: middle cingulate cortex, MFG: middle frontal gyrus, MOG, middle occipital gyrus, MTG, middle temporal gyrus, PHG: parahippocampal gyrus, RO: rolandic operculum, SFG: superior frontal gyrus, SMA: supplementary motor area, SMG: supramarginal gyrus, STG: superior temporal gyrus.

Table 3. Transdiagnostic abnormalities: regions showing a smaller gray matter volume in at least three disorders compared to healthy controls.

	Peak		Cluster		
	MNI	**Hedges'g**	**N voxel**	**Breakdown**	**Mental disorders**
R heschl gyrus	54,-6,4	-0.43	2118	R superior temporal gyrus (772) R rolandic operculum (424) R middle temporal gyrus (316) R heschl gyrus (95) R insula (83)	Anxiety disorder, BD, MDD, schizophrenic disorders
L supplementary motor area	2,18,52	-0.35	1362	B superior frontal gyrus medial (468) B anterior cingulate cortex (630) B middle cingulate cortex (123) B supplementary motor area (94)	BD, MDD, OCD, PTSD, schizophrenic disorders
L insula	-34,-2,-24	-0.38	456	L superior temporal gyrus (184) L insula (68)	Anorexia nervosa, BD, MDD, schizophrenic disorders
L gyrus rectus	2,34,-24	-0.33	467	B gyrus rectus (262) B superior frontal gyrus, orbital (148)	BD, OCD, schizophrenic disorders
R inferior frontal gyrus	50,18,4	-0.41	316	R inferior frontal gyrus (225) R insula (90)	BD, MDD, schizophrenic disorders

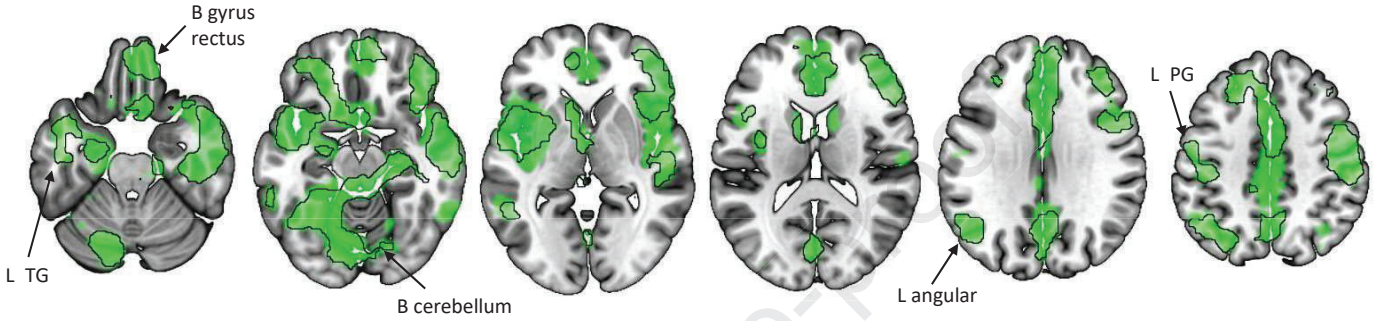
BD: bipolar disorder, MDD: major depressive disorder, OCD: obsessive-compulsive disorder, PTSD: post-traumatic stress disorder.



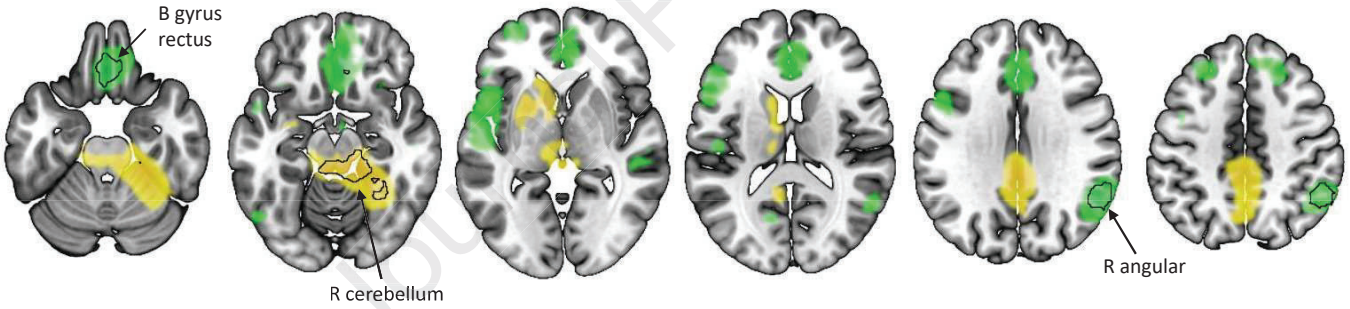


BPD

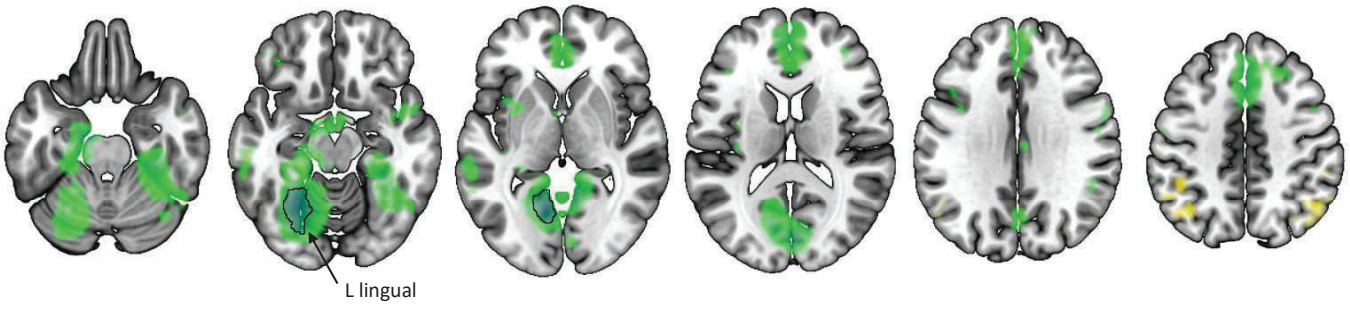
MDD



O D



PTSD



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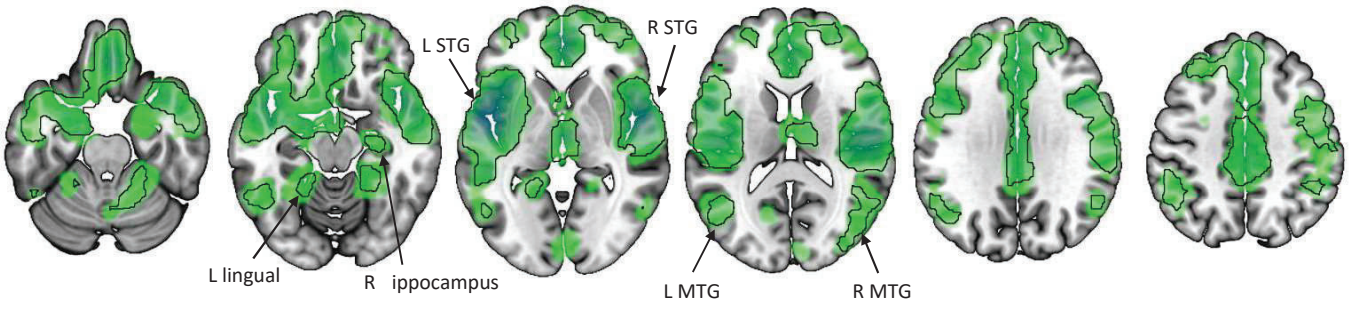
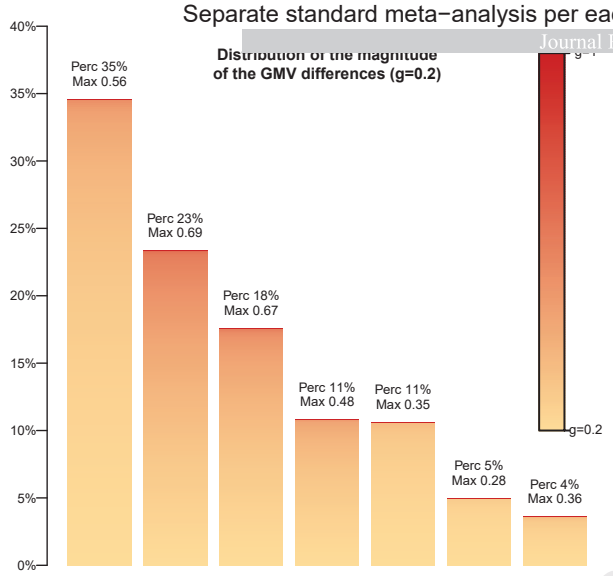
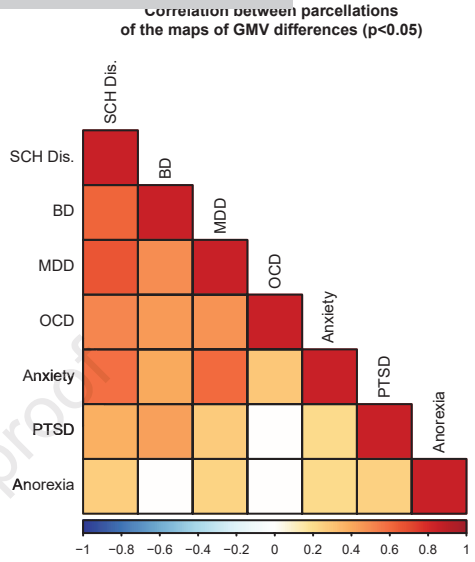
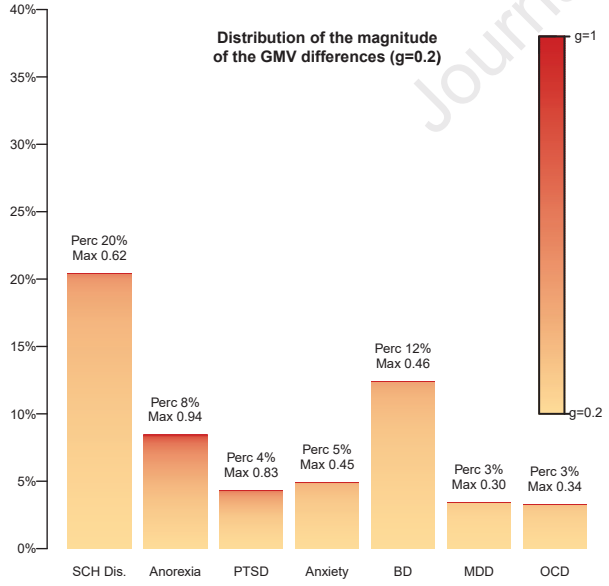


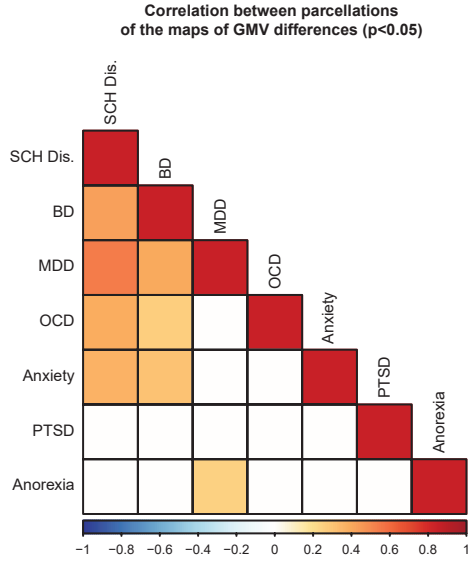
Separate standard meta−analysis per each disorder, ignoring co−occurring disorders





Novel meta−analysis for all disorders, considering co−occurring disorders





Supplementary information

1. Supplementary Methods
2. Supplementary Results
3. Supplementary Discussion
4. **Figure S1.** Brain regions showing larger and smaller gray matter volume in mental disorders compared to comparison subjects obtained by a separate meta-analysis using the standard methods. Statistical significance is set at FWE < 0.05.
5. **Figure S2.** Brain regions showing a low gray matter volume in at least three disorders compared to comparison subjects, using the meta-analytic maps from the novel meta-analysis considering co-occurring disorder.
6. **Figure S3.** Brain regions showing a low gray matter volume in at least three disorders compared to comparison subjects, using the meta-analytic maps from the standard meta-analysis ignoring co-occurring disorders
7. **Table S8.** Brain regions showing larger and smaller gray matter volume in mental disorders compared to comparison subjects obtained by a separate meta-analysis using the standard methods. Statistical significance is set at FWE < 0.05.
8. **Table S14.** Brain regions showing larger and smaller gray matter volume in mental disorders compared to comparison subjects using an interaction meta-analysis with two overlapping disorders. Statistical significance is set at FWE < 0.05.

Note: The complete supplementary material from this article can be download from: https://www.biologicalpsychiatryjournal.com/cms/10.1016/j.biopsych.2024.10.020/attachment/a7305190-7894-403e-8bcc-f7dc4f67e175/mmc1.pdf

SUPPLEMENTARY METHODS

Systematic literature search

First, we systematically searched for meta-analyses of VBM studies comparing whole-brain regional GMV differences in individuals with each psychiatric disorder listed in the ICD-11 (1), and comparison subjects. Second, we enriched our samples by including studies that were not included in these meta-analyses (i.e., studies excluded from the original meta-analysis that had different eligibility criteria from ours or studies disseminated after the publication of those meta-analyses). Therefore, we finally included all eligible studies, regardless of whether they were included in the meta-analysis. Following our strategy, we searched for new case-control VBM studies of GMV features associated with mental disorders published between the meta-analysis' search date (start or end date depending on their criteria) and 31st January 2023.

First stage – systematic search of SDM meta-analyses

In the search of the most recent SDMN meta-analysis of each psychiatric disorder listed in the ICD-11 classification of mental, behavioral, or neurodevelopmental disorders, we used the following keywords: (psychiatric disorder) AND ("meta-analysis") AND ("voxel-based morphometry" OR "VBM" OR "gray matter" OR "grey matter") (see below full search queries). From this classification, we excluded substance use disorders, neurocognitive disorders, and disorders associated with pregnancy, childbirth, or the puerperium. For each mental disorder, we included the most recent SDM meta-analyses of VBM studies that investigated whole-brain regional GMV differences between individuals with the disorder and HCs. This search aimed to reduce the amount of work and thus optimize the efficiency of the data search/collection. This search was limited to SDM meta-analyses because, in contrast to other approaches, they extracted the effect size of the peaks and included studies reporting no differences between patients and controls.

Second stage – multisource search for individual case-control studies

Afterward, we collected all VBM studies investigating whole-brain regional GMV differences between individuals diagnosed with one of the selected psychiatric disorders and HCs. We retrieved them from several sources:

First, we assessed whether the studies included in the selected SDM meta-analyses adhere to our inclusion criteria. Subsequently, in cases where a given meta-analysis employed different inclusion/exclusion criteria than ours (e.g., excluding studies investigating individuals diagnosed with more than one disorder, which would be eligible according to our criteria), we extended our following search of individual studies. To achieve this, we adjusted the initial search date to match the start date employed in the meta-analysis. Second, we searched in PubMed and Scopus databases to find new case-control structural VBM studies of GMV features associated with mental disorders published between the meta-analysis' search date (start or end date depending on their criteria) and 31st January 2023 using keywords of the mental disorder and VBM/GMV (see full search queries in the Supplement).

Inclusion and exclusion criteria

Across the two stages, we included those studies that: i) reported whole-brain regional GMV comparison between individuals diagnosed with the included disorders by standard criteria (e.g., DSM-IV/V or ICD-10/11) and comparison subjects; ii) employed VBM, iii) age≥18 years old, iv) sample size≥10 individuals per group, v) available statistical parametric map, reported peaks coordinates of the significant clusters or null findings; vi) covered the whole gray matter and not white matter; vii) using a constant statistical threshold throughout the whole gray matter; viii) published as peer-reviewed original articles in English in indexed journals.

Studies were excluded if: i) the subtypes' disorder came from a known organic origin (e.g., pediatric autoimmune neuropsychiatric disorders associated with streptococci); ii) diagnosis made by self-reported rated scales; iii) small volume correction; iv) ANOVA analysis without whole-brain post hoc pairwise comparison. Special inclusion criteria are presented in the Supplement. Notably, we discarded mental disorders with fewer than ten eligible datasets to limit our analysis to extensively studied mental disorders only.

In case of overlap, we only included the study analyzing the larger sample (i.e., measurements were taken from distinct samples). Similarly, we only included baseline data from longitudinal studies. Studies investigating posttraumatic stress disorder (PTSD) may use two types of comparison groups: traumatized HCs and non-traumatized HCs; we preferred the former because it investigates alterations associated with the diagnosis rather than with the trauma but used the latter if the study did not include traumatized HCs. We acknowledge that this decision implied that the HC from PTSD studies were all traumatized while only a part of the HC from other studies was traumatized (i.e., as in the general population). However, our analyses only aimed to find the alterations associated with the disorders for which the potential lack of transitivity should have a minor impact. Note that some studies reported more than one patient dataset per eligible study (e.g., medicated, and non-medicated individuals with major depressive disorder (MDD)); in this case, we included the different patients' datasets but divided the sample size of the comparison controls by the number of datasets.

Data extraction

For each dataset separately, we saved the original statistical parametric map when available or extracted and coded the peak coordinates, and effect sizes (standardized mean difference, Cohen's d) or the absence of significant findings. If the studies had used multiple whole-brain statistical significance levels (e.g., uncorrected p-value<0.001 and corrected familywise error rate (FWER)<0.05), we selected the least stringent threshold (2). Additionally, we collected: sample sizes, demographic information (age distribution, percentage of male and female participants), clinical information (percentages of individuals with different co-occurring mental disorders, medication usage breakdown, and severity of the primary disorder with standard scales), methodological details needed for the meta-analysis (pre-processing analysis software, stereotactic space). And the selection of study groups and group comparability required by the quality assessment of the Newcastle-Ottawa Scale (3).

Novel meta-analysis considering co-occurring disorders

SDM-PSI meta-analysis

Once we had the required data for the SDM-PSI analysis (2,4), we recreated the effect size map of each dataset separately for each of the 50 imputations. Then, we fitted voxel-based random-effects meta-linear models, where the voxel's effect size, measured by Hedges' g, serves as the dependent variable and the percentage of individuals with each mental disorder as the independent variable. Finally, we combined the results from the 50 imputations using Rubin's rules (5), in line with previous descriptions and validations of these methods (4,6,7).

Finally, we explored the potential interaction of co-occurring mental disorders using the novel meta-analytic method. We focused on every pair of disorders that appear together in at least ten studies, with one of them as the primary disorder of the study. For each pair of co-occurring mental disorders (e.g., anxiety and MDD), we performed a meta-analysis using the following regressors: i) individuals with anxiety but not MDD, ii) individuals with MDD but not anxiety, and iii) individuals with both anxiety and MDD.

Extent, intensity, and specificity of the GMV differences

To further explore the observed GMV anomalies, we first quantified the extent, intensity of the GMV alterations associated with each disorder by computing the percentage of gray matter voxels with Hedges' g>0.2 (extent) and finding the maximum Hedges' g (intensity). Second, we assessed the specificity of these alterations by correlating the unthresholded Hedges' *g* between each pair of disorders across brain voxels (4) and by evaluating the extent of transdiagnostic alterations. To quantify correlations, we used Pearson's coefficients (r), where r close to 1 indicated similar patterns of GMV alterations, whereas r close to 0 indicated different patterns We developed R package ("nifti.pbcor") to estimate correlations across disorders by parcellating the brain using k-means 50 times and selecting the median correlation from the various parcellations. To assess transdiagnostic alterations, we selected those voxels in which at least three disorders showed smaller or larger GMV, with a Hedges' g≥0.2.

SUPPLEMENTARY RESULTS

Description of the sample

The search of most recent SDM meta-analyses and individual studies of mental disorders listed in the ICD-11 classification yielded an inclusion of 11 mental disorders in our meta-analysis: anorexia, anxiety (including SAD, GAD, PD, agoraphobia and specific phobia), attention-deficit/hyperactivity disorder (ADHD), BD, borderline personality disorder (BPD), internet gaming disorders, MDD, obsessive-compulsive disorder (OCD), PTSD, and schizophrenic from 7 meta-analytic publications (8–15). The search of new individual VBM studies not included in these meta-analyses retrieved a total of 2481 studies potentially suitable (Fig. 1), from which 105 met all eligibility criteria. We counted 29 (6%) statistical parametric maps (1 for anxiety disorders, 9 for BD, 1 for BPD, 14 for MDD, and 3 for OCD). Flowcharts of study selections specific to each mental disorder and the demographic and clinic characteristics of every included study are available in the Supplementary Material (Table S14 and Fig. S4-S14). According to the NOS scale (3), the methodological

quality of the included investigations was good (scored 7-9) in 206 studies (47%), fair (scored 4-6) in 220 (51%), and poor (scored <4) in 8 studies (2%).

Results from the novel and standard meta-analyses

Anorexia nervosa

Of the 19,286 patients, 464 were reported to have anorexia (92% females; age m±SD=28±8.3, range=20-36.3). In studies investigating anorexia as the primary disorder and providing full information about co-occurring disorders, 11% (n=30) of the patients (n=261) had co-occurring anxiety disorders, 10% (n=26) had MDD and 6% (n=16) had OCD. The mean age of onset was 18.5 (SD=7.7) years, and the mean illness duration was 7.8 (SD=8) years. The mean body mass index (BMI) was 17.2 (SD=2.4). Of these patients, 380 (79%) were acute, whereas only 104 (21%) were weight recovered. Of these patients, 21% were taking antidepressants, 5% antipsychotics, and 2% anxiolytics.

The main results (Table 2, Fig. 2-3) showed that individuals with anorexia presented smaller GMV than CS in the bilateral supplementary motor area (g=-0.94), extending to the middle cingulate cortex, precuneus (g=-0.94), left and right middle temporal gyrus (g=-0.67). There was no evidence for publication bias (all $p > 0.17$), but we found high heterogeneity in the right precuneus cortex ($I^2 = 52\%$).

In the standard meta-analysis (Table S8, Fig. S12), similarly to the main analysis, individuals with anorexia showed smaller GMV compared to comparison subjects in the bilateral precuneus (g = -0.66), extending to the ACC and middle cingulate, right middle temporal gyrus (g = -0.50), extending to the insula and amygdala. In contrast with the main results, we also found smaller GMV in the bilateral cerebellum (g = [-0.58, -0.56]) and left inferior temporal gyrus including the amygdala (g= -0,53).

Anxiety disorders

Of the 19,286 patients, 1548 were reported to have one or more anxiety diagnoses (59% females; age mean±SD=32.9±11.1, range=21.8-47.0). In studies investigating anxiety as the primary disorder and providing full information about co-occurring disorders, 28% (n=227) of the patients (n=800) had co-occurring MDD. The mean age of onset was 21.4 (SD=11) years, and the mean illness duration was 8.4 (SD=9.2) years. The mean score of the Hamilton Anxiety Rating Scale (HAM-A) (34) was 14.43. Of 1085 patients with available information, 306 were diagnosed with GAD (28.2%), 348 with PD (32.1 %), 420 with SAD (38.7%), 140 with specific phobia (12.9 %; the reported types were snake and dental phobia), and 57 with agoraphobia (5.3%). Of these patients, 21.5% were taking antidepressants and 10% anxiolytics.

The main results (Table 2, Fig. 2-3) showed that individuals with anxiety presented smaller GMV than comparison subjects in the bilateral superior temporal gyrus, (g= [-0.36, -0.39]), right striatum (g=-0.38), right thalamus (g=-0.45), and left middle occipital gyrus (g=-0.37). In addition, individuals with anxiety presented larger GMV in the right cerebellum (g=0.31). None of these findings showed relevant heterogeneity between studies (all I^2<247) or publication bias (all p>0.09).

In the standard meta-analysis (Table S8, Fig. S12), similarly to the main analysis, individuals with anxiety disorders showed smaller GMV compared to comparison subjects in the bilateral rolandic operculum (g=-0.46), extending to the insula, left thalamus (g=-0.45), and left middle occipital gyrus (g=-0.37). However, they also presented smaller GMV in the bilateral superior frontal gyrus (g=0.38) including the ACC and middle cingulate, and right precentral gyrus (g=-0.30)-

Attention-deficit/hyperactivity disorder

Of the 19,286 patients, 734 were reported to have ADHD (42% females; age mean±SD=32±12.4, range=20-66.9). In studies investigating ADHD as the primary disorder and providing full information about co-occurring disorders, 20% (n=85) of the patients (n=432) had co-occurring MDD, and 17% (n=72) had anxiety disorders. There was no information about the age of onset. Of 329 patients with available information, 80 were diagnosed as inattentive (24.3%), nine as hyperactivity (3%), and 240 as combined type (72.9%). Of these patients, 29% were taking stimulants.

In the main analysis (Table 2, Figure 2), individuals with ADHD showed smaller GMV in the right supramarginal gyrus compared to comparison subjects. This cluster did not show relevant heterogeneity between studies ($I^{2=}$12%) or publication bias (p=0.4)

In contrast, in the standard meta-analysis (Table S8, Fig. S12), we observed no significant differences between individuals with ADHD and comparison subjects.

Autism spectrum disorder

Of the 19,286 patients, 502 were reported to be diagnosed with ASD (12% females; age mean±SD=29.7±8.7, range=21.9-38). In studies investigating ASD as the primary disorder and providing full information about co-occurring disorders, 8% (n=25) of the patients (n=326) had co-occurring MDD. There was no information about the age of onset. Of 502 patients, 11% were taking antidepressants, 6% anxiolytics, and 5% antipsychotics.

The main results (Table 2, Fig. 2-3) showed that individuals with ASD presented smaller GMV than comparison subjects in the right cerebellum (g=-0.47), and bilateral calcarine fissure cortex (g=-0.49). The cluster in the bilateral calcarine fissure showed a relevant heterogeneity between studies in the meta-analyses with studies (I^2>60%), but none of them showed publication bias (p > 0.15).

Contrary to the main results, we observed no significant differences between individuals with ASD and comparison subjects in the standard meta-analysis.

Bipolar disorder

Of the 19,286 patients, 3369 were reported to have BD (56% females; age mean±SD=36.8±12.9, range=19.9-61.9). In studies investigating BD as the primary disorder and providing full information about co-occurring disorders, 5% (n=84) of the patients (n=1747) had co-occurring anxiety disorders. The mean age of onset was 23.9 (SD=9.5) years, and the mean illness duration was 12.1 (SD=10) years. The mean score of the Hamilton

Depression Rating Scale – 17 items (HARDS-17) (35) was 10.8, and the mean score of the Young Mania Rating Scale (YMRS) (32) was 7. Of 2990 patients with available information, 2644 were diagnosed with type I (79.4%) and 346 with type II (10.4 %). In addition, 1230 patients were in remission (36.9%), 532 in a mania episode (15.9%), and 885 in a depressed episode (26.5%) at the time of the MRI acquisition. Of these patients, 85.5% were under medication and taking mood stabilizers (65%), antipsychotics (45%), antidepressants (19%), and anxiolytics (12%).

The main results (Table 2, Figure 2) showed that individuals with BD showed smaller GMV than comparison subjects in the several clusters across cortical regions, the right caudate (g=-0.32) and right cerebellum (g=-0.32). The cortical regions included the bilateral superior frontal gyrus dorsomedial (g=-0.33), extending to the ACC, middle cingulate and insula, left middle and superior temporal gyrus (g= [-0.27,-0.31]), right parahippocampal gyrus (g=-0.41), left fusiform gyurs (g=-0.32), extending to the left cerebellum, bilateral gyrus rectus (g=-0.32), right middle occipital gyrus (g=-0.38), right angula gyrus (g=-0.29) and left calcarine fissure (g=-0.32). Additionally, they showed larger GMV in other cortical regions such as the left precuneus (g=0.30), right superior frontal gyrus (g=0.30), and left superior occipital gyrus (g=0.28). None of these findings showed relevant heterogeneity between studies (all I^2<35%) or publication bias (all p>0.06).

In the standard meta-analysis (Table S8, Fig. S12), similarly to the main analysis, individuals with BD showed smaller GMV in several cortical regions, including the bilateral superior frontal gyrus (g=[-0.22, -0.26]), extending to the ACC, middle cingulate and right insula, left postcentral gyrus (g=-0.22), right cuneus cortex (g=-0.22), gyrus rectus (g=-0.20), left insula, bilateral fusiform gyrus (g=[-0.17,-0.27]), thalamus (g=-0.30), lingual gyrus (g=-0.26), left superior occipital gyrus (g=-0.24) and left inferior temporal gyrus (g=-0.22). Please note that some cluster present a very small effect size (g<0.2).

Borderline personality disorder

Of the 19,286 patients, 382 were reported to have BPD (84% females; age mean±SD=30.9±8.9, range=22.9-36). In studies investigating BPD as the primary disorder and providing full information about co-occurring disorders, 45% (n=133) of the patients (n=293) had co-occurring MDD, 26% (n=72) had PTSD and 23% (n=66) had anxiety disorders. There was no information about the age of onset or illness duration. Of these patients, 35% were taking medication, antidepressants (21%), anxiolytics (8%), antipsychotics (17%), and mood stabilizers (15%).

In the main results (Table 2, Fig. 2-3), we did not observe significant differences in individuals with BPD when compared to comparison subjects. However, we found larger GMV in the right superior temporal gyrus when using a less stringent threshold ($p < 0.005$).

In contrast, the standard meta-analysis (Table S8, Fig. S12) showed that individuals with BPD presented smaller GMV in the left superior frontal gyrus orbital (g=-0.45), bilateral inferior frontal gyrus orbital (g=-0.44) and left middle temporal gyrus (g=-0.43).

Internet gaming disorder

Of the 19,286 patients, 312 were reported to have internet gaming disorder (6% females; age mean±SD=22.6±3.9, range=19.1-29.5). The mean illness duration was 6.2 (SD=4) years. There was no information about the age of onset. No patients were taking psychotropic medication. We excluded this disorder from the main analysis, as the number of studies reporting full information about co-occurring disorder was less than 10.

In the standard meta-analysis with all studies, we observed that individuals with internet gaming disorder presented lower GMV than comparison subjects in the bilateral gyrus rectus (g=-0.55), extending to the rostral ACC.

Major depressive disorder

Of the 19,286 patients, 6624 were reported to have MDD (62% females; age mean±SD=35.8±13.1, range=20.5-61.6). In studies investigating MDD as the primary disorder and providing full information about co-occurring disorders, 10% (n=314) of the patients (n=3195) had co-occurring anxiety disorders. The mean age of onset was 27.3 (SD=13.6) years, and the mean illness duration was 7.6 (SD=10) years. The mean score of HARDS-17 was 21.3. Of the 4115 patients with available information, 3898 were depressed (63.1%), and 217 were in remission (3.5%) at the time of the MRI acquisition. Of these patients, 41.6% were taking antidepressants, 6.4% antipsychotics, and 4.8% anxiolytics.

The main results (Table 2, Figure 2) showed that individuals with MDD showed smaller GMV than ssomparison subjects in a big cluster with the highest peak in the right cerebellum (g=-0.25), but extending to the bilateral superior frontal gyrus dorsal, ACC, middle cingulate, right insula, among others, in the left inferior temporal gyrus (g=-0.22), extending to the insula, left angular (g=-0.23), bilateral gyrus rectus (g=-0.23), and left inferior parietal gyrus (g=-0.18). None of these findings showed relevant heterogeneity between studies (all I^2<17%) or publication bias (all p>0.34).

In the standard meta-analysis (Table S8, Fig. S12), similarly to the main analysis, individuals with MDD showed smaller GMV in the bilateral superior temporal gyrus extending to the insula, left ACC, bilateral gyrus rectus, left superior frontal gyrus orbital, bilateral cerebellum, and left middle frontal gyrus. In contrast, they also showed smaller GMV in the left cuneus cortex, left fusiform gyrus, and left caudate.

Obsessive-compulsive disorder

Of the 19,286 patients, 961 were reported to have OCD (49% females; age mean±SD=32.2±9.8, range=25-38). In studies investigating BPD as the primary disorder and providing full information about co-occurring disorders, 23% (n=146) of the patients (n=745) had co-occurring MDD and 17% (n=110) anxiety disorders. The mean age of onset was 20.1 (SD=8.3), and the mean illness duration was 10.1 (SD=9) years. The mean score of the total Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (37) was 25.1. The obsessive composite was 12.7, and the compulsive composite was 12.1. Of these patients, 56.4% were taking antidepressants, 4% anxiolytics, and 7% antipsychotics.

The main results (Table 2, Fig. 2-3) showed that individuals with OCD presented smaller GMV compared to somparison subjects in the right angular gyrus (g=-0.33), and bilateral gyrus rectus (g=-0.31). Additionally, they presented larger GMV in the right cerebellum (g=0.34). None of these findings showed relevant heterogeneity between studies (all I^2<25%) or publication bias (all p>0.78).

In the standard meta-analysis (Table S8, Fig. S12), similarly to the main analysis, individuals with OCD showed smaller GMV right angular gyrus (g= -0.29) and larger GMV in the right cerebellum (g=0.26) compared to comparison subjects. In contrast, they also showed smaller GMV in the bilateral superior frontal gyrus including ACC (g=-0.32), and superior temporal gyrus (g= [-0.26, -0.30]).

Post-traumatic stress disorder

Of the 19,286 patients, 423 were reported to have PTSD (54% females; age mean±SD=34.5±11.7, range=26.3-52.8). In studies investigating BPD as the primary disorder and providing full information about co-occurring disorders, 26% (n=53) of the patients (n=202) had co-occurring MDD. The mean illness duration was 7.3 (SD=8) years. There was no information about the age of onset. Of these patients, 21% were taking antidepressants.

The main results (Table 2, Figure 2) showed that individuals with PTSD presented smaller GMV than comparison subjects in the left lingual gyrus (g=-0.83), extending to the fusiform gyrus and cerebellum. This cluster showed no relevant heterogeneity between studies (I^2= 7%), nor publication bias (p = 0.66).

In the standard meta-analysis (Table S8, Fig. S12), similarly to the main analysis, individuals with PTSD showed smaller GMV in left fusiform gyrus (g=-0.57). In contrast, they also showed smaller GMV in the bilateral superior frontal gyrus (g=-0.66), left postcentral gyrus (g=-0.63), and right insula (g=-0.53).

Schizophrenic disorders

Of the 19,286 patients, 5377 were reported to have schizophrenic disorders (36% females; age m±SD=33.1±11.2, range=19.9-59.9). In studies investigating BPD as the primary disorder and providing full information about co-occurring disorders, none of the patients (n=2140) had other co-occurring disorder. The mean age of onset was 24.5 (SD=7.8) years, and the mean illness duration was 9.4 (SD=10) years. The total mean score of the Positive and Negative Syndrome Scale (PANSS) (48) was 74.4, positive symptoms scores were 18.3, negative symptoms scores were 19.5, and global symptoms scores were 38.1. Of these patients, 80% were taking antipsychotics.

The main average results (Table 2, Fig. 2-3) showed that individuals with schizophrenic disorders presented smaller GMV than comparison subjects in several clusters covering most of the cortical and subcortical regions. The highest peaks were located in the left superior temporal gyrus (g = -0.48), right postcentral gyrus (g=-0.46), left middle temporal gyrus (g=-0.29), left middle temporal gyrus (g=-0.23), right middle occipital gyrus (g=-0.25), right hippocampus (g=-0.25) and left lingual gyrus (g=-0.32). None of the cluster showed heterogeneity between studies (I^2 < 22%) nor publication bias (p > 0.55).

In the standard meta-analysis (Table S8, Fig. S12), similarly to the main analysis, we also observed several significant clusters covering most of the cortical and subcortical regions. The highest peaks were located in the right superior temporal gyrus (g=-0.42), left Heschl gyrus (g=-0.50), right fusiform gyrus (g=-0.27), and left superior frontal gyrus (g=-0.22).

Results from the novel meta-analysis accounting for the interaction between disorders

In this secondary analysis, we further studied the interaction between overlapping mental disorders, specifically between anxiety and MDD, anxiety and OCD, MDD and OCD, and MDD and BPD (Table S13). Results are presented in the Supplement and Table S14. Interestingly, in the case of anxiety and MDD, we observed that individuals with anxiety but not MDD, among others, showed a part of the main results, also exhibited smaller GMV in the bilateral middle cingulate cortex, bilateral superior temporal gyrus, extending to the right insula, and left superior frontal gyrus dorsolateral in addition to the main findings. Individuals with MDD but not anxiety also displayed exhibited less significant clusters compared to the main analysis.

Extent, intensity, and specificity of the GMV differences in the standard meta-analysis but only including the studies with complete information on co-occurring disorders

Using the standard meta-analysis but only including the studies with complete information on co-occurring disorders, we observed that the percentages of voxels showing GMV differences was similar to those of the standard meta-analyses with all studies and larger than those of the novel meta-analyses, with three exceptions: A) For schizophrenic disorders, the percentage (21%) was similar to that of the novel meta-analysis, which may be expected because studies on schizophrenia reported nearly no co-occurring disorders and thus the extent would only depend on the statistical power (larger in the standard meta-analysis of all studies); B) For BD, the percentage (11%) was similar to those of both the standard meta-analysis of all studies and the novel meta-analysis, but note that we had already found that that the extent of this disorder anomalies was similar between the standard meta-analysis of all studies and the novel meta-analysis; and C) For anorexia, the percentage (15%) was smaller than in the standard meta-analysis of all studies but still larger than in the novel meta-analysis. Intensities were similar to the standard meta-analysis of all studies and the novel meta-analysis.

In the correlation analysis, the spatial patterns of GMV differences in mental disorders significantly correlated with each other as in the standard meta-analysis of all studies, except for anorexia with OCD and PTSD. Finally, in the transdiagnostic analysis, we observed significant clusters similar to those of the standard meta-analysis of all studies except for the precuneus.

SUPPLEMENTARY DISCUSSION

Results from the novel and standard meta-analyses

Anorexia nervosa

The precuneus is a core region from the default mode network (DMN), which is involve in cognitive performance and self-directed processing (16). A GMV abnormality in this area could alter the function of the DMN related to ruminative preoccupation with eating, body weight and impaired cognitive flexibility (17). Indeed, several resting-state functional MRI studies reported abnormal functional connectivity in the DMN in patients with anorexia (18).

The supplementary motor area is involved in the planning and control of motor actions and plays a crucial role in task switching (19). An impairment in this region may contribute to the cognitive rigidity in patients with anorexia (20). Finally, The middle cingulate plays a key role salient network and is involved in identifying the emotional significance of stimuli and producing appropriate affective and behavioral responses, particularly fear and avoidance (21). A reduction of GMV in this middle cingulate could lead to abnormal functionality, previously reported (18), contributing to typical symptoms of anorexia such as excessive perfectionism, cognitive rigidity and excessive attention to detail (20).

Anxiety disorders

The striatum has been previously associated with threat attentional bias, and fear conditioning (22), playing a crucial role in the anxiety circuitry. Smaller GMV in this region may produce the avoidance of treat stimuli, avoiding the exposure to those environments (23). The temporal lobes are part of the ventral attention network (VAN), involved in orientating stimulus-driven attention. Therefore, alterations in this network may disrupt the shift from internally directed stimuli (e.g., worrisome thoughts) to external events. In addition, the insula is associated with perceiving strong emotions and processing introspective awareness (24), and together with the thalamus, are parts of the fear network model modulating fear through the fronto-temporo-insula network (25,26). Therefore, alterations in both areas may be associated with intense response to negative events and enhancement of their expectations of negative incomes. Finally, aberrant structure in the PFC can contribute to impairments in executive function, impulse control, and social cognition, which are symptoms often experienced by individuals with anxiety (27).

Attention-deficit/hyperactivity disorder

The novel meta-analyses showed smaller GMV in the right supramarginal gyrus compared to comparison subjects. In contrast, the standard meta-analysis did not show any significant GMV differences associated with ADHD. Our findings partially align with those from previous meta-analysis (13), where they report aberrant structure in the parietal lobe. Additionally, another consistent finding is a smaller GMV in the ventromedial orbitofrontal cortex, including the gyrus rectus, associated with adult ADHD (11,13). Notably, we identified smaller GMV in the bilateral gyrus rectus using a less stringent threshold (uncorrected $p < 0.005$).

The right supramarginal gyrus plays an important role in attention, spatial processing, and the integration of sensory information (28). Structural deficits in this region may contribute to the attentional and executive function impairments seen in ADHD. For example, previous research has demonstrated that the supramarginal

gyrus is crucial for tasks requiring sustained attention and working memory, both of which are often compromised in ADHD (29,30).

The orbitofrontal cortex is involved in decision-making, impulse control, and the regulation of emotional responses (31). Alterations in this region have been frequently reported in ADHD, supporting the notion that structural changes in the orbitofrontal cortex may be related to the impulsivity and emotional dysregulation characteristic of the disorder (32).

Autism spectrum disorder

In contrast to the null findings obtained by the standard meta-analysis, the novel approach revealed lower GMV in the bilateral calcarine fissure, and right cerebellum associated with ASD. These findings align with previous meta-analysis (13,33).

The calcarine fissure is a region involved in primary visual processing. Thus, smaller GMV in that region may underpin the altered sensory processing and visual perceptual difficulties often observed in ASD. This finding is consistent with previous reports suggesting abnormal visual cortex development and function in ASD (34). The cerebellum, traditionally associated with motor control, has been increasingly recognized for its role in cognitive processes, including attention, language, and social cognition (35). Our finding of smaller GMV in the right cerebellum further corroborates earlier studies highlighting cerebellar structural and functional alterations in ASD, suggesting a potential link to the motor and cognitive impairments characteristic of the disorder (36). However, it is important to note that the reported cerebellar anomalies in ASD present high heterogeneity between studies, indicating variability in the specific regions and extent of cerebellar involvement. Collectively, these results underscore the importance of considering both sensory and motor-related brain regions in understanding the neurobiological underpinnings of ASD.

Bipolar disorder

The dorsal/ventral PFC and ACC are involved in mood and emotion regulation (37), specifically the ACC has been shown an important role in the regulation of affective states (38). In addition, the PFC is also a fundamental structure within the frontoparietal network, with functions that include executive functions, working memory, inhibition, and task-switching (39). The volumetric reduction of this structure observed in our analyses may contribute to the multiple cognitive difficulties described by patients with bipolar disorder (40). Insulas have also been reported as a potential biomarker of mood disorder. This region is involved in several functions including affective processing and awareness of bodily states (41,42). Notably, functional meta-analysis has reported atypical functional activity in these areas (14).

Increasing attention has focused on the cerebellum's role in BD symptomatology, including cognitive deficits and emotion dysregulation (43). Indeed, some cerebellar lesions have been associated with the so-called "cerebellar cognitive affective syndrome" (44). Our findings support the potential role of the cerebellum

in BD, where smaller volume is linked to more severe clinical courses (45) or alterations in social cognition (46).

Borderline personality disorder

In the case of BPD, the comorbidity-based meta-analysis showed no significant GMV differences compared to comparison subjects. In contrast, the standard meta-analysis identified smaller GMV in the orbitofrontal cortex, extending to the ACC, which aligns with previous meta-analyses (15). A plausible explanation for this discrepancy may be the high prevalence of co-occurring disorders among individuals with BPD, higher than in other mental disorder (45% MDD, 26% PTSD, and 23% anxiety), a factor not adequately adjusted in previous meta-analyses. Indeed, 100% of the included studies had at least one individual with another co-occurring disorder. Interestingly, smaller GMV in the orbitofrontal cortex has been previously associated with anxiety (8) and also in our findings.

Furthermore, our meta-analysis investigating the interaction between BPD and MDD found that individuals with MDD, but not BPD, exhibited smaller GMV in the orbitofrontal cortex, among other regions. In individuals with both disorders, the effect size of this cluster was g=-0.39, though it was not significant, likely due to the low sample size. These results suggest that individuals with BPD alone do not exhibit structural GMV alterations, but such alterations are present when there is a co-occurrence of MDD or anxiety.

Obsessive-compulsive disorder

The parietal lobe is a core region of the fronto-parietal network and is involve in cognitive functions such as attention, planning and response inhibition (39,47). Structural alterations in this region may underlie the cognitive deficits seen in individuals with OCD, such as the lack of cognitive flexibility related to the repetitive nature of OCD symptoms and behaviors (48). Notably, this is a symptom that differs from other anxiety-related disorders.

The orbitofrontal cortex plays and important role in fear extinction, cognitive reappraisal and reward-related decision making (49). Structural alterations in this region could affect the top-down control over affect and motivation (50). Notably, several functional studies had reported an under activation of this area when doing fear extinction of symptoms provocation (51).

Posttraumatic disorder

The lingual gyrus is situated in the occipital lobe, which is responsible from processing visual information. Aberrant structure and function in this region have been linked to dissociative responses in PTSD patients, and emotional processing of visual stimuli (52).

Schizophrenia-spectrum disorder

Several structural alterations had also been linked to functional alterations across both treated and untreated patients (53,54), highlighting a complex interplay between structural and functional changes in schizophrenic

disorders. Specifically, smaller GMV overlapping areas showing decrease activation within the DMN, and conversely with areas showing increase activation in the auditory network. These findings are consistent with the hypothesis that schizophrenic disorders involves widespread disruption in brain structure that affect multiple functional neural networks (9,53,54). Additionally, studies reported the antipsychotic medication, being the primary clinical intervention, can further impact the GMV and neural activity in psychosis (55,56). Therefore, future studies should investigate the impact of antipsychotics on this brain model.

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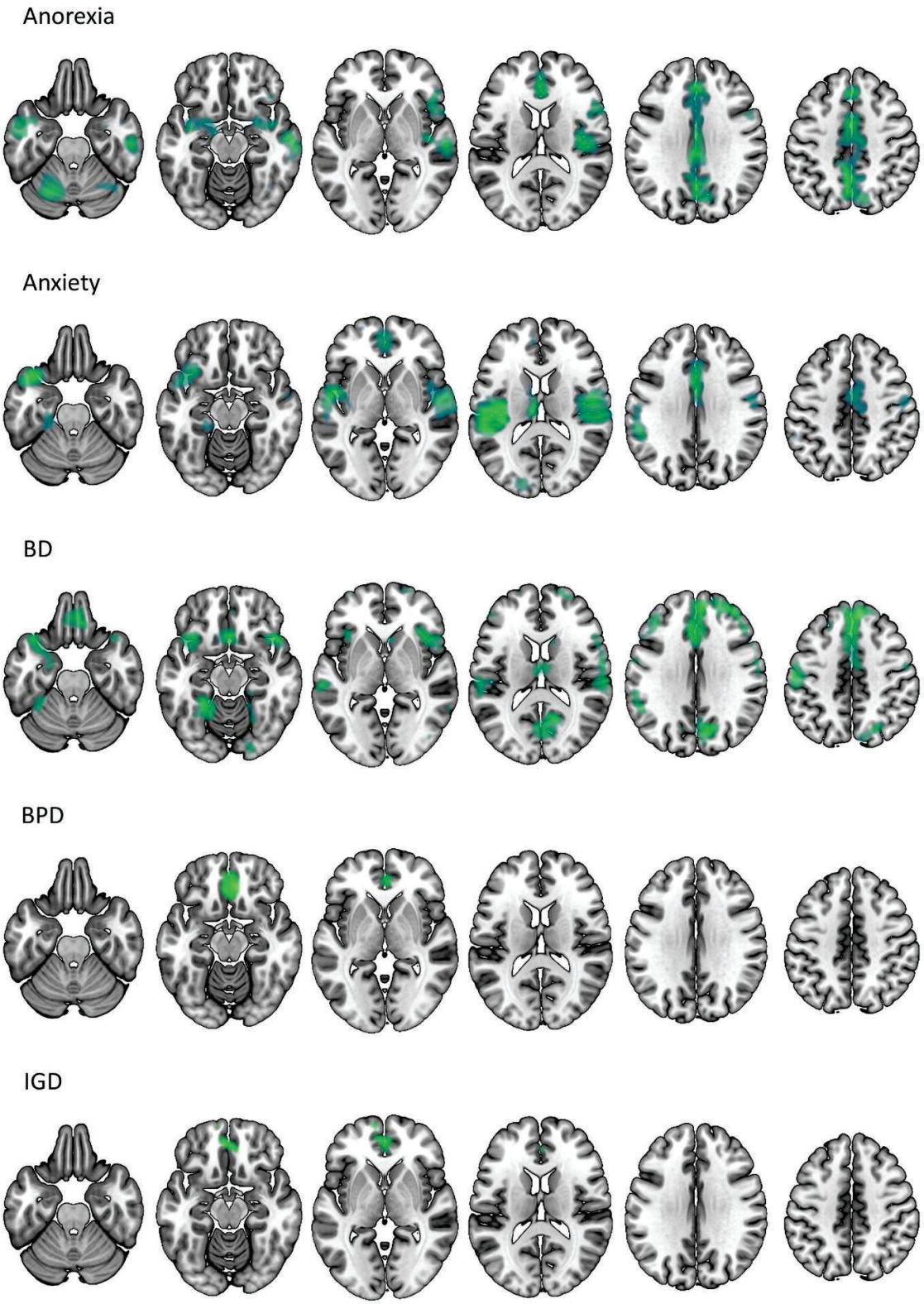
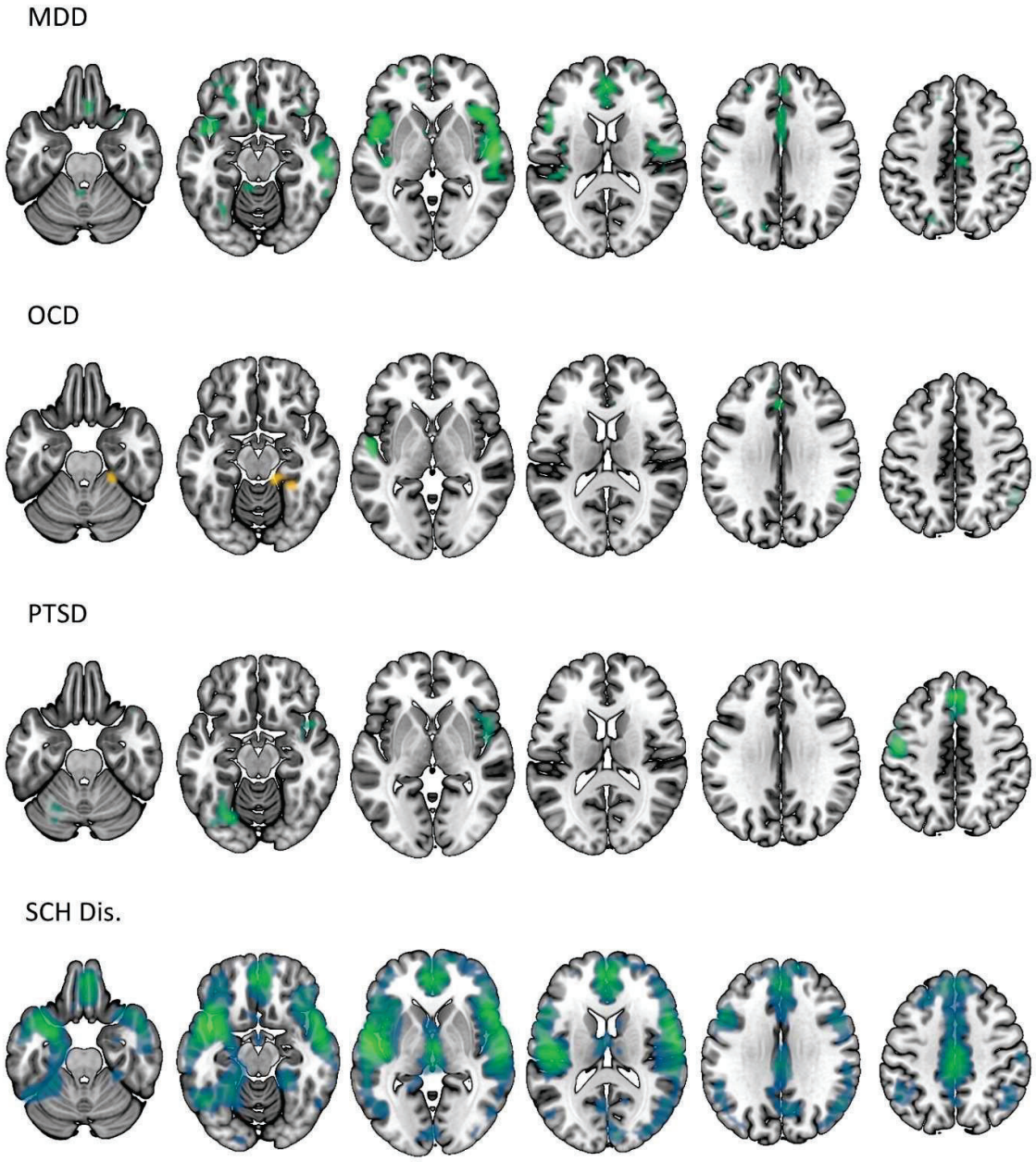
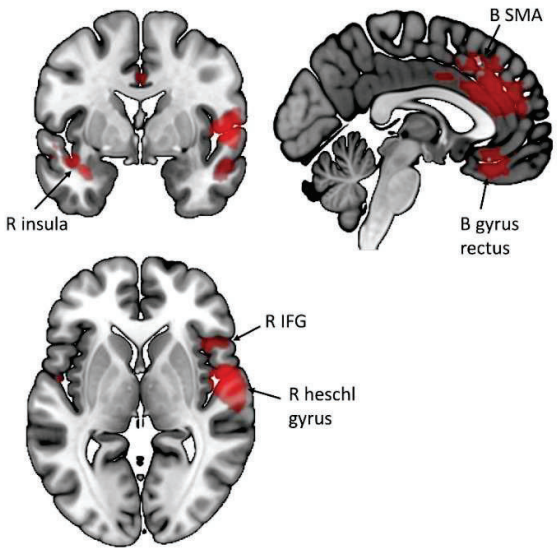
Figure S1. Brain regions showing larger and smaller gray matter volume in mental disorders compared to comparison subjects obtained by a separate meta-analysis using the standard methods. Statistical significance is set at FWE < 0.05.





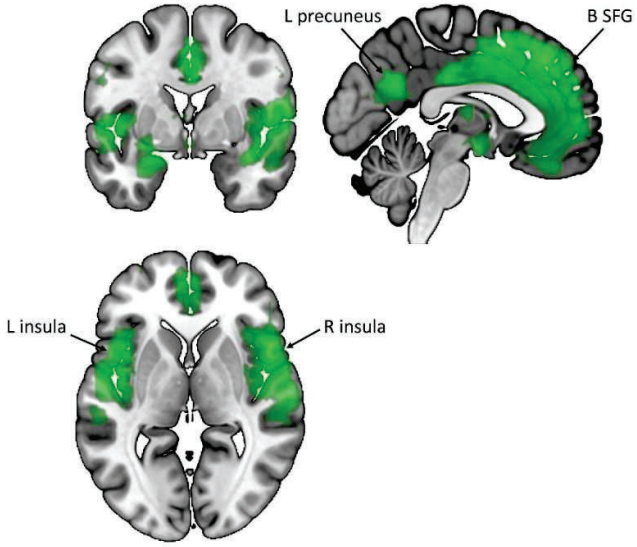
Regions with larger GMV are displayed in yellow. Regions with smaller GMV are displayed in green/blue. The right side of the brain image represents the right hemisphere. The displayed slices correspond to z=-25, -15, 0, 15 30, 45. ADHD: attention-deficit/hyperactivity disorder, ASD: autism spectrum disorder, BD: bipolar disorder, BPD: borderline personality disorder, MDD: major depressive disorder; OCD: obsessive-compulsive disorder, PTSD: posttraumatic stress disorder, SCH Dis.: schizophrenic disorders.

Supplementary Table 2. Brain regions showing a low gray matter volume in at least three disorders compared to comparison subjects, using the meta-analytic maps from the novel meta-analysis considering co-occurring disorders.



IFG: inferior frontal gyrus, SMA: supplementary motor area

Supplementary Table 3. Brain regions showing a low gray matter volume in at least three disorders compared to comparison subjects, using the meta-analytic maps from the standard meta-analysis ignoring co-occurring disorders.



SFG: superior frontal gyrus.

Table S8. Brain regions showing larger and smaller gray matter volume in mental disorders compared to comparison subjects obtained by a separate meta-analysis using the standard methods. Statistical significance is set at FWE < 0.05.

	Peak				
	MNI	**Hedges'g**	**Z-value**	**p-value**	**N voxel**
Anorexia Nervosa (Z > |3.09|)					
Anorexia < CS					
B precuneus, SMA, MCC, ACC	-2,-50,48	-0.66	6.87	<0.001	9395
R middle temporal gyrus, insula, amygdala	62,-14,-20	-0.50	5.82	<0.001	4317
L cerebellum	-26,-66,-28	-0.56	6.17	<0.001	1975
R cerebellum	26,-62,-36	-0.59	5.08	0.001	1398
L inferior temporal gyrus, amygdala	-58,-6,-28	-0.53	5.56	0.003	1144
Anxiety disorders (Z > |3.09|)					
Anxiety < CS					
L heschl gyrus, insula, rolandic operculum	-46,-18,8	-0.46	7.33	<0.001	5939
R rolandic operculum, insula, superior temporal gyrus	50,-6,12	-0.43	6.22	<0.001	3021
B MCC, ACC, SFG	2,2,32	-0.38	6.24	<0.001	2520
L thalamus, B ACC,	-10,-22,12	-0.45	6.58	0.001	1707
L middle occipital gyrus	-22,-90,20	-0.37	5.33	0.033	469
R precentral gyrus	50,-14,52	-0.30	4.57	0.035	476
Attention-Deficit/Hyperactivity Disorder (ADHD) (Z > |3.09|)					
No significant results					
Autistic spectrum Disorder (ASD) (Z > |3.09|)					
No significant results					
Bipolar Disorder (BD) (Z > |4.58|)					
BD < CS					
B SFG medial, insula, MCC, ACC	-2,30,40	-0.22	8.99	<0.001	7088
L postcentral gyrus	-58,-18,44	-0.22	7.75	<0.001	2426
R cuneus cortex	10,-62,20	-0.22	8.99	<0.001	2092
B gyrus rectus	2,18,-12	-0.20	7.32	<0.001	1327
L insula	-34,18,-12	-0.20	7.68	<0.001	1287
L fusiform gyrus, cerebellum	-26,-46,-16	-0.19	7.31	<0.001	1029
L middle frontal gyrus	-38,42,28	-0.22	7.05	<0.001	417
B thalamus	-2,-2,8	-0.30	6.73	<0.001	352
R fusiforme gyrus	22,-62,-12	-0.27	6.45	<0.001	291
R SFG, dorsolateral	26,10,64	-0.30	6.5	<0.001	190
R fusiform gyrus	30,-18,-32	-0.26	6.39	<0.001	163
L SFG dorsolateral	-18,38,40	-0.26	6.66	<0.001	152
R lingual gyrus	22,-90,-16	-0.26	5.71	<0.001	113
L SFG dorsolateral	-22,62,16	-0.23	5.64	<0.001	89
L superior occipital gyrus	-26,-90,24	-0.24	5.67	0.001	79
L inferior temporal gyurs	-54,-66,-8	-0.22	6.28	0.002	55
Borderline personality disorder (BPD) (Z > |3.09|)					
BPD < CS					
L SFG orbital	-2,34,-12	-0.71	4.81	<0.001	1071
Internet gaming disorder (Z > |3.09|)					
Internet gaming disorder < CS					
B gyrus rectus, ACC	-2,46,-16	-0.55	4.87	0.004	762

Major Depressive Disorder (Z > |6.12|)					
MDD < CS					
R rolandic operculum, insula, STG	50,-2,4	-0.18	10.66	<0.001	4309
L insula, STG	-42,10,-4	-0.18	10.57	<0.001	2879
L ACC	2,42,12	-0.21	9.25	<0.001	2583
B gyrus rectus	6,26,-20	-0.26	8.97	<0.001	571
L SFG orbital	-30,58,-4	-0.26	8.19	<0.001	557
L cuneus cortex	-18,-78,36	-0.24	7.09	<0.001	254
L fusiform gyrus	-34,-58,-16	-0.22	7.46	<0.001	224
R cerebellum	34,-62,-44	-0.21	7.52	<0.001	148
R precentral gyrus	54,-6,40	-0.18	7.52	<0.001	124
L cerebellum	-10,-42,-12	-0.18	7.37	<0.001	108
L middle frontal gyrus	-30,46,24	-0.19	7.48	<0.001	76
L caudate	-6,6,4	-0.19	8.07	<0.001	62
Obsessive-Compulsive Disorder (Z > |4.33|)					
OCD < CS					
R angular gyrus	58,-50,32	-0.29	5.02	0.004	511
B ACC	2,30,20	-0.32	4.96	0.014	383
L superior temporal gyrus	-50,-6,-4	-0.26	4.58	0.021	343
OCD > CS					
R fusiform gyrus, cerebellum	26,-38,-20	0.26	4.55	0.031	309
Posttraumatic Stress Disorder (Z > |3.09|)					
PTSD < CS					
B SFG, SMA	2,34,44	-0.66	5.93	0.004	1010
L postcentral gyrus	-50,-6,40	-0.63	6.32	0.010	805
L fusiform gyrus	-26,-74,-16	-0.57	5.45	0.013	755
R insula	50,14,-4	-0.53	4.85	0.027	606
Schizophrenic disorders (Z > |6.67|)					
Schizophrenic disorders < CS					
R superior temporal gyrus, MCC, ACC	58,-10,-8	-0.42	17.11	<0.001	36133
L heschl gyrus, insula, inferior frontal gyrus, thalamus	-54,-10,8	-0.50	18.69	<0.001	22514
R fusiform gyrus	26,-38,-16	-0.27	10.57	<0.001	745
L SFG dorsolateral	-18,2,64	-0.22	7.74	<0.001	58

ACC: anterior cingulate cortex, ADHD: attention-deficit/hyperactivity disorder, ASD: autism spectrum disorder, BD: bipolar disorder, BPD: borderline personality disorder, CS: comparison subjects; MCC: middle cingulate cortex, MDD: major depressive disorder; OCD: obsessive-compulsive disorder, PTSD: posttraumatic stress disorder, SFG: superior frontal gyrus; SMA: motor area.

Table S14. Brain regions showing larger and smaller gray matter volume in mental disorders compared to comparison subjects using an interaction meta-analysis with two overlapping disorders. Statistical significance is set at FWE < 0.05.

	MNI	Peak Hedges'g	Peak Z-value	p-value	N voxel
Anxiety disorders & MDD					
Individuals with Anxiety disorders and not MDD < CS					
R superior temporal gyrus, insula, striatum	58,-6,4	-0.54	7.35	<0.001	6059
L superior temporal gyrus, insula	-50,-30,16	-0.58	7.72	<0.001	4174
B MCC	2,-2,32	-0.43	5.85	<0.001	1262
L superior/middle occipital gyrus	-22,-90,20	-0.44	5.63	0.016	543
L fusiform gyrus, cerebellum, parahippocampal	-26,-26,-28	-0.5	6.48	0.018	528
L SFG, dorsolateral	-18,66,8	-0.42	5.00	0.021	504
L inferior frontal gyrus, orbital, superior temporal gyrus	-34,22,-16	-0.4	5.33	0.031	447
Individuals with MDD and not anxiety disorders < CS					
B cerebellum	6,-74,-12	-0.39	5.01	0.002	571
B SFG, medial	6,50,36	-0.43	5.13	0.006	469
L precuneus	-10,-50,60	-0.43	5.13	0.026	329
B precuneus	-2,-66,32	-0.43	5.28	0.039	294
Individuals with MDD and not anxiety disorders > CS					
L superior temporal gyrus	-50,-30,20	0.34	4.22	0.004	522
R superior temporal gyrus	58,-6,4	0.32	3.77	0.018	365
Individuals with Anxiety disorders and MDD vs. CS					
No significant results					
Anxiety disorders & OCD					
Individuals with Anxiety disorders and not OCD < CS					
L superior temporal gyrus, insula	-54,-38,16	-0.54	8.31	<0.001	9785
R superior temporal gyrus insula	50,-14,24	-0.34	5.39	<0.001	6552
B MCC	2, 2, 32	-0.34	5.33	0.04	838
Individuals with OCD and not anxiety disorders < CS					
L supramarginal gyrus, superior temporal gyrus, inferior frontal gyrus	-54,-22,16	-0.34	4.64	0.002	1888

Individuals with Anxiety disorders and OCD vs CS
No significant results

MDD & OCD

Individuals with MDD and not OCD < CS					
B superior temporal gyrus, insula, SFG, MCC, ACC,	-46,6,-12	-0.31	8.81	<0.001	48966
L postcentral/precentral gyrus	-50,-14,36	-0.20	6.03	0.02	850
Individuals with OCD and not MDD < CS					
B SFG, orbital, ACC	14,38,-20	-0.43	4.93	<0.001	877
R sperior/middle temporal gyrus	50,-26,-8	-0.43	5.12	0.04	267

Individuals with both MDD and OCD vs CS
No significant results

MDD & BPD

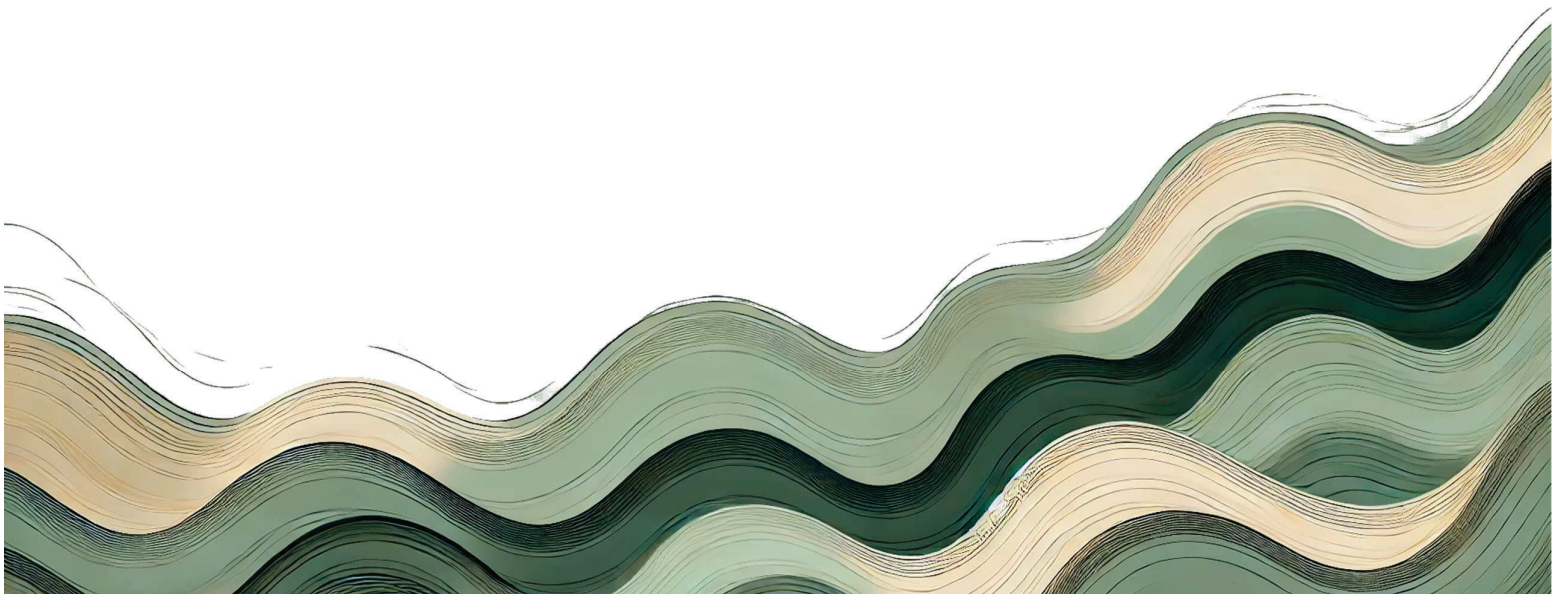
Individuals with MDD and not BPD < CS					
B superior temporal gyrus, insula, SFG, MCC, ACC,	-50,6,-4	-0.32	9.23	<0.001	48531
L postcentral/precentral gyrus	-54,-14,36	-0.21	6.27	0.02	836

Individuals with BPD and not MDD vs CS
No significant results

Individuals with both MDD and BPD vs CS
No significant results

ACC: anterior cingulate cortex, BPD: borderline-personality disorder, CS: comparison subjects, MDD: major depressive disorder, MCC: middle cingulate cortex, N: number, OCD: obsessive-compulsive disorder, SFG: superior frontal gyrus; SMA: supplementary motor area.

Discussion



In the discussion of this thesis, I will describe new insights into the causes of the heterogeneity observed in the neural correlates of mental disorders, specifically due to genetic haplotypes, comorbid cognitive impairments, and co-occurring mental disorders. Finally, I will present a neuroanatomical atlas of GMV alterations associated with major non-substance use mental disorders accounting for the impact of co-occurring disorders.

1. Genetic haplotypes as confounding factors

Study I examined the role of genetic haplotypes as a source of heterogeneity in the neural correlates of mental disorders and their potential as a confounding factor. This study specifically investigated how protective and risk Adhesion G Protein-Coupled Receptor L3 (ADGRL3) haplotypes impact brain structure and function in individuals with ADHD and healthy controls. Contrary to our first hypothesis, the presence of a specific ADGRL3 haplotype did not significantly influence the structural or functional neural correlates associated with ADHD. However, consistent with our fourth hypothesis, both haplotypes showed widespread strong effects on brain response during a working memory task, regardless of ADHD status. These findings suggest that, while ADGRL3 haplotypes may not modulate the neural correlates of ADHD directly, they exert a considerable overall influence on brain function. Given the high prevalence of ADGRL3 risk haplotype in individuals with ADHD (130), this effect may introduce a substantial confounding factor that complicates the interpretation of ADHD-related neural findings.

In this study, individuals with both protective and risk ADGRL3 haplotypes exhibited hypo-activation compared to non-carries. When the task difficulty increased, individuals with the risk haplotype showed more pronounced hypo-activation patterns in the 2-back versus baseline contrast than individuals with the protective haplotype. However, when comparing patients with ADHD to healthy controls, patients demonstrated hyper-activation during cognitive tasks, which contrasts with previous research that typically reports widespread hypo-activation in ADHD patients (131). One potential explanation for this discrepancy is that this reported hypo-activation could be attributed to the higher prevalence of ADGRL3 risk haplotype in ADHD patients (130) rather than to ADHD-related executive cognitive deficits alone. However, other factors may also contribute to the observed differences in brain activation. For instance, individuals who are not fully engaged in the task may show minimal or no activation, and both ADHD and ADGRL3 haplotypes may influence task engagement. Additionally, some studies

have associated brain activation with task accuracy and reaction time (132,133). Even methylphenidate may play a role (134), although its involvement in working memory networks is unclear (135).

Given these considerations, the hypo-activation observed in individuals with the protective haplotype and the hypo-activation previously seen in ADHD patients may stem from different underlying causes. For instance, those with the protective haplotype may require less brain activation to sustain attention during tasks, whereas ADHD patients may struggle to engage their cognitive networks effectively. Under this hypothesis, individuals predisposed to ADHD but carrying the protective haplotype may be less likely to develop the disorder, as their reduced activation requirement could compensate for difficulties in activating cognitive networks.

In terms of structural brain differences, although this study found some interactions between the effects of ADGRL3 haplotypes and ADHD, they did not survive after correcting for multiple comparisons. In this regard, a recent meta-analysis showed that ADGRL3 haplotypes confer a relevant risk in pediatric ADHD, but the association was less significant in adult ADHD (130). This suggests that the weaker association between ADGRL3 haplotypes and ADHD in adults may account for the lack of significant brain effects related to these interactions. However, this lack of statistical significance is not surprising in ADHD literature, where some studies have reported frontostriatal abnormalities that may change with age and/or treatment, while others have failed to detect them (69,114,136–139). In agreement with previous literature, we found more robust evidence of functional brain abnormalities than structural brain abnormalities in ADHD.

Study I have several limitations. First, despite efforts to achieve a well-balanced sample, the ratio of homozygous vs. heterozygous individuals for the protective and risk ADGRL3 haplotypes was higher in ADHD patients than in healthy controls. This imbalance could have led to potential misattribution of haplotypic effects to ADHD status or its interaction with haplotypes. However, this seems unlikely, given that the main findings were related to haplotypes rather than ADHD status. Second, while the overall sample size was relatively large for a neuroimaging study, it may still have provided limited statistical power to detect weaker effects, particularly in comparisons between patients and controls or in examining interactions between haplotypes and ADHD. However, the study could still detect significant hypo-activations, suggesting that larger effects were robust. Third, the sample consisted of adults,

and a recent meta-analysis has indicated that the effects of ADGRL3 haplotypes may vary by age, which limits the generalizability of the findings across different age groups.

This study underscores the critical role genetic haplotypes play as confounding factors in neuroimaging research, particularly regarding brain function studies. Our findings suggest that haplotypes strongly associated with specific mental disorders, such as the ADGRL3 risk haplotype with childhood ADHD (130), can confound disorder-specific neural patterns, leading to broader, less specific results that may not accurately reflect the neural correlates of the disorder itself. These findings have significant clinical implications, as they highlight the necessity of accounting for genetic variability in developing precise machine-learning tools for diagnosis. Predictive models that overlook genetic differences or rely solely on generalized biomarkers may produce confounded and, thus, less accurate predictions. This study suggests that integrating genetic information into neuroimaging analyses of mental disorders could improve the specificity and accuracy of disorder biomarkers, supporting more personalized diagnostic approaches and paving the way for more targeted and effective treatment.

2. The impact of cognitive impairments

Study II examined the impact of comorbid cognitive impairments on the heterogeneity of neural correlates in mental disorders. Specifically, this study assessed differences in brain function among cognitively impaired individuals with BD, cognitively normal individuals with BD, and healthy controls. In line with our second hypothesis, patients with cognitive impairments showed significant differences in resting-state functional connectivity compared to healthy controls, whereas cognitively normal patients showed no such differences. These findings suggest that cognitive impairments significantly contribute to the neural variability in BD, influencing the distinct resting-state functional connectivity differences observed in affected individuals.

Several studies have consistently reported hypo-connectivity within the DMN in individuals with BD during acute episodes (140,141). However, findings from the remission are more variable. Some studies, consistent with our results, indicate a shift towards hyper-connectivity during remission (140), whereas others report a normalization of DMN connectivity (142). A plausible explanation for these differences is that previous studies treated BD patients as a homogeneous sample, independently of their cognitive status. This suggests that the likelihood

of detecting significant resting-state functional connectivity in remitted BD patients may depend on the proportion of cognitively impaired patients in the sample. Supporting this idea, our study found that cognitively normal patients did not exhibit significant differences in connectivity compared to healthy controls.

Previous research using the same study sample has identified distinct structural and task-based functional neural correlates in BD when considering cognitive status (143,144). In these studies, cognitively impaired patients showed increased thickness in the left dorsomedial PFC, a crucial region of the DMN, compared to cognitively normal patients and healthy controls (144). Additionally, compared to cognitively normal patients, they exhibited hypo-activity in regions associated with the cognitive control network and hyper-activity in the DMN during a working memory task (143). These findings, alongside ours, suggest that cognitively impaired patients may struggle to suppress DMN activity during cognitive tasks, such as working memory, potentially explaining their poorer task performance (143,145). The observed alterations within the CEN may indicate a reduced capacity to regulate cognitive control, a key component of executive functioning, which may further contribute to the impaired cognitive performance seen in this group.

From a theoretical perspective, it is interesting that resting-state functional connectivity alterations were seen both within and between DMN and CEN, particularly overlapping regions from the parietal and posterior cingulate cortex. These alterations may arise from a disruption of structural connectivity, potentially due to white matter deficits found in cognitively impaired patients with mood disorders relative to cognitively normal patients and healthy controls (144,146). Supporting this hypothesis, an MRI study found a lower circularity of the splenium of the corpus callosum in a sample of pediatric patients with bipolar disorder relative to healthy controls, suggesting that such white matter alterations may occur early in the course of bipolar disorder (147).

Based on previous literature, the observed differences may not be unique to bipolar disorders but could represent a broader neural correlate of cognitive impairments seen across various mental disorders, such as MDD and schizophrenia (123,148,149). These similarities suggest that shared neural pathways may underlie cognitive impairments across different conditions, reinforcing the need for cross-disorder investigations to understand these shared mechanisms better and highlighting the importance of considering comorbid cognitive impairments when identifying specific neural correlates of a mental disorder.

Study II has several limitations. First, the cross-sectional design limits the ability to make causal inferences about the neuronal mechanisms underlying cognitive impairments. Additionally, the priori selection of cognitive networks may introduce bias, as cognitive impairments could be influenced by other networks not directly related to cognition. Another limitation was the lack of a statistically significant difference between the cognitively impaired and cognitively normal groups, which challenges the utility of resting-state fMRI biomarkers for use in treatment trials. However, the observed differences between the cognitively impaired patients and healthy control groups suggest that illness-related alterations in resting-state functional connectivity are associated with cognitive impairments in bipolar disorder. Medications may have influenced the connectivity differences between groups, although association analyses did not survive correction for multiple comparisons, indicating that medication was unlikely to explain the findings. Finally, the absence of data on psychotic symptom history, which could have affected the results, represents another limitation of this study.

This study highlights the significant impact of comorbid cognitive impairments on the neural correlates in mental disorders. These findings suggest that observed differences between individuals with BD and healthy controls may be partly attributed to cognitive status, potentially indicating a shared neurobiological mechanism for cognitive impairments across several mental disorders. These insights underscore the importance of accounting for cognitive status when developing diagnostic tools and treatment strategies for BD. The functional alterations identified in this study present promising targets for pro-cognitive interventions, which, if replicated, could inform go-no/go decisions on advancing treatment strategies for BD and other mental disorders (150). This emphasizes the need for personalized approaches in psychiatric care that consider individual cognitive profiles, thereby enhancing the precision of interventions and improving overall treatment outcomes by directly addressing cognitive deficits in patients with mental disorders.

3. The role of co-occurring mental disorders

Study III explored the role of co-occurring mental disorders as a source of heterogeneity in the neural correlates of major mental disorders and examined their potential confounding effect in neuroimaging analyses. This study implemented a novel meta-analytic approach designed to address the effects of co-occurring disorders on brain structure across major non-substance

mental disorders. Supporting our third hypothesis, the interaction meta-analysis revealed that the neural correlates of mental disorders, such as anxiety disorders, MDD, and OCD, differ depending on whether these disorders occur alone or co-occur with one another. Consistent with our fifth hypothesis, the GMV alterations identified through this adjusted meta-analysis were more focal (fewer voxels included) and disorder-specific (less correlated and shared among disorders) compared to standard meta-analyses that do not account for co-occurring disorders. These findings suggest that co-occurring disorders influence the neural correlates of specific mental disorders in two different ways: i) by directly shaping the observed neural patterns and ii) by introducing confounding effects that lead to broader, over-correlated alterations and inflated transdiagnostic patterns. Additionally, this study provides a comprehensive neuroanatomical atlas of GMV alterations associated with major non-substance use mental disorders, including anorexia, anxiety disorders, ADHD, ASD, BD, borderline personality disorder (BPD), MDD, OCD, PTSD, and schizophrenia spectrum disorders (SSD).

3.1. Modulatory effects

The findings from the interaction meta-analysis revealed that the neural correlates of anxiety disorders, MDD, OCD, and BPD differ depending on whether these disorders occur alone or in combination with others. Below, we detail the findings for each disorder, emphasizing the influence of co-occurring conditions.

The main meta-analytic results for anxiety disorders confirmed several previously established findings, although regions like the middle cingulate cortex and right insula were not identified (35,54,151). However, when controlling for interactions with MDD and OCD, these regions showed statistically significant differences. These findings suggest that co-occurring disorders, particularly MDD and OCD, may influence GMV alterations, highlighting the role of comorbid interactions in shaping the neurobiological profile of anxiety disorders.

For MDD, meta-analytical results mainly aligned with prior research (35,39,152). However, this study identified additional GMV alterations in several subcortical regions beyond the hippocampus. Interestingly, after accounting for interactions with anxiety disorder and OCD, these subcortical differences lost significance, suggesting that co-occurring disorders may amplify certain neurobiological variations in MDD. These findings suggest that comorbid conditions significantly modulate the neuroanatomical profile of MDD.

For OCD, the meta-analytical results were partially consistent with previous research, though some discrepancies emerged (153–155) likely attributable to the comorbidity effects. When

controlling for interactions with anxiety disorders and MDD, the neural correlates of OCD exhibited distinct characteristics, with fewer regions demonstrating significant volumetric alterations. This suggests that comorbid conditions significantly shape the neuroanatomical profile observed in OCD.

For BPD, the novel meta-analysis found no significant GMV alterations contrary to previous research (156). Interestingly, the interaction meta-analysis showed that BPD co-occurring with MDD was associated with smaller GMV in the orbitofrontal cortex (g=-0.39). However, this result was not statistically significant, likely due to the low sample size. These results suggest that individuals with BPD alone may not lead to GMV alterations, but such changes appear when co-occurring with MDD, emphasizing the modulatory effect of co-occurring disorders in BPD.

3.2. Confusion effects

The GMV alterations derived from this novel meta-analysis were more focal (fewer voxels included) and disorder-specific (less correlated and shared among disorders) than when we conducted separate standard meta-analyses per disorder (i.e., ignoring co-occurring disorders), even when we included the same studies. The presence of more focal and disorder-specific alterations supports the increased validity of the novel approach. Or, seen from the opposite side, the maps from the standard meta-analyses would mix alterations from different co-occurring disorders, resulting in more extensive alterations over-correlated across disorders with inflated transdiagnostic alterations. The results for each disorder are discussed below, including the extent and intensity of the alterations. The specificity of these findings is addressed separately, focusing on the correlations between disorders and the extent of transdiagnostic alterations

Anxiety Disorders

The novel meta-analysis for anxiety disorders, in addition to confirming findings from earlier studies (35,54,151), identified smaller GMV in subcortical regions and larger GMV in the right cerebellum, offering further insight into anxiety-related neuroanatomy. The striatum has been previously associated with threat attentional bias, and fear conditioning (157), playing a crucial role in the anxiety circuitry. Smaller GMV in this region may produce the avoidance of treat stimuli, avoiding the exposure to those environments (158). The temporal lobes, part of the ventral attention network, are involved in orientating stimulus-driven attention, so alterations in this network may disrupt the shift from internally directed stimuli (e.g., worrisome thoughts)

to external events. In addition, the insula is associated with perceiving strong emotions and processing introspective awareness (159), and together with the thalamus, are parts of the fear network model modulating fear through the fronto-temporo-insula network (160,161). Therefore, alterations in both areas may be associated with intense response to negative events and enhancement of their expectations of negative incomes. Finally, aberrant structure in the PFC can contribute to impairments in executive function, impulse control, and social cognition, which are symptoms often experienced by individuals with anxiety (162).

Bipolar Disorder

The findings for BD in the novel meta-analysis largely align with previous research, revealing smaller GMV in several cortical and subcortical regions (39,163,164), and partially overlapping the results observed in MDD. These findings suggest that GMV reductions in the dorsal/ventral PFC, including the ACC, may represent a common neurobiological substrate for mood disorders, further supporting the existence of shared neural mechanisms across these conditions. The dorsal/ventral PFC, along with ACC, are involved in mood and emotion regulation (165,166). The PFC is also essential within the frontoparietal network, supporting executive functions, working memory, inhibition, and task-switching (167), so smaller GMV may contribute to the multiple cognitive difficulties described by patients with bipolar disorder (168). Additionally, the insula, involved in affective processing and awareness of bodily states (169,170), has been suggested as a potential biomarker for mood disorders, with functional meta-analyses reporting abnormal activity in these regions (164). Increasing attention has focused on the cerebellum's role in bipolar disorder, including cognitive deficits and emotion dysregulation(171), where smaller volume has been linked to more severe clinical courses (172) or alterations in social cognition (173).

Major Depressive Disorder

The findings for MDD are partially consistent with prior research (35,39,152), though some discrepancies likely arise from the inclusion of samples with co-occurring disorders, which were generally excluded in earlier studies. Given the recognized heterogeneity in MDD, including subtypes or "biotypes" (174), previous studies may have overlooked these biotypes more likely to co-occur with other psychiatric conditions. Finally, despite several regions showing smaller GMV, the effect sizes were generally small ($g<0.25$), suggesting that MDD is primarily driven by brain functional irregularities rather than structural ones (44,98).

Schizophrenia Spectrum Disorders

The findings for SSD were largely consistent with previous research (40,65), supporting the notion that SSD involves widespread structural disruptions affecting multiple functional neural networks, overlapping with those observed in mood and anxiety disorders (40,175,176). These alterations included GMV decreases associated with relapse risk following a first episode of psychosis (177). Structural alterations have also been associated with functional alterations in both treated and untreated patients, highlighting the complex interplay between structure and function in SSD (175,176). Specifically, smaller GMV was found in areas showing decreased activation within DMN, while areas with increased activation were observed in the auditory network. Additionally, antipsychotic medication can further impact both the structural and brain activity in psychosis (178,179).

Attention-deficit/hyperactivity disorder

The findings identified for ADHD by the novel meta-analysis partially align with previous research (69). The right supramarginal gyrus plays an important role in attention, spatial processing, and the integration of sensory information (180). Structural deficits in this region may contribute to the attentional and executive function impairments seen in ADHD (181,182). The orbitofrontal cortex is involved in decision-making, impulse control, and the regulation of emotional responses (183). Alterations in this region have been frequently reported in ADHD, supporting the notion that structural changes in the orbitofrontal cortex may be related to the impulsivity and emotional dysregulation characteristic of the disorder (184).

Autism spectrum disorder

The findings identified for ASD by the novel meta-analysis partially align with previous research (69,75). Calcarine fissure is a region involved in primary visual processing, so smaller GMV may underpin the altered sensory processing and visual perceptual difficulties often observed in ASD. This finding is consistent with previous reports suggesting abnormal visual cortex development and function in ASD (185). The cerebellum, traditionally associated with motor control, has been increasingly recognized for its role in cognitive processes, including attention, language, and social cognition (186). The findings of smaller GMV in the right cerebellum support previous studies that highlight cerebellar structural and functional alterations in ASD, suggesting a potential link to the motor and cognitive impairments characteristic of the disorder (187). However, it is important to note the significant study heterogeneity in this region, indicating variability in the specific regions and extent of

cerebellar involvement. These findings underscore the importance of considering sensory and motor-related brain regions in understanding the neurobiological underpinnings of ASD.

Obsessive-Compulsive Disorder

The findings for OCD were consistent with previous research, though some discrepancies were noted (153–155). These discrepancies may be attributed to the presence of co-occurring disorders, as 23% of the patients also had MDD, and 17% had anxiety disorders. For instance, smaller GMV in the insula, not observed in this meta-analysis, have often been associated with MDD and anxiety disorders (35,39), and was also observed in the present findings. The parietal lobe, a core region of the frontoparietal network, is involved in cognitive functions such as attention, planning, and response inhibition (167,188). Structural alterations in this region may underlie the cognitive deficits seen in individuals with OCD, such as reduced cognitive flexibility, which is linked to the repetitive nature of their behaviors (189). Interestingly, this symptom is unique to OCD, and alterations in the parietal lobes were not found in other anxiety-related disorders. The structural alterations in the orbital frontal cortex crucial for fear extinction, cognitive reappraisal, and reward-related decision-making (190), may contribute to the top-down control over affect and motivation (191). Several functional studies had reported a hypo-activation of this area during fear extinction of symptoms provocation, further underscoring its role in OCD (192).

Post-Traumatic Stress Disorder

Contrary to previous studies, which highlighted the frontolimbic circuit alterations in PTSD (35,193), the novel meta-analysis only identified smaller GMV in the left lingual gyrus with a large effect size. This discrepancy may reflect the higher sensitivity of our approach and the fact that earlier studies specifically targeted the hippocampus. The lingual gyrus is in the occipital lobe, which is responsible for processing visual information. Aberrant structure and function in this region have been linked to dissociative responses in PTSD patients and emotional processing of visual stimuli (194).

Anorexia Nervosa

The GMV alterations identified for anorexia nervosa were largely consistent with previous research (83,195,196). However, unlike prior studies, no significant GMV reduction was found in the ACC or cerebellum, likely due to adjustment for co-occurring disorders such as MDD. Notably, the GMV reduction in the precuneus appeared unique to anorexia, though this finding

should be interpreted with caution due to study heterogeneity, potentially driven by factors like weight recovery. The precuneus is a core region of the DMN that is involved in cognitive performance and self-directed processing (197). A GMV abnormality in this area could alter the function of the DMN related to ruminative preoccupation with eating, body weight, and impaired cognitive flexibility (198). Indeed, several resting-state functional MRI studies reported abnormal functional connectivity in the DMN in patients with anorexia (83). The supplementary motor area is involved in the planning and controlling motor actions and plays a crucial role in task switching (199). An impairment in this region may contribute to cognitive rigidity in patients with anorexia (200). Finally, the middle cingulate cortex plays a key role salience network and is involved in identifying the emotional significance of stimuli and producing appropriate affective and behavioral responses, particularly fear and avoidance (201). A reduction of GMV in this middle cingulate cortex could lead to abnormal functionality, previously reported (83), contributing to typical symptoms of anorexia such as excessive perfectionism, cognitive rigidity, and excessive attention to detail (200).

Borderline personality disorder

Contrary to previous research, the novel meta-analysis found no significant GMV differences in BPD (156). A plausible explanation for this discrepancy may be the high prevalence of co-occurring disorders among individuals with this disorder, which is higher than in other mental disorders (45% MDD, 26% PTSD, and 23% anxiety disorders), a factor not adequately accounted for in previous meta-analyses. In fact, all included studies had at least one individual with another co-occurring disorder. Interestingly, smaller GMV in the orbitofrontal cortex, commonly reported in BPD, has been previously associated with anxiety (35) and supported by the findings of this study. These results suggest that individuals with BPD alone do not show GMV alterations, but such changes may be present when co-occurring with another disorder.

Specificity of the GMV differences – correlations across disorders

This study found that the spatial pattern of GMV alterations in SSD correlated with those in BD, MDD, OCD, and anxiety disorders, consistent with previous studies that identified strong correlations among mood disorders, SSD, and OCD (96,97). Similarly, the GMV abnormality pattern of BD also correlated with MDD, OCD, and anxiety disorder. The correlation between the GMV abnormality pattern of MDD and anorexia nervosa was likely due to common depressive symptoms in these patients, even when not meeting the full criteria for MDD.

Interestingly, PTSD displayed a unique GMV abnormality pattern, showing no significant correlations with other mental disorders.

These findings contrast with standard meta-analyses, where almost all mental disorders showed significant correlations with each other. This discrepancy may rely on the high prevalence of co-occurring disorders not accounted for in the standard meta-analysis. For instance, in the standard analysis, the GMV abnormality pattern of MDD significantly correlated with anxiety disorders (r=0.60) and OCD (r=0.47). The observed similarities are likely driven by the common co-occurrence of these disorders, as 28% of individuals with anxiety and 23% with OCD also presented MDD. These findings support the importance of adjusting for co-occurring mental disorders when investigating disorder-specific brain alterations and suggest that the novel method successfully mitigated this potential confounding effect.

Specificity of the GMV differences – extent of transdiagnostic alterations

The findings for transdiagnostic alterations support previous hypotheses of common neurobiological substrates across mental disorders (96–98), specifically in the dorsal ACC and insula, highlighting that co-occurring disorders do not drive these common alterations. Additionally, previous studies have also reported smaller GMV in the PFC associated with mood disorders (39), and in the middle cingulate cortex linked to mood, anxiety, and trauma-related disorder (35). These regions, crucial for emotion regulation and social behavior, also play key roles in cognitive and executive functions (93,202), which are commonly impaired across mental disorders. Therefore, these observed GMV alterations may be associated with cognitive impairments rather than diagnosis-specific symptoms (93,96).

Although evidence suggests that these common substrates are associated with the disorders rather than a predispose risk state, the possibility that these findings are influenced by early life trauma cannot be ruled out. Notably, early trauma has been shown to increase the risk of developing mood or psychotic disorders in adulthood (202), and childhood maltreatment has been associated with smaller GMV in several brain regions, including the ACC, even in individuals who do not develop a mental disorder (21). Another potential explanation may rely on the shared genetic pattern across disorders. For instance, a study investigating the genetic architecture of 11 mental disorders identified four factors linked to (i) compulsive behaviors (anorexia, OCD), (ii) psychotic features (SSD, BD), (iii) neurodevelopmental disorders (ADHD, ASD), and (iv) internalizing disorders (anxiety, MDD) (88). Additionally, there is converging evidence of a shared genetic pattern across mood and psychotic disorders (MDD,

BD, and SSD) (89). These findings suggest that genetics and neuroanatomy can provide different yet complementary information about the neurobiological underpinnings of mental disorders, as the genetic clustering identified in previous studies partially differs from the neuroanatomical patterns (e.g., there are no overlapping structures between anorexia and OCD).

3.3. Limitations and implications

Study III has several limitations. Firstly, there is a debatable nosology of current mental disorders based on clinical consensus rather than known biological underpinnings (203). Major mental disorders often share some genetic risk factors, and there are high rates of co-occurring disorders and diagnostic shifts over time. However, this overlap does not invalidate the existence of disorder-specific brain correlates, as diagnostic labels are among the best predictors of future outcomes, highlighting their clinical relevance (177). Secondly, the cross-sectional nature of the included studies impedes the causality inference; thus, findings must be interpreted as statistical associations. Another limitation is the commonly poor report of some co-occurring disorders in the literature, as well as the omission of subthreshold disorder-specific symptoms due to the complexity of the analysis and the expected large amount of missing data. Additionally, the proportion of co-occurring disorders in the sample does not reflect those in the general population. Still, the objective was to disentangle the specific neuroanatomy of co-occurring mental disorders, not to analyze the patterns of co-occurring disorders in the general population. Furthermore, like a limitation in many meta-analyses, the study relied on summarized data (e.g., peak and effect sizes) rather than raw data (204). Similarly, potential clinical and methodological moderators such as symptom severity, body mass index, or software used were not accounted for, as including these covariates would have added considerable complexity to the current study, leaving them for future research. Another limitation is that only mental disorders with a previously published meta-analysis comprising at least ten studies were included. Finally, although the study refers to GMV differences, it is more appropriate to describe these differences in T1-MRI signal, given that the acquired MRI data are not a direct measure of brain structure (205).

This study underscores the importance of accounting for co-occurring disorders and their interactions in neuroimaging research, particularly in structural analysis, to identify robust and disorder-specific neural correlates of mental disorders. Several important implications emerge from this study. First, the novel meta-analytical methodology can be extended to other MRI

modalities, such as fMRI and diffusion tensor imaging, paving the way for a comprehensive atlas of structural and functional brain correlates in mental disorders. Such atlas would deepen our understanding of the neurobiological mechanisms underlying these conditions. Clinically, the GMV atlas generated in this study enhances the precision of the brain alterations localization, which may improve the effectiveness of targeted interventions, such as deep brain stimulation or non-invasive brain stimulation therapies, aimed at alleviating specific symptoms (206). Furthermore, this atlas could serve as a valuable resource for future machine-learning research in mental health by contributing to improved diagnostic accuracy for mental disorders. Current MRI-based machine-learning tools often face limited accuracy due to the reliance on conventional diagnostic classifications (103,105). By using this atlas, models could shift from direct diagnostic prediction to risk estimation, offering clinicians valuable additional, nuanced insights that enhance diagnostic precision and enable more proactive, targeted interventions. In this way, this meta-analytical approach and, consequently, GMV atlas hold promise for advancing machine-learning applications in psychiatry, ultimately leading to more personalized treatments that improve patient outcomes.

4. Future directions

This thesis advances our understanding of the sources of heterogeneity in neuroimaging research aimed at identifying the neural correlates of mental disorders, with a focus on genetic haplotypes**,** comorbid cognitive impairments, and co-occurring disorders. However, further research is needed to expand our knowledge of these factors and investigate additional variability sources, such as stages of life, medication, and clinical variables like illness duration or symptom severity. Building on the current findings, future studies could offer deeper insights into the underlying neurobiological processes and support the development of reliable machine-learning tools for clinical application.

In the following section, I will outline several potential future research directions that could build upon this thesis to enhance our understanding of other causes of heterogeneity, the neural underpinnings of mental disorders, and advance personalized medicine in psychiatry.

4.1. Additional moderator factors and longitudinal studies

As discussed in the introduction, several factors can influence neuroimaging findings. While this thesis primarily investigates the impact of genetic haplotypes, comorbid cognitive impairments, and co-occurring disorders, other important moderators remain unexplored, such as medication use or patient stage. Additionally, the development of the GMV atlas did not include these additional moderators to avoid adding further complexity to the model. Therefore, future research should address these gaps by investigating how these factors influence structural and functional neural correlates of mental disorders by grouping participants based on criteria such as medication status (e.g., medicated vs. never medicated) or patient stage (e.g., currently depressed vs. remission). Findings from such studies could deepen our understanding of the neurobiological underpinnings of mental disorders and enhance the specificity of brain alterations associated with distinct subtypes. Incorporating these moderators could ultimately improve the clinical relevance of neuroimaging research, leading to the identification of more precise biomarkers for diagnosis and treatment planning.

All the studies within this thesis focused exclusively on adult samples, limiting the generalizability of the findings to other life stages. For instance, previous research suggests that the effects of ADGRL3 haplotypes may vary across developmental stages, with stronger effects observed during critical periods of brain development. This underscores the need for future studies to explore the impact of genetic haplotypes in pediatric populations. Developing a GMV atlas that maps alterations across key life stages, such as childhood and adolescence, would be especially valuable for neurodevelopmental disorders, such as ADHD and ASD, where the brain undergoes rapid growth and reorganizations that can have lasting effects into adulthood. Such an atlas could provide critical insights into early neural changes related to the onset and progression of these disorders, ultimately supporting more age-appropriate diagnostic and treatment strategies. Additionally, exploring the impact of genetic haplotypes and co-occurring conditions on brain development in children could further clarify the mechanisms underlying early-onset mental disorders. Furthermore, identifying early neural biomarkers may facilitate the development of targeted interventions during critical periods of neuroplasticity, potentially preventing or mitigating the severity of these disorders as children transition into adulthood.

Finally, findings from this thesis are derived from cross-sectional studies, which limit the ability to infer causality and should, therefore, be interpreted as statistical associations. To

advance this research, future studies should prioritize longitudinal design to investigate the progression of brain alterations related to cognitive impairments and co-occurring disorders over time. Longitudinal data would offer crucial insights into how these factors evolve and interact as the disorder progresses, enabling a more thorough understanding of the neurobiological mechanisms driving brain structure and function changes. Such studies are essential for identifying early markers of disease onset and progression, allowing for more accurate predictions of disorder trajectories.

4.2. Additional confounding factors

In this thesis, we investigated the potential confounding effects of genetic haplotypes and co-occurring disorders in neuroimaging research. However, as highlighted in the introduction, other factors can significantly confound neuroimaging findings. For instance, variability in MRI devices and methodologies can introduce noise and reduce the replicability of results across studies. Additionally, clinical variables such as symptom severity and duration of illness may act as confounders in studies of mental disorders. For example, neural alterations may show larger effect sizes in individuals with more severe symptoms, potentially confounding the true relationship between brain changes and the disorder itself. Future research should prioritize the systematic investigation of these factors to better understand their potentially confounding effects on the neural correlates of mental disorders. Addressing these confounding factors is crucial for advancing the field of neuroimaging. Standardizing MRI protocols and incorporating advanced harmonization techniques could mitigate variability across studies and improve the reliability of findings.

Additionally, accounting for clinical variables in statistical analyses would help estimate their effects and obtain more specific findings. This approach could lead to identifying more precise and clinically meaningful biomarkers. Future research should integrate these considerations to enhance neuroimaging findings' robustness, reproducibility, and clinical relevance in mental health research.

4.3. Advancing the neuroanatomical atlas

The atlas presented in this thesis provides comprehensive maps of GMV alterations associated with mental disorders, derived from a meta-analysis of VBM studies. While VBM offers valuable insights into structural brain correlates, it captures a limited view of the complex neurobiological processes underlying these disorders. Future research should expand this work

by incorporating additional MRI modalities, such as fMRI, diffusion tensor imaging (DTI) or magnetic resonance spectroscopy (MRS), to build a more comprehensive understanding of the brain's structural, functional, connectivity and chemical changes underlying mental disorders.

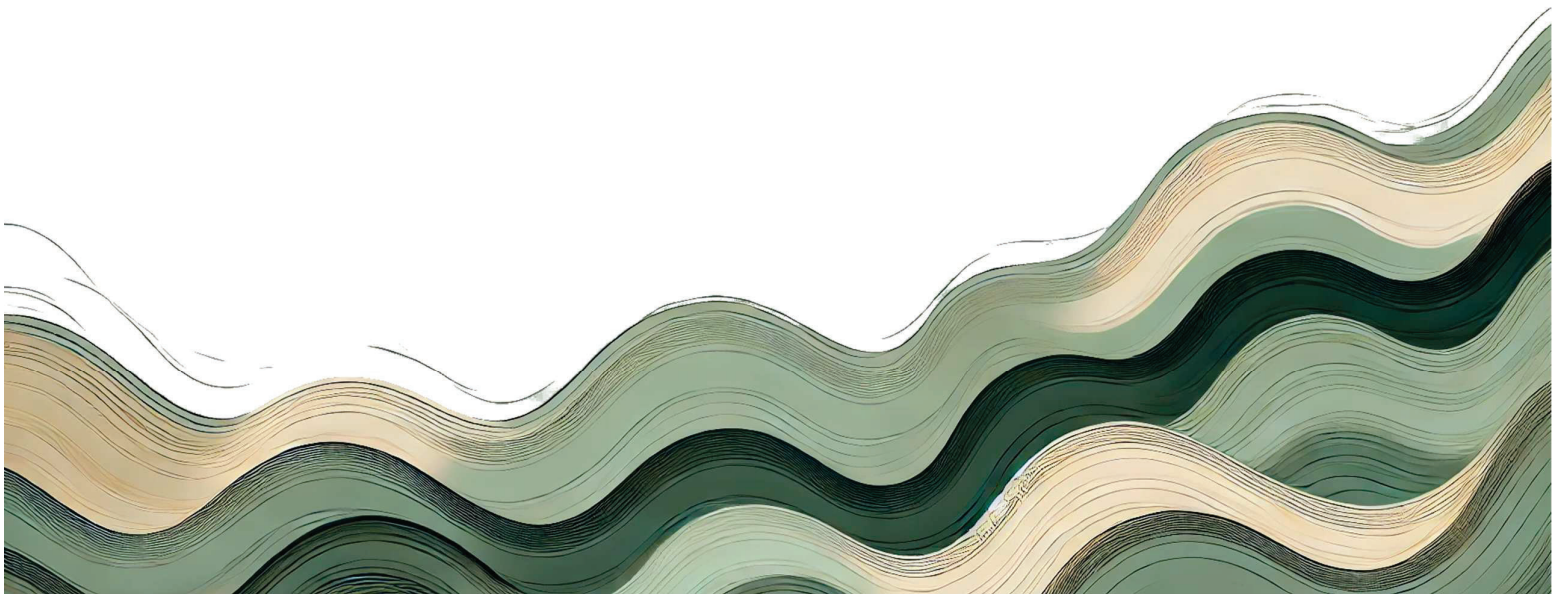
Extending this approach to fMRI could complement structural findings by identifying disorder-specific patterns of altered brain activity and network dysfunctions. For instance, task-based fMRI could reveal alterations in neural responses during tasks targeting specific cognitive or emotional processes, such as working memory, emotional regulation, or reward processing, in individuals with mental disorders. Resting-state fMRI, meanwhile, could uncover disruptions in functional connectivity within networks such as DMN, salience network, and CEN, which are commonly altered in several mental disorders.

DTI would enable the assessment of white matter integrity and connectivity pathways, revealing the disruption in structural connectivity networks of mental disorders. Additionally, MRS could provide insights into the brain's chemical environment of mental disorders by quantifying the alterations of metabolites, such as glutamate or GABA, in specific brain regions associated with neurotransmitter function.

Developing multimodal atlases of alterations in mental disorders by applying the novel meta-analytical methodology to fMRI, DTI and MRS data, and integrating these findings with the current GMV atlas, would yield a detailed map of brain architecture and functional interactions associated with mental disorders. This comprehensive approach would offer a more holistic understanding of the complex neural mechanisms underlying these conditions.

Finally, the GMV atlas and future multimodal atlases could serve as valuable resources for developing machine-learning tools that enhance diagnostic accuracy. By incorporating the atlases into machine-learning algorithms, researchers could develop predictive models capable of confirming diagnoses, distinguishing mental disorders, and estimating the treatment response based on individual brain imaging data. This approach could inform clinical decisions, enabling the selection of interventions that specifically target identified brain alterations, ultimately leading to more effective, individualized care. In this way, these comprehensive atlases could play a crucial role in advancing machine-learning applications in psychiatry, supporting the development of more personalized, precise, and effective interventions.

Conclusions



This work provides new insights into factors contributing to the heterogeneity of neural correlates observed in mental disorders, including genetic haplotypes, cognitive impairments, and co-occurring mental disorders. The conclusions of my thesis are summarized below:

C1. The presence of protective or risk ADGRL3 haplotypes does not influence the structural and functional neural correlates of attention-deficit/hyperactivity disorder. Therefore, this result does not provide evidence to support that the neural correlates of mental disorders depend on genetic haplotypes.

C2. Cognitive impairments affect resting-state functional connectivity in patients with bipolar disorder. Therefore, this result provides evidence to support that neural correlates of mental disorders are influenced by comorbid cognitive impairments.

C3. Structural alterations in major depression, anxiety disorder, and obsessive-compulsive disorder differ when these conditions are present alone versus co-occurring in the same individual. Therefore, this result provides evidence to support that the neural correlates of mental disorders depend on co-occurring mental disorders.

C4. ADGRL3 haplotypes, associated with attention-deficit/hyperactivity disorder, have relevant brain functional correlates, for which they can confound the analysis of the brain correlates of attention-deficit/hyperactivity disorder. Thus, this result provides evidence to support that genetic haplotypes can confound the analysis of neural correlates in mental disorders.

C5. Co-occurring mental disorders influence structural alterations in mental disorders, leading to broader and over-correlated patterns. Therefore, this result provides evidence to support that co-occurring disorders can confound the analysis of neural correlates in mental disorders.

C6. The neural correlates of mental disorders are influenced by several factors at least including comorbid cognitive impairments and co-occurring mental disorders.

C7. The analysis of the neural correlates of mental disorders may be confounded by several factors at least including genetic haplotypes and co-occurring mental disorders.

C8. The presence of moderator and confounding effects in the neural correlates of mental disorders complicates the identification of robust and specific biomarkers but opens new possibilities.

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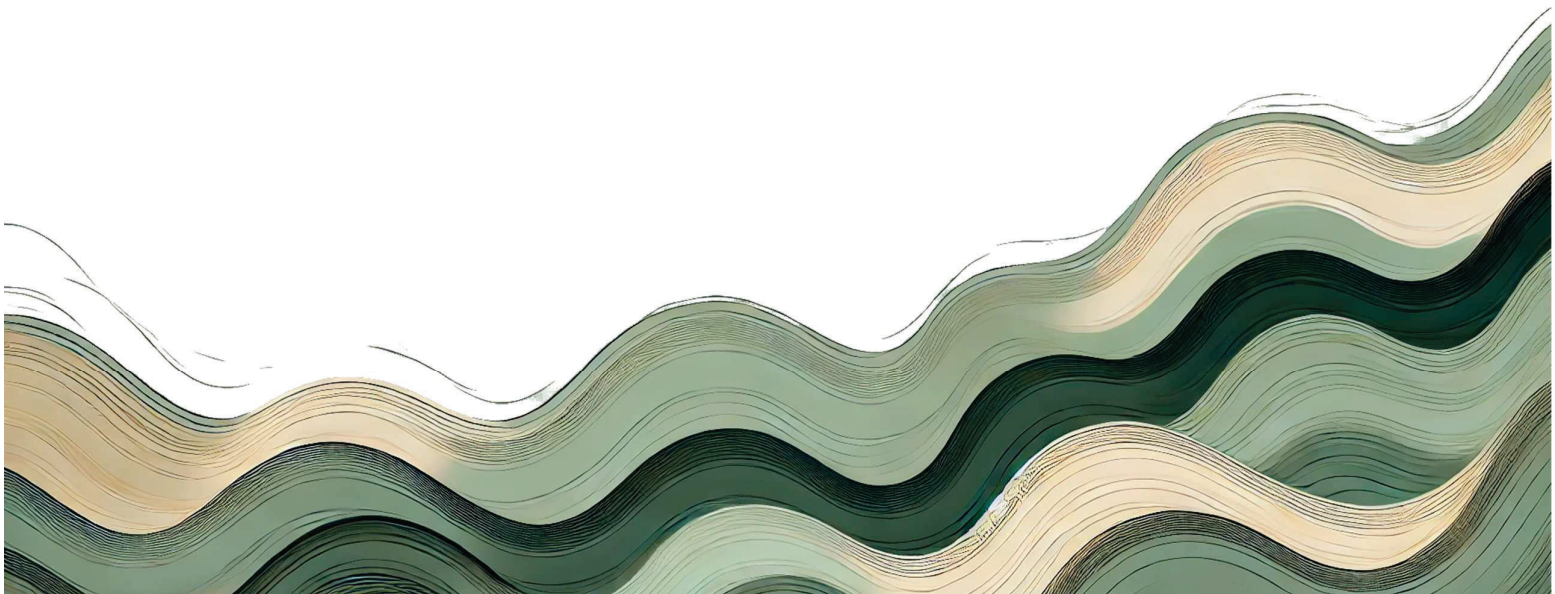

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