Review/Meta-analyses

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Transdiagnostic and disease-specific abnormalities in the default-mode network hubs in psychiatric disorders: A meta-analysis of resting-state functional imaging studies

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Abstract

Background. The default mode network (DMN) dysfunction has emerged as a consistent biological correlate of multiple psychiatric disorders. Specifically, there is evidence of alterations in DMN cohesiveness in schizophrenia, mood and anxiety disorders. The aim of this study was to synthesize at a fine spatial resolution the intra-network functional connectivity of the DMN in adults diagnosed with schizophrenia, mood and anxiety disorders, capitalizing on powerful meta-analytic tools provided by activation likelihood estimation.
Methods. Results from 70 whole-brain resting-state functional magnetic resonance imaging articles published during the last 15 years were included comprising observations from 2,789 patients and 3,002 healthy controls.
Results. Specific regional changes in DMN cohesiveness located in the anteromedial and posteromedial cortex emerged as shared and trans-diagnostic brain phenotypes. Disease-specific dysconnectivity was also identified. Unmedicated patients showed more DMN functional alterations, highlighting the importance of interventions targeting the functional integration of the DMN.
Conclusion. This study highlights functional alteration in the major hubs of the DMN, suggesting common abnormalities in self-referential mental activity across psychiatric disorders.

Introduction

The default mode network (DMN) refers to a set of brain regions that are more active in conditions unconstrained by explicit task instructions [1, 2], commonly termed "resting-state" conditions. The DMN gained prominence in cognitive neuroscience through the seminal work of Raichle and colleagues, who coined the term "default mode" [3], and that of Greicius et al. [4], who established the presence of this network during resting-state functional magnetic resonance imaging (rsfMRI). The DMN has been shown to be reproducible [5–8] and has relatively low inter- and intra-subject variability [7–9] across different acquisition and analysis protocols [5, 10]. Brain regions reliably identified as part of the DMN include the medial prefrontal cortex (MPFC)/anterior cingulate cortex (ACC), the precuneus/posterior cingulate cortex (PCu/PCC), the angular gyrus, and regions of the medial and lateral temporal cortex [3,11–14]. Among these regions, the MPFC and the posteromedial cortex (PMC), which includes the PCu and PCC, are often considered core components of the network, showing widespread patterns of connectivity and activity across a range of internally directed tasks/processes [13,15,16].

The DMN has been associated with wide array of cognitive functions including self-referential mental activity [11,17,18] (particularly self-monitoring and autobiographical thoughts [19], stimulus-independent thought [1,13,20], and predictive planning [17,19]). Available evidence suggests that different DMN regions may contribute preferentially to the varied functions attributed to the DMN. Notably, the MPFC has been linked to the processing of visceromotor reactions elicited by self-referential information [21,22], while the PMC has been implicated in the monitoring of the external and internal environment and in self-related mental representations during spontaneous cognition [13,23,24].

Although DMN dysfunction has emerged as a consistent biological correlate of multiple neuropsychiatric disorders [11,25–27], the focus of this paper is on the role of the DMN in

psychiatric disorders. Specifically, better understanding of the intra-network functional connectivity (i.e., cohesiveness) of the DMN may shed light on the pathophysiology of psychiatric disorders and reveal targets for improving brain network synchrony with therapeutic potential. A number of key studies have recently synthesized the available evidence on DMN cohesiveness in the major psychiatric disorders. A review of the relevant literature in schizophrenia not only highlighted significant interstudy variation, but also identified increased functional connectivity between the ventral MPFC and other DMN regions as the most common finding [28]; these results were considered relevant to the self-referential nature of psychotic symptoms and the poor insight that are common features of this disorder [28]. In major depressive disorder (MDD), a meta-analysis of 25 studies provided evidence of increased functional connectivity between the MPFC and medial temporal DMN regions centered on the hippocampus, which is thought to underpin affective self-referential cognitions that are typical of MDD [29]. This regional pattern of hyperconnectivity may be nested within a more widespread reduction in DMN cohesiveness as indicated by a large-scale study involving rsfMRI data from 1,300 depressed patients and 1,128 healthy individuals [30]. In obsessive–compulsive disorder (OCD), meta-analysis of 18 studies identified the ventral MPFC and the ACC as the two DMN regions with abnormal functional connectivity with the rest of the network regions [31]; this pattern of dysconnectivity has been linked to patients' difficulties in switching away from self-generated obsessive thoughts and compulsive actions. In post-traumatic stress disorder (PTSD), a meta-analysis of 14 studies showed decreased connectivity within the DMN of the PCC, posterior hippocampus, and ventral MPFC [32], which could be associated with patients' preoccupation with autobiographical information. On the other hand, a meta-analysis of 20 studies on patients with anxiety disorders [33] and a review of 23 studies in bipolar disorder (BD) [34] did not produce evidence for alternations in the intra-network functional connectivity of the DMN. Finally, a meta-analysis of 242 rsfMRI studies covering schizophrenia, MDD, BD, OCD, PTSD, anxiety disorders, and childhood neurodevelopmental disorders identified hypoconnectivity of the MPFC as a common transdiagnostic feature of intra-network DMN dysconnectivity [26].

The aim of this study was to examine the intra-network connectivity of the DMN specifically in adults diagnosed with schizophrenia, mood or anxiety disorders. The focus on schizophrenia, mood and anxiety disorders was predicated on their overlapping clinical features, frequent serial or concurrent comorbidity [35], and highly correlated profiles of task-related abnormalities in brain functional activation [36,37]. Accordingly, we capitalized on powerful meta-analytic tools provided by activation likelihood estimation (ALE) [38–41] to analyze data from whole-brain resting-state connectivity studies published during the last 15 years that examined the functional cohesiveness of the DMN in these disorders. Based on the available evidence, our working hypotheses were that (a) alterations in DMN cohesiveness in adults across the major psychiatric disorders would implicate the major hubs of the network centered in the anteriomedial cortex and PMC and (b) our analyses would uncover novel information about disease-specific dysconnectivity in the regional pattern of the DMN.

Method

Literature search and article eligibility

We applied the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria (http://www.prisma-statement.org/)

(Figure S1) to identify rsfMRI whole-brain studies published between January 1, 2005 and January 31, 2019 that reported significant differences in DMN intra-network connectivity between healthy adults and adult patients diagnosed with schizophrenia, MDD, BD, anxiety disorders, OCD, or PTSD (in the range 18–65 years old). In addition, we required that (a) in each study the spatial composition of the DMN was defined according to Raichle et al. [3] and Buckner et al. [11]; (b) the DMN was extracted by independent component analysis (ICA) or by using a DMN region as a seed; (c) the temporal correlations between the time-series of distinct DMN brain regions were computed in a time-locked fashion over the entire resting-state scan thus yielding static, nonshifted functional connectivity measures; and (d) studies used a whole-brain analysis approach. Studies using other functional measures such as dynamic functional connectivity, amplitude of low-frequency fluctuation, regional homogeneity, graph-theory, or effective connectivity were not included (further details on search strategy and article eligibility in eMethods).

Coding and database construction

From each selected study, we extracted coordinates of significant case–control differences in the functional connectivity among DMN regions as we were interested in DMN functional cohesiveness. When necessary, the coordinates of the primary studies were converted from the Montreal Neurological Institute space to Talairach space using the icbm_other2tal transformation. These coordinates were coded by clinical diagnosis and by the direction of change; hyperconnectivity was defined as increased positive functional connectivity in the patient group relative to the healthy control group, and hypoconnectivity was defined as decreased positive functional connectivity in the patient group relative to the healthy control group. Additionally, coordinates of case–control differences were coded according to the strength of the magnetic field of the scanner, the analytical method used to compute interregional correlations (ICA or seed-based analyses), and according to whether participants were instructed to keep their eyes open or closed during data acquisition. Separately for patient and control groups, we coded sample size, age, and sex (percentage male). In patients only, (a) medication status in each study was coded as the percentage of patients' sample receiving any psychotropic medication and (b) ratings of psychopathology from the different clinical instruments used in the primary studies were coded as "minimal," "mild," "moderate," and "severe" to enable analyses across clinical populations. Further details of the database construction are provided in the Supplementary eMethods.

Activation likelihood estimation

We used ALE [38–41] implemented in MATLAB, to test whether the whole-brain coordinates of case–control differences across studies converged into discrete clusters with a nonrandom spatial distribution. Per best practice standards [38–41], clusters of aberrant connectivity were identified using a cluster-level familywise-error-corrected threshold of $p < 0.05$ (cluster-forming threshold at voxel-level $p < 0.001$). Subsequently, for each cluster of significant DMN dysconnectivity, we extracted the per-voxel probability of case–control differences from the modeled functional connectivity maps. We then calculated the contribution of age, sex, symptomatic severity, acquisition (eyes closed/open), analyses parameters (ICA/seed-based), and location of the seed (Pcu/PCC, ACC/MPFC, lateral parietal gyrus, lateral temporal gyrus, and medial temporal

Table 1. Samples included in the database.

		Patients				Healthy individuals		
Diagnostic coding	Studies	Sample (N)	Age	Male sex (%)	Medicated (%)	Sample (N)	Age	Male sex (%)
Schizophrenia	31	1,486	32.54 (7.03)	65 (14)	72 (40)	1,814	31.94 (6.47)	58 (14)
Major depressive disorder	22	779	33.30 (8.68)	36 (10)	23 (38)	688	32.73 (8.76)	41 (10)
Bipolar disorder	4	191	33.04 (7.41)	47 (9)	49 (49)	202	34.93 (6.35)	47 (9)
Obsessive compulsive disorder	5	121	27.40 (2.64)	55 (10)	16 (24)	116	26.67 (3.19)	49 (12)
Post-traumatic stress disorder	7	192	35.04 (7.29)	65 (32)	11 (17)	163	33.59 (8.11)	69 (27)
Social anxiety disorder	1	20	22.90 (3.99)	70 (0)	0 (0)	19	21.89 (3.77)	74 (0)

Values age, percentage (%) of male, and percentage (%) of medicated are shown as mean (standard deviation); age in years.

cortex) using nonparametric Kruskal–Wallis tests and Spearman correlations as appropriate.

To identify clusters of transdiagnostic changes, we performed an ALE analysis on the pooled coordinates of aberrant DMN intra-network connectivity, regardless of the direction of change, across all diagnoses. This global analysis on transdiagnostic aberrant brain connectivity has the advantage that it provides an optimal summary of neuroimaging findings across all disorders [42]. Additional diagnosis-specific analyses were conducted (a) using the coordinates of case–control differences in DMN connectivity from studies that included only unmedicated patients and (b) using the coordinates of case–control differences in DMN hypo- and hyperconnectivity in each diagnostic category separately.

Ancillary analyses

In order to ensure that the disorder contribution to the transdiagnostic clusters was not driven by the overrepresentation of MDD and schizophrenia in literature (see Table 1 and Table S1), we further applied a normalization procedure to the % contribution extracted for the disorders. Specifically, a normalization score was calculated for each disorder by dividing the % contribution of the disorder to the transdiagnostic cluster with the percentage of included studies related to this disorder. Values higher than 1 indicate an overrepresentation of this disorder.

Results

Studies and coordinates

In total, 70 articles were selected, comprising observations from 2,789 patients and 3,002 healthy individuals (Table 1). Full citations and details of the selected articles are provided in Table S1. There were no case–control differences in age ($p = 0.05$) or sex ($p = 0.65$). However, there was a significant effect of diagnosis ($\chi^2 = 17.8$; $p = 1.4 \times 10^{-4}$). Diagnosis-specific ALE analyses were only performed for schizophrenia (number of studies: 31) and MDD (number of studies: 22); the data for all other disorders were insufficient as the minimum number of studies for robust results is currently considered to be 17 [40].

Activation likelihood estimation

DMN regions showing aberrant connectivity across all diagnoses
Coordinates of aberrant connectivity within the DMN clustered in the left perigenual medial prefrontal cortex (pgMPFC) (peak coordinates: $x = -2$, $y = 56$, and $z = -2$; 295 voxels) and in the PCu (peak coordinates: $x = 0$, $y = -58$, $z = 32$; 254 voxels) (Figure 1). Coordinates from studies on schizophrenia contributed the most in both regions (pgMPFC: 42%, PCu: 42%), followed by MDD (pgMPFC: 20%, PCu: 34%). The other disorders showed limited contribution to either cluster (<20%). The contribution of coordinates reflecting hypo- or hyper-connectivity was relatively similar for each cluster (pgMPFC: 53 vs. 47%, PCu: 67 vs. 33%). No significant effects were found for the moderator variables examined: age, sex, symptom severity, acquisition, and analyses parameters (all uncorrected $p > 0.05$).

Importantly, the relative high contribution of schizophrenia and MDD to these two clusters was not related to the overrepresentation of the studies on MDD and schizophrenia included in the analyses. The normalization scores of the % contribution for both disorders and clusters ranged between 0.65 and 1.05.

When we restricted the ALE analysis to coordinates from studies from patients who were unmedicated at the time of the scanning (schizophrenia: $n = 7$; MDD: $n = 15$; BD: $n = 3$; OCD: $n = 3$; PTSD: $n = 4$; social anxiety disorder: $n = 1$), we identified three clusters located in the pgMPFC ($x = 0$, $y = 60$, $z = -4$, $k = 182$ voxels), the dmPFC ($x = -12$, $y = 54$, 28, $k = 122$ voxels), and the angular gyrus ($x = 42$, $y = -64$, $z = 44$, $k = 93$ voxels) (Figure S2). The pgMPFC cluster included mostly contribution from PTSD (47%), followed by schizophrenia (31%) that mostly reflected hypoconnectivity (63%). The dmPFC cluster included mainly contributions from MDD (47%) followed by schizophrenia (30%) reflecting hyperconnectivity (99.6%). The cluster in the right angular gyrus included mainly contributions from studies on MDD (77%) with equal contribution of hypo- and hyperconnectivity (55 vs. 45%). No significant moderator effects were found for age, sex, symptom severity, acquisition, and analyses parameters (all uncorrected $p > 0.05$).

#### DMN regions showing aberrant connectivity in schizophrenia
Results emerging from the schizophrenia group alone reinforced the role of PCu in schizophrenia where hypoconnectivity was further confirmed in a cluster which overlapped with the corresponding cluster in the transdiagnostic analysis (peak coordinates: $x = -2$, $y = -56$, $z = 32$; 79 voxels) (Figure 2). No significant moderator effects were found for age, sex, symptom severity, acquisition, and analyses parameters (all uncorrected $p > 0.05$).

DMN regions showing aberrant connectivity in MDD
Within the MDD group, an additional cluster of hyperconnectivity emerged in the left dmPFC (peak coordinates: $x = -8$, $y = 56$, $z = 30$; 99 voxels) (Figure 2). No significant moderator effects were found for age, sex, symptom severity, acquisition, and analyses parameters (all uncorrected $p > 0.05$).
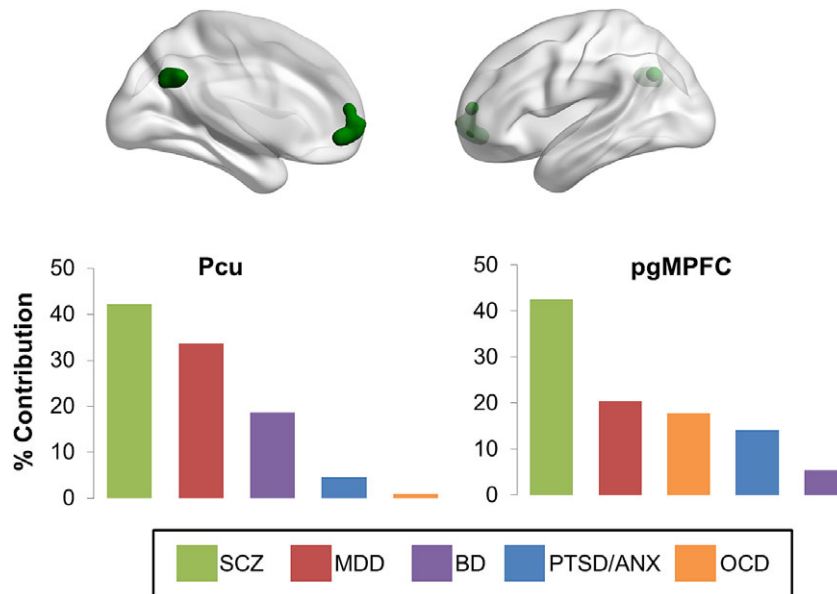
Figure 1. Transdiagnostic clusters of aberrant connectivity in the default mode network. Abbreviations: ANX, social anxiety disorder; BD, bipolar disorder; MDD, major depressive disorder; OCD, obsessive compulsive disorder; Pcu, precuneus; pgMPFC, perigenual medial prefrontal cortex; PTSD, post-traumatic stress disorder; SCZ, schizophrenia.
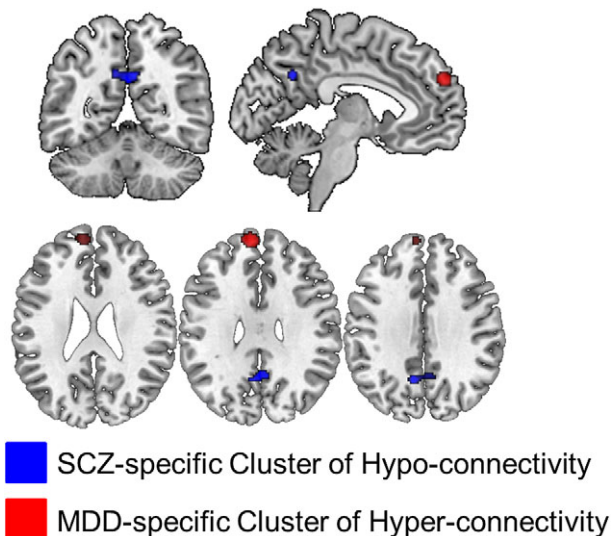
Figure 2. Disease-specific clusters of aberrant connectivity in the default mode network. Abbreviations: MDD, major depressive disorder; SCZ, schizophrenia.

Discussion

We conducted a large-scale meta-analysis on the intra-network DMN functional connectivity comprising data from 70 rsfMRI studies derived from 2,789 patients with schizophrenia, mood and anxiety disorders and 3,002 healthy controls. We specifically focused on the DMN because this network has been shown to be the most reliable network among the major resting-state networks [5–8]. Case–control difference in this network functional connectivity may be therefore less sensitive to the high variability in acquisition and analysis protocols across studies [43]. In accordance with our hypothesis, the results implicated the major hubs of the DMN located in the anteromedial cortex and PMC and suggest that abnormalities in self-referential mental activity are common across these major psychiatric disorders. The posteromedial cluster corresponded to the PCu and showed evidence of dysconnectivity within the DMN across all diagnoses, as well as specific hypoconnectivity for schizophrenia. The pattern observed in the anteromedial cortex was more complex; the pgMPFC appeared to show abnormal intra-network connectivity across diagnoses while the dmPFC showed hyperconnectivity which was specific to MDD. The results of this study highlight the importance of the anteromedial cortex and of the PMC, for psychiatric disorders, and reinforce their known function as hub regions of the DMN [11,13,15,44,45] and the brain more generally [46–48].

It is well known that MPFC is functionally diverse [48–51]. In describing the MPFC subregions implicated here, we follow the functional parcellation proposed by de la Vega and colleagues [49], which largely overlaps with the multimodal parcellation put forward by Glasser et al. [51]. De la Vega et al. [52] mapped mental operations to MPFC subregions following functional parcellation based on patterns of connectivity derived from a meta-analysis of approximately 10,000 studies available in the Neurosynth neuroimaging database. Their findings confirmed prior reports linking the anterior MPFC to affective and social processes and value-based decision-making, but the degree of engagement by these processes differed in MPFC subregions. Social cognition (comprising social perception, self-referential thought, and mentalizing) was maximally associated with the dmPFC, followed by the pgMPFC and then the ventromedial prefrontal cortex.

The PMC has been associated with multiple mental processes [13,23,24]. In addressing the question of the relative functional specificity of the PCu, we draw on the work of Bzdok et al. [53] who capitalized on the large functional imaging database provided by the BrainMap platform to define functional profile of the PCu. They found that the PCu, as well as most PMC regions, was significantly associated with mental operations relating to social cognition, theory of mind, and episodic memory (including autobiographic memory). Notably, mental operations relating to cognitive control, including attentional engagement, inhibition, reasoning, and orienting responses, were distinctly associated with the PCu [53]. This finding confirms prior observations that

attenuation of PCu activity during the transition from rest to task enables the engagement of sustained mechanism related to attention and working memory that are required for successful task performance [1].

The dysconnectivity profiles identified are likely to influence the functional integration of the PCu and MPFC subregions with networks outside the DMN as predicted by their high level of functional and anatomical connectivity across the brain [15,44,54]. In the context, DMN cohesiveness, the preferential functional profiles of the regions identified in the current meta-analysis points to disrupted integration between affective processing/value-based decision making, social cognition, and cognitive control. The differential regional dysconnectivity observed goes a long way toward reconciling conflicting results from prior studies particularly those on schizophrenia [28] and MDD [29,30], which also contributed the majority of the data analyzed here. Of note, the analyses conducted separately in each disorder also highlighted the importance of the dmPFC hyperconnectivity for MDD. This region is considered a nexus of clinical significance for patients with MDD [55], especially those with elevated levels of rumination [56]. Relatedly, increased dMPFC connectivity with other prefrontal regions has been shown to be associated with higher levels of negative self-referential cognition [57] while increased dMPFC connectivity with the PCC post-electroconvulsive therapy may be conducive to improved clinical response [58].

Abnormalities in affect [59], valuation [60], self-referential [27,61], and social cognition [62–64] and cognitive control [65,66] represent domain-general dimensions that have been consistently implicated in all the disorders considered here. We acknowledge that psychiatric disorders also show marked variations in their clinical presentation both between diagnoses and between individuals with the same diagnosis. The current results suggest that mapping DMN regional dysconnectivity is also domain-general and likely to underpin variable within-domain deficits in different individuals and diagnoses. This issue should be explored further in large single samples studies where both clinical, cognitive and connectivity measures can be examined simultaneously.

This study has several strengths and limitations. The number of articles selected in this meta-analysis was lower than that in prior meta-analyses on individual disorders [29–34] because we considered only rsfMRI studies in adults and among those only studies focusing on the intra-network cohesiveness of the DMN. The restriction on adult individuals was predicated by age-related impact on functional connectivity that could have biased results [67,68]. We included studies that used both ICA and seed-based analyses to compute connectivity and found that the results were robust to this methodological variation. The concern with using seed-based analyses only is that the interstudy variability in the exact localization of the seed may influence the pattern of connectivity; however, there is evidence that this is not the case [32]. The number of studies in BD, PTSD, OCD, and anxiety disorders describing significant case–control differences in the DMN was very small, and hence we were unable to undertake diagnosis-specific analyses for these disorders. This is a general limitation of the ALE method, which does not account for negative results. Furthermore, the use of different acquisition protocols and statistical thresholds in the included studies could influence measurement reliability [43]. In this regard, any meta-analysis is prone to publication bias, as we cannot control for statistical methodologies used in the original studies for thresholding the results. However,

this is an issue that is out of the scope of this study. Further effort to optimize analytic strategies for reliability should be done across clinical studies [43]. Nevertheless, we found that the transdiagnostic results were not influenced by the larger number of studies in schizophrenia and MDD and were in line with previous transdiagnostic studies [26,69]. The cross-sectional nature of the studies included does not allow us to comment on the evolution of these patterns of connectivity and their association with disease stage. We addressed the issue of medication by undertaking a sub-analysis on coordinates derived from studies with unmedicated patients. The majority of these studies involved patients with MDD, and the results obtained appear more pertinent to this disorder. Our findings suggest that medication may have an effect on DMN connectivity that may be most consistently observed in the angular gyrus which is in line with previous reports on the "normalizing" effect of antidepressant medication on hyperconnectivity of this region [70]. It is also in line with the study by Schilbach et al. [69] that described that medicated patients with MDD and SCZ showed hypoconnectivity in the lateral parietal cortex of the DMN.

Overall, this meta-analysis identified regional changes in DMN cohesiveness in the anterior and posterior hubs of the DMN as shared and specific brain phenotypes of psychiatric disorders. These brain phenotypes have the potential to serve as targets for interventions aiming to improve the functional integration of the DMN across diverse psychiatric populations. The clusters found in this meta-analysis are freely available (see Supplementary Material) and can then be used as a priori regions of interest for future studies.

Conflict of Interest. The authors declare none.

Authorship Contributions. G.E.D., D.J., and S.F. designed the study and were involved in the conduct of the study. G.E.D., R.H., and M.O.B. analyzed the data. G.E.D., D.J., J.R.A.-H., and S.F. wrote the manuscript. All authors interpreted data and contributed to writing the final manuscript.

Data Availability Statement. Default mode network clusters of dysconnectivity resulting from the meta-analyses are freely available for download (see Supplementary Material).

Supplementary Materials. To view supplementary material for this article, please visit http://dx.doi.org/10.1192/j.eurpsy.2020.57.

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