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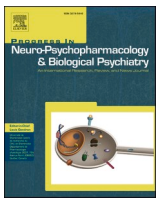

Label-based meta-analysis of functional brain dysconnectivity across mood and psychotic disorders

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ABSTRACT

Background: Resting-state functional magnetic resonance imaging (rsfMRI) studies have revealed patterns of functional brain dysconnectivity in psychiatric disorders such as major depression disorder (MDD), bipolar disorder (BD) and schizophrenia (SZ). Although these disorders have been mostly studied in isolation, there is mounting evidence of shared neurobiological alterations across them.

Methods: To uncover the nature of the relatedness between these psychiatric disorders, we conducted an innovative meta-analysis of dysconnectivity findings reported separately in MDD, BD and SZ. Rather than relying on a classical voxel level coordinate-based approach, our procedure extracted relevant neuroanatomical labels from text data and examined findings at the whole brain network level. Data were drawn from 428 rsfMRI studies investigating MDD (158 studies, 7429 patients/7414 controls), BD (81 studies, 3330 patients/4096 patients) and/or SZ (223 studies, 11,168 patients/11,754 controls). Permutation testing revealed commonalities and differences in hypoconnectivity and hyperconnectivity patterns across disorders.

Results: Hypoconnectivity and hyperconnectivity patterns of higher-order cognitive (default-mode, fronto-parietal, cingulo-opercular) networks were similarly observed across the three disorders. By contrast, dysconnectivity of lower-order (somatomotor, visual, auditory) networks in some cases differed between disorders, notably dissociating SZ from BD and MDD.

Conclusions: Findings suggest that functional brain dysconnectivity of higher-order cognitive networks is largely transdiagnostic in nature while that of lower-order networks may best discriminate between mood and psychotic disorders, thus emphasizing the relevance of motor and sensory networks to psychiatric neuroscience.

1. Introduction

The advent of functional magnetic resonance imaging (fMRI) three decades ago has greatly facilitated the investigation of neurobiological alterations in major psychiatric disorders such as major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SZ) (Etkin, 2019; Horien et al., 2021; Linden, 2012). The primary focus of psychiatric fMRI was the localization of segregated brain regions with abnormal activation during performance of various cognitive tasks (Sprooten et al., 2017). A major development has then been the characterization of aberrant functional brain integration in mental disorders, which are now increasingly conceptualized as brain network disorders (Buckholtz and Meyer-Lindenberg, 2012; Fornito et al., 2017; Menon, 2011; Williams, 2016). This endeavor has been greatly promoted by relying on resting-state fMRI, with spontaneous slow fluctuations in brain activity defining large-scale networks of brain areas with correlated activity (Bijsterbosch et al., 2017). Such intrinsic functional brain networks recapitulate with good correspondence the repertoire of brain regions co-activated during various behaviors (Smith et al., 2009). Current models of functional brain dysconnectivity in mental illness most

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consistently highlight abnormalities within and between three higher-order functional brain networks – noting their naming varies across the literature (Uddin et al., 2019): the default-mode (medial prefrontal cortex, posterior cingulate cortex, posterior inferior parietal lobule), fronto-parietal (middle frontal gyrus, anterior inferior parietal lobule) and cingulo-opercular (anterior insula and anterior midcingulate cortex) networks (Brandl et al., 2019; Buckholtz and Meyer-Lindenberg, 2012; Kaiser et al., 2015; Menon, 2011; Sha et al., 2019; Williams, 2016).

As is the case for task-based activation studies, most resting-state connectivity research in mental illness has relied on case-control designs looking at psychiatric disorders in isolation. Consequently, findings from individual studies may attribute undue specificity of brain dysfunction patterns to one disorder or another. Indeed, there is growing acknowledgment that clinical (Kotov et al., 2021), neurobiological (Vanes and Dolan, 2021) and genetic (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013, 2019) boundaries between psychiatric disorders are blurrier than postulated by traditional classifications of mental illness such as the DSM-5. For instance, it is now clear that there is a greater continuum than once thought between mood and psychotic disorders, encompassing MDD, BD and SZ (Chang et al., 2021; Cohen et al., 2021; Pearlson, 2015; Pelin et al., 2021; Ravichandran et al., 2021). Transdiagnostic research is thus needed to uncover the nature of the relatedness between psychiatric disorders, explaining their high comorbidity and facilitating the discovery of improved treatments (Buckholtz and Meyer-Lindenberg, 2012; Marshall, 2020; Mitelman, 2019; Vanes and Dolan, 2021). From a dimensional perspective, a common psychopathological factor shared among disorders has been associated with functional brain dysconnectivity patterns that transcend psychiatric diagnoses (Barber et al., 2019; Elliott et al., 2018; Kebets et al., 2019; Lees et al., 2021; Sato et al., 2016). Alternatively, direct comparative analysis of multiple diagnostic categories has allowed to evidence both commonalities and specificities in functional brain connectivity alterations (Baker et al., 2019; Huang et al., 2020; Li et al., 2021; Ma et al., 2020; Spronk et al., 2021; Xia et al., 2019; Yange et al., 2018). However, while findings that emerge from this burgeoning field of research are promising, original transdiagnostic studies are still scarce to date. Hence, a meta-analytic approach pooling and contrasting studies that focused on individual disorders can importantly contribute transdiagnostic insights.

To date, transdiagnostic meta-analyses of both task-based (Janiri et al., 2020; McTeague et al., 2016, 2017, 2020; Sprooten et al., 2017) and resting-state (Doucet et al., 2020; Sha et al., 2018, 2019) fMRI findings in neuropsychiatric disorders have mostly relied on coordinate-based approaches (Costafreda, 2009; Radua and Mataix-Cols, 2012; Samartsidis et al., 2017). When applied to case-control studies, methods such as activation likelihood estimation (ALE, Eickhoff et al., 2012), multilevel kernel density analysis (MKDA, Wager et al., 2007) or signed differential mapping (SDM, Radua et al., 2012) quantitatively assess the spatial convergence of results from primary studies based on stereotactic coordinates of peak statistical differences between patients and controls. While coordinate-based meta-analysis has proven successful in unravelling consistent patterns across prior findings from activation studies, it is not best suited for synthesizing connectivity results. First, stereotactic coordinates are almost universally reported in activation studies (Carp, 2012) but much less so in the connectivity literature, among other reasons because analyses are often conducted at spatial resolutions other than the voxel level. Second, the prerequisite of a similar search coverage across studies (Müller et al., 2018) is met in most activation (most commonly the whole brain) but only few connectivity studies, in which region-of-interest analyses have long been the rule rather than the exception. Consequently, meta-analyses have often been restricted to including only studies with seeds falling within a few seed networks of interest (Brandl et al., 2019; Dong et al., 2018; Kaiser et al., 2015; O'Neill et al., 2019; Sha et al., 2019), typically focussing on large, higher-order networks such as the default-mode, fronto-parietal, cingulo-opercular networks, and thereby ignoring less commonly explored networks (e.g., visual and somatomotor lower-order networks). To address these limitations, we conducted an innovative label-based meta-analysis (Costafreda, 2009; Laird et al., 2005; Phan et al., 2002; Radua and Mataix-Cols, 2012) aimed at revealing commonalities and specificities in hypoconnectivity and hyperconnectivity patterns across MDD, BD and SZ. Our meta-analytical approach first avoids excluding studies that did not report coordinates by extracting findings from prior studies based on text data. In addition, it unravels consistent dysconnectivity patterns across both lower- and higher-order distributed networks covering the whole brain while controlling for unequal search coverage across studies.

2. Methods and materials

2.1. Study selection

A literature search was conducted in the PubMed database up to October12, 2021, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org) (see flowchart in Supplementary Fig. S1). The search terms were: ("depression" OR "depressive" OR "bipolar" OR "schizophrenia" OR "psychosis") AND ("functional magnetic resonance imaging" OR "fMRI") AND ("rest" OR "resting") AND "connectivity". Original studies using resting-state functional magnetic resonance imaging to characterize functional brain dysconnectivity in psychiatric patients with an explicit diagnosis of major depressive disorder (MDD), bipolar disorder (BD) or schizophrenia (SZ) were eligible for inclusion. Noteworthy, studies were included regardless of whether stereotactic coordinates reflecting the peak locations of significant group differences were reported. Exclusion criteria were as follows: (1) not in English; (2) no direct comparison of patients with a healthy control group; (3) functional brain connectivity investigated through approaches other than the seed-based voxel-wise (SBVW), seed-to-region (STR), network-based connectome-wide (NBCW), independent component analysis (ICA) with dual regression, voxel-mirrored homotopic connectivity (VMHC), regional homogeneity (ReHo), and amplitude of low-frequency fluctuation (ALFF) methods (Supplementary Table S1); (4) no adequate correction for multiple comparisons; and (5) entirely overlapping sample with identical search coverage reported in another publication.

2.2. Data extraction

2.2.1. Label-based meta-analysis

Our meta-analytical method is based on the systematic and principled extraction of neuroanatomical terms describing which functional brain connections were investigated or were evidenced as significantly impaired in psychiatric patients compared to healthy controls. Text from all paper sections (abstract, introduction, methods, results, discussion, as well as figure legends and tables) was mined by experts in macroneuroanatomy. Our approach dealt with the following confounds: first, there are large variations in search coverage from one paper to another – a minority of papers considers pairwise connectivity for all brain regions, most of them instead focus on a small part of whole-brain connectivity; second, the spatial granularity at which connectivity is explored varies drastically across papers – from voxels to regions to networks; third, there is significant variability in the neuroanatomical nomenclature used in the literature.

We implemented a two-step procedure that first manually transcribed the gathered neuroanatomical information at the original level of description (region, network, whole brain), then translated it with reference to a single common network-level framework. We separately coded connections that were the object of a statistical test (*tested* connections) and those that showed a statistically significant ($p < 0.05$ after correction for multiple comparisons) alteration (*impaired* connections). In the latter case, we further differentiated *hypoconnected* from

hyperconnected connections. We however did not distinguish between enhanced and weakened connectivity patterns, as this distinction is seldom made in the literature. Thus, hypoconnectivity may indicate either larger negative or reduced positive connectivity while hyperconnectivity may refer to either larger positive or reduced negative connectivity.

2.2.2. Two-step extraction

For each paper, we extracted pairs of neuroanatomical terms describing functional brain connections. Because distinct terms may refer to similar brain areas or networks, we first manually transcribed the terms used in original papers with best fits from a limited set of labelling schemes covering the entire spatial granularity range. Brain regions were labelled based on the Automated Anatomical Atlas (AAL, 116 regions, Tzourio-Mazoyer et al., 2002), AAL3 (170 regions, Rolls et al., 2020) or Brodmann atlas (48 regions, WFU PickAtlas software, Maldjian et al., 2003); distributed brain networks were labelled based on the Cole-Anticevic Brain Network Partition (CAB-NP, 12 networks, Ji et al., 2019); and larger brain components such as lobes or the entire hemisphere were defined using the TD atlas (WFU PickAtlas software, Maldjian et al., 2003). The whole gray matter was defined by a mask including all regions from the AAL3 atlas (Rolls et al., 2020). For each type of contrast (MDD vs. HC, BD vs. HC, SZ vs. HC) found in a study and each type of connection (tested, hypoconnected, hyperconnected), comprehensive transcription of the relevant neuroanatomical information was accomplished with as few pairs of labels as possible.

The second step involved translating, in an automated manner, the labels obtained at various spatial resolutions into a single common large-scale network space, the 12-network CAB-NP (Ji et al., 2019) (see Supplementary Material for a secondary analysis at the region level). This functional brain atlas covers the whole brain, with many networks spanning the cortex, basal ganglia and cerebellum (Fig. 1). Higher-order cognitive networks (default-mode, frontoparietal, dorsal attentional, cingulo-opercular) are dissociated from lower-order networks (primary and secondary visual, somatomotor, auditory) as well as from language and ventral (orbito-affective, ventral and posterior multimodal) networks. Because the original cortical parcels of the CAB-NP are surface-based, we created a publicly available volumetric version of the atlas for the whole brain. Of note, all networks are not of equal size (Supplementary Table S2), with three higher-order networks (default-mode, frontoparietal and cingulo-opercular networks) together amounting for over 50% of the total atlas volume. Brain regions corresponding to manually extracted labels were automatically assigned to the large-scale network with which they maximally overlapped, and region labels were translated into the network space accordingly. For each study, separately for each type of contrast available (MDD vs. HC, BD vs. HC, SZ vs. HC) and each type of connection (tested, hypoconnected, hyperconnected), we then coded the absence (0) or presence (1) of pairs of network labels defining each of the 12 within-network and 66 between-network connections.

2.2.3. Data extraction reliability

In addition to the main labels extraction for all 428 studies (SG1), separate raters (SP, MD, VP) together independently re-extracted labels for a subset of 100 studies. These latter studies were pseudo-randomly selected to ensure good representativity of the different types of studies (diagnostic group, connectivity method), in proportions similar to those found in the entire set (Fig. 2). The similarity of the main and confirmatory network labels extractions for this subset of studies was computed with Dice similarity coefficients for binary matrices coding for

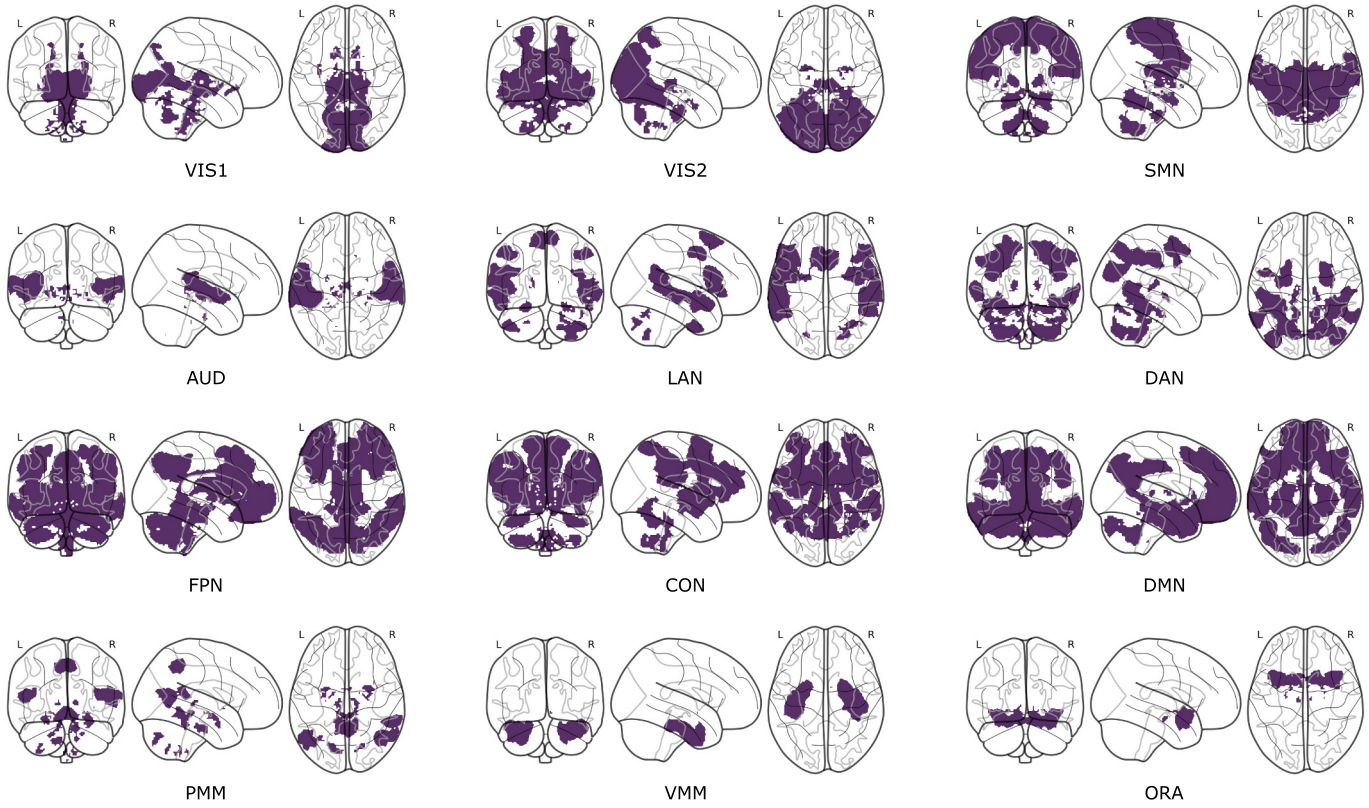

Fig. 1. The Cole-Anticevic Brain Network Partition (CAB-NP) (Ji et al., 2019) was used as a reference space to report meta-analytic findings at the large-scale brain network level. This functional brain parcellation includes 12 cortico-subcortical distributed networks, here displayed on coronal, sagittal and axial views of glass brain representations. VIS1, primary visual network; VIS2, secondary visual network; SMN, sensorimotor network; AUD, auditory network; LAN, language network; DAN, dorsal attentional network; FPN, fronto-parietal network; CON, cingulo-opercular network; DMN, default-mode network; PMN, posterior multimodal network; VMN, ventral multimodal network; ORA, orbito-affective network.

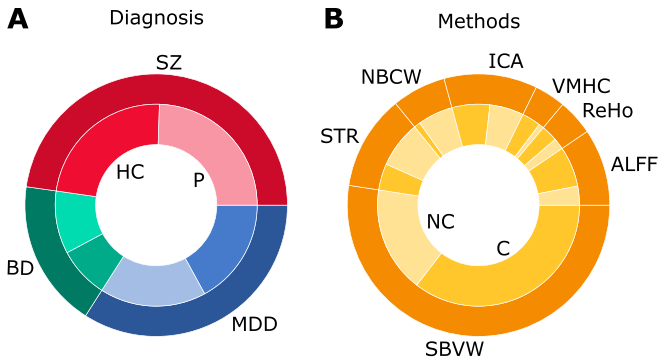

Fig. 2. Proportions of the 428 studies that reported dysconnectivity effects for each psychiatric disorder (left, outer circle) and the respective proportions of patients (lighter color) and controls (darker color) for each diagnosis (left, inner circle). MDD, major depressive disorder; BP, bipolar disorder; SZ, schizophrenia; HC, healthy controls; P, patients. Proportions of the type of methodology used to characterize functional brain connectivity (right, outer circle), and the respective proportions of studies that reported stereotactic coordinates of peak effects (darker color) and did not (lighter color) for each type of methods (right, inner circle). SBVW, seed-based voxel-wise; STR, seed-to-region; NBCW, network-based connectome-wide; ICA, independent component analysis; VMHC, voxel mirrored homotopic connectivity; ReHo, regional homogeneity; ALFF, amplitude of low frequency fluctuations; C, with coordinates; NC, without coordinates. See Supplementary Material for details.

the presence or absence of connection being tested or evidenced as impaired, over all studies and across all brain network connections defined by the CAB-NP. The similarity of labels extractions was quantified separately for the connections being tested and the connections being reported as impaired.

2.3. Statistical analysis

Permutation tests were conducted on one or more of 9 two-way binary tables indicating for each of the 78 connections whether it was tested, hypoconnected, hyperconnected (1) or not (0) in each of the studies looking at MDD, BD or SZ, respectively. Permutation tests (k = 100,000) investigated effects that were directly tested in original studies (hypoconnectivity or hyperconnectivity relative to HC in either of the three disorders) or not directly tested (hypoconnectivity vs. hyperconnectivity in either of the three disorders as well as pairwise comparisons between disorders for either hypoconnectivity or hyperconnectivity). Mathematical formulations are provided in the Supplementary Material.

To test for hypoconnectivity (or hyperconnectivity) of each pair of networks (connection), we used a permutation testing approach whereupon a sample proportion test statistic (computed as a ratio of observed reported effects over baseline of whether the pair of networks in question was tested or not) was used. These ratios had numerators equal to the sum of number of studies that observed a significant level of either hypoconnectivity (or hyperconnectivity) for each pair of networks of interest, and had denominators equal to the number of studies that tested the pair of networks of interest as a baseline. We then sampled from a subset of the permutations applied to the observed outcomes of each study to randomize whether each observed connection effect was hypoconnected (or hyperconnected), separately for each disorder (6 contrasts). By accounting for how often a given pair of networks was tested across studies, our procedure thus controlled for the increased number of discoveries merely explained by the larger size of some networks and/or the bias towards a larger interest in some networks in the literature. To test for differences between hypoconnectivity and hyperconnectivity proportions within each disorder (3 contrasts), we employed a similar permutation testing approach, except with a test statistic equal to the absolute difference between the proportions of studies reporting hypoconnectivity and hyperconnectivity effects. Differences in the proportion of hypoconnectivity (or hyperconnectivity) between pairs of disorders (6 contrasts) were tested in the same way, except with a test statistic equal to the absolute difference between the proportion test statistics of two disorders. While coordinate-based meta-analyses typically allow assigning varying weights to individual studies as a function of their sample sizes (Radua and Mataix-Cols, 2012; Samartsidis et al., 2017), it was deemed preferable not to implement such a weighting in our permutation testing approach (for a detailed rationale, see Supplementary Material).

Permutation testing for 15 contrasts for each of the 78 connections resulted in 1170 tests. To control the false discovery rate (FDR) of the tests, we employed an empirical Bayes approach that directly modelled the distributions of null and alternative *p*-values (Nguyen et al., 2019). This approach accounted for the atypical distributions of discretely supported *p*-values generated via Monte-Carlo methods and for the observed positive and negative correlations among p-values, which violate the assumptions of the classical Benjamini-Hocheberg FDR procedure (Benjamini and Yekutieli, 2001). All results reported at the connection level were significant at $q^{FDR} < 0.1$, this threshold being chosen to best balance the risks of false positives (type I error) and false negatives (type II error), which are respectively problematic for drawing conclusions about transdiagnostic and disorder-specific dysconnectivity patterns.

2.3.1. Data and code availability

All data as well as Python and R scripts necessary to reproduce the findings reported here are available on Github: https://github.com/pnplab/LBMA. The volumetric version of the CAB-NP atlas can be obtained on Figshare: https://figshare.com/articles/dataset/CAB-NP_projected_on_MNI2009a_GM_volumetric_in_NIfTI_format/14200109.

3. Results

3.1. Selected studies

There was some disparity in the extent to which the three disorders were investigated in the literature. Of the 428 studies included in our meta-analysis, 37% of them characterized MDD (7429 patients/7414 controls), 19% examined BD (3330 patients/4096 controls) and 52% investigated SZ (11,168 patients/11,754 controls) (Fig. 2A). Most studies (61%) employed a seed-based approach to characterize functional connectivity of regions of interest with the whole brain, at the voxel level (Fig. 2B). Critically, a large part (40%) of the selected studies did not report stereotactic coordinates (Fig. 2B).

3.2. General network dysconnectivity patterns

At the level of individual studies, 32% of all within- and between-network connections were tested for statistical effects across studies. Twenty-five per cent of those tested connections were reported as significantly impaired, being either hypoconnected or hyperconnected. Similar proportions were observed in MDD, BD and SZ. The distribution of tested and impaired (hypoconnected or hyperconnected) connections across studies was shown to be reproducible when contrasting two independent labels extractions, with Dice similarity coefficients of 0.93 and 0.81 for tested and impaired connections, respectively.

Not all networks, with 12 connections each, were similarly tested (Supplementary Fig. S2). The bias towards testing some network connections more than others took a similar form across disorders (r = 0.92–0.97, all $ps < 0.001$) (Fig. 3A, Supplementary Fig. S3A). Overall, the more a network connection was tested, the more there was evidence for its impairment while controlling for increased testing of some connections. This was observed for both hypoconnectivity ($r = 0.73$, $p < 0.001$) and hyperconnectivity ($r = 0.71$, $p < 0.001$) patterns, similarly in all three disorders (r = 0.61–0.72, all $ps < 0.001$) (Fig. 3B,

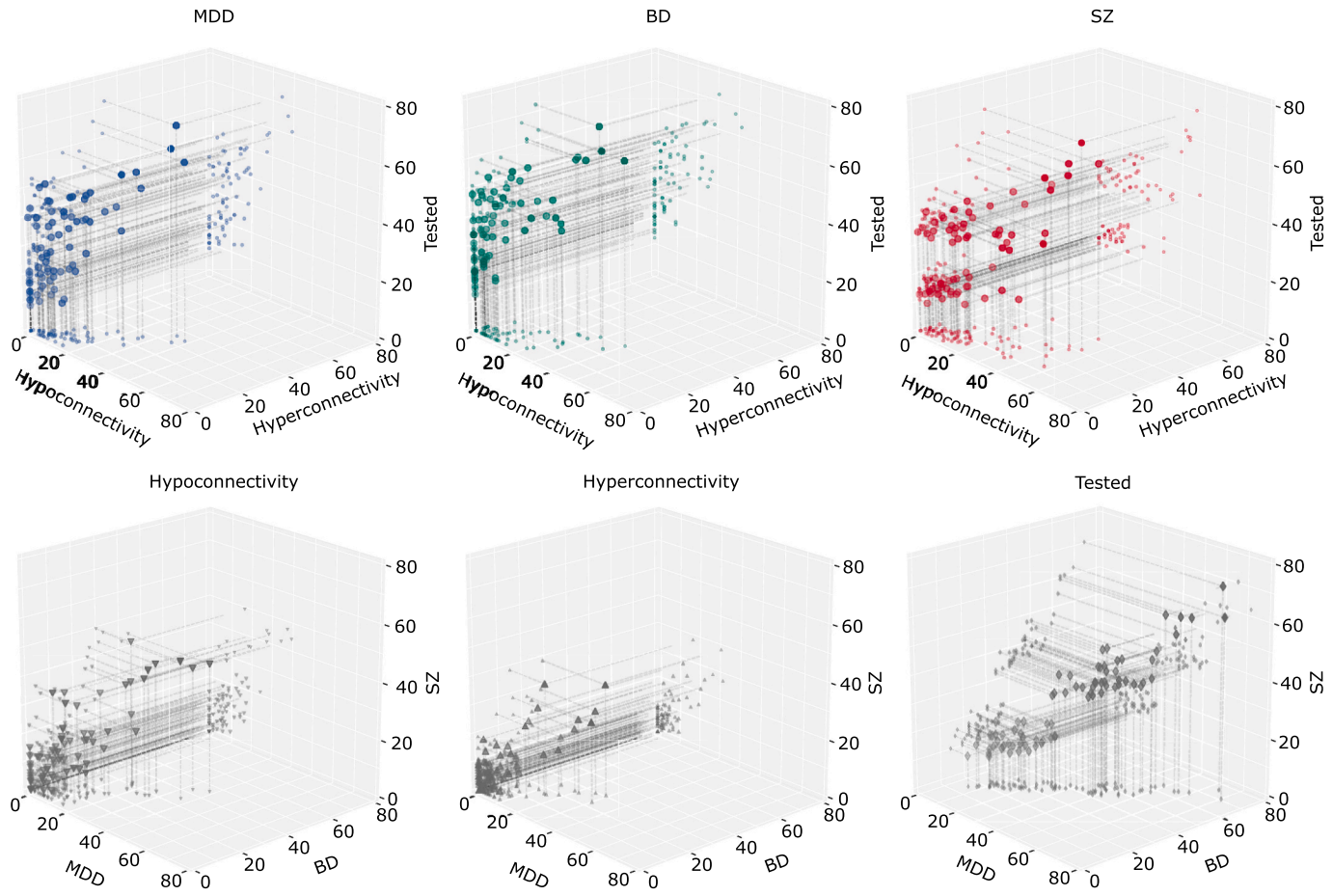

Fig. 3. General network dysconnectivity patterns across psychiatric disorders are depicted in 3D correlations plots. In each psychiatric disorder, there were marked positive correlations between how often the 78 connections between pairs of networks were tested for a statistical effect across studies, how often there was a report of hypoconnectivity among those tested connections, and how often hyperconnectivity was shown (upper row). The proportions (%) of how often the 78 connections were tested or reported as functionally impaired (hypoconnectivity or hyperconnectivity) were strongly positively correlated among psychiatric disorders (lower row). Large symbols are in 3D space while smaller symbols are their projections in 2D spaces. MDD, major depressive disorder; BP, bipolar disorder; SZ, schizophrenia.

Supplementary Fig. S3B). The general trend was that the amount of evidence for hypoconnectivity or hyperconnectivity varied across network connections similarly for MDD, BD and SZ ($r = 0.77$–0.86, all $ps < 0.001$) (Fig. 3B, Supplementary Fig. S3B). Across disorders and connections, there was more evidence for hypoconnectivity than hyperconnectivity overall ($t = 8.10$, $p < 0.001$). Yet, somewhat paradoxically, connections with larger evidence for hypoconnectivity were also those with more demonstration of hyperconnectivity ($r = 0.88$, $p < 0.001$), again similarly in all three disorders ($r = 0.69$–0.88, all $ps < 0.001$) (Fig. 3B, Supplementary Fig. S3B).

3.3. Network dysconnectivity among higher-order networks

All within- and between-network connections among the FPN, CON and DMN showed both significant hypoconnectivity and hyperconnectivity in all three disorders (all significant results reported hereafter survived a $q^{FDR} < 0.1$ threshold). While there was a consistent trend towards more evidence of hypoconnectivity than hyperconnectivity for all those connections across disorders, this effect was only significant for 4 out of 6 connections (excluding DMN-DMN and FPN-DMN) in SZ (Fig. 4). The consistent trend towards more evidence of hypoconnectivity among the FPN, CON and DMN networks in SZ compared to MDD and BD was not significant for any within- or between-network connection. Direct pairwise comparisons between disorders did not reveal any significant difference in the amount of evidence for either hypoconnectivity or hyperconnectivity among these higher-order networks (Fig. 5). It should however be noted that exploratory analysis at the region rather than network level, as reported here, suggests that between-disorders differences may emerge once considering dysconnectivity between small brain regions rather than large-scale brain networks (Supplementary Fig. S4).

3.4. Network dysconnectivity of lower-order networks

Lower-order networks showed impaired connectivity with some of the above higher-order networks, either transdiagnostically or with significant differences between disorders (Fig. 4). Regarding the SMN, SMN-CON hypoconnectivity was observed in all three disorders, yet with SMN-CON hyperconnectivity being also evidenced in SZ. SMN-FPN hypoconnectivity was seen in MDD and BD, while SMN-FPN hyperconnectivity was observed in MDD and SZ. Noteworthy, SMN-FPN hyperconnectivity was more observed in SZ than MDD and BD. SMN-DMN hypoconnectivity was only seen in BD. Regarding VIS2, VIS2-FPN hyperconnectivity was evidenced in both BD and SZ while VIS2-DMN hyperconnectivity was seen in MDD and SZ, yet with VIS2-DMN hypoconnectivity being also observed in MDD. Finally, regarding AUD, AUD-DMN hypoconnectivity was observed in both BD and SZ, with more evidence of AUD-DMN in SZ than MDD. AUD-CON, for which hypoconnectivity was more observed than hyperconnectivity in SZ only, was more hypoconnected in SZ than MDD. AUD-FPN hyperconnectivity

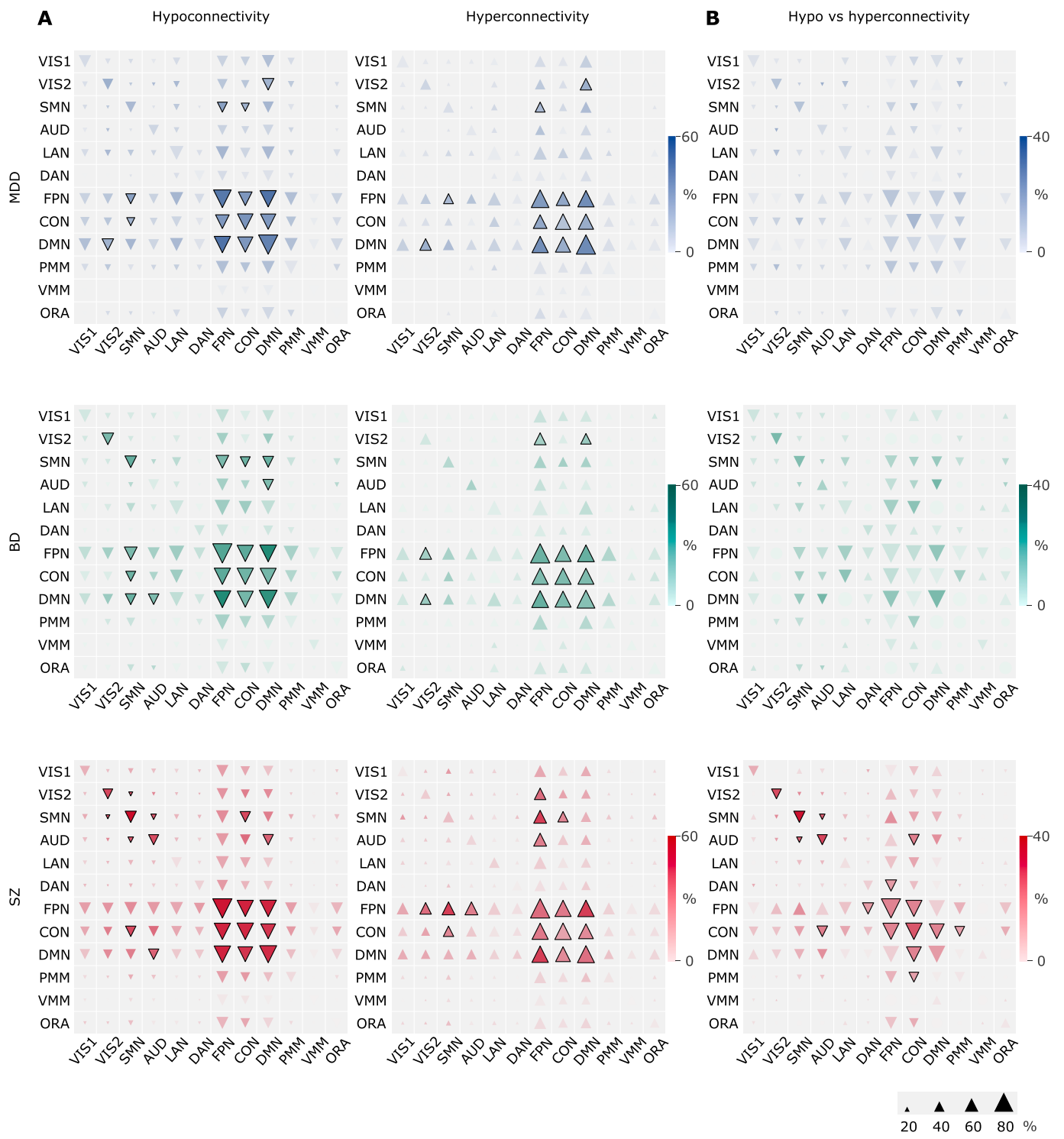

Fig. 4. Network dysconnectivity in each psychiatric disorder (MDD, major depressive disorder, blue; BP, bipolar disorder, green; SZ, schizophrenia, red) is shown separately for hypoconnectivity (down-pointing triangles) and hyperconnectivity (up-pointing triangles) effects. Indication of more evidence for hypoconnectivity than hyperconnectivity, and conversely, is shown separately. The size of triangles reflects the proportion (%) of studies that conducted a statistical test for each of the 78 connections. The colors darkness indicates the proportion of studies (%) that reported a statistical effect, relative to how often a connection was tested. Thick edges around triangles. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

was only seen in SZ.

Among lower-order networks, there was evidence of shared SMN-SMN and VIS2-VIS2 hypoconnectivity in BD and SZ, but not MDD (Fig. 4). SMN-VIS2, SMN-AUD and AUD-AUD hypoconnectivity was only observed in SZ. There was evidence of more hypoconnectivity than hyperconnectivity for SMN-SMN, VIS2-VIS2, AUD-AUD and SMN-AUD in SZ. Pairwise comparisons between disorders indicated that there is more evidence for AUD-AUD hypoconnectivity in SZ compared to both MDD and BD and SMN-SMN hypoconnectivity in SZ compared to MDD (Fig. 5).

Fig. 5. Network dysconnectivity differences between psychiatric disorders (MDD, major depressive disorder, blue; BP, bipolar disorder, green; SZ, schizophrenia, red) is shown separately for greater hypoconnectivity (down-pointing triangles) and greater hyperconnectivity (up-pointing triangles) effects in one disorder than another. The size of triangles reflects the proportion (%) of studies (averaged between disorders) that conducted a statistical test for each of the 78 connections. The colors darkness indicates the between-disorders difference in the proportion of studies (%) that reported a statistical effect, relative to how often a connection was tested (on average in two disorders). Thick edges around triangles represent differences in dysconnectivity effects that were significant at $q^{FDR} < 0.1$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

Meta-analytic findings reveal similar functional brain dysconnectivity within and between the FPN, CON and DMN networks across mood and psychotic disorders, suggesting higher-order network dysconnectivity is mostly transdiagnostic in nature at the large-scale network level. By contrast, dysconnectivity patterns within lower-order networks such as the SMN and AUD networks as well as between these lower-order networks and higher-order networks were shown to differ between disorders, notably differentiating SZ from BD and MDD. Consistent dysconnectivity patterns were not evidenced for other networks such as LAN and ORA networks.

4.1. Higher-order network dysconnectivity

Highly significant evidence for dysconnectivity patterns shared by all three disorders (MDD, BD, SZ) among heteromodal networks implicating the prefrontal cortex (FPN, CON, DMN) reflect their key role in current models of psychopathology (Buckholtz and Meyer-Lindenberg, 2012; Menon, 2011; Williams, 2016). The various cognitive functions supported by these networks, such as executive control and self-referential monitoring (Marek and Dosenbach, 2018; Menon and D'Esposito, 2021; Uddin, 2015; Whitfield-Gabrieli and Ford, 2012), are indeed impaired across mood and psychotic disorders (East-Richard et al., 2020; Green et al., 2019; Rock et al., 2014). Accordingly, both original (Baker et al., 2019; Li et al., 2022; Ma et al., 2020; Xia et al., 2019) and meta-analytical (Doucet et al., 2020; Sha et al., 2018, 2019) transdiagnostic works highlight shared functional brain connectivity abnormalities of the FPN, CON and DMN across a wide range of psychiatric disorders or in relation to a general psychopathology factor (Mitelman, 2019; Vanes and Dolan, 2021).

Both increased and decreased abnormal connectivity was evidenced for each neurocognitive network, although hypoconnectivity was more frequently reported, particularly in SZ. This paradoxical result might not only be explained by inconsistencies in the literature but also by our choice to explore dysconnectivity at the large-scale network rather than region level. Distinct regions that compose a network are likely to be characterized by opposite dysconnectivity patterns. For instance, the DMN has been reported to be hypoconnected to the ventral insula but hyperconnected to the dorsal insula across several psychiatric disorders (Sha et al., 2019). This spatial granularity issue may similarly account for the lack of significant differences in the dysconnectivity of neurocognitive networks between MDD, BD and SZ in this study. Our targeted analysis conducted at the region level and some past studies that

reported findings at the region or voxel level (Baker et al., 2019; Brandl et al., 2019; Dong et al., 2018; Huang et al., 2020; Kaiser et al., 2015) lend support to this hypothesis.

4.2. Lower-order network dysconnectivity

Strong evidence that the functional brain connectivity of unimodal networks (SMN, VIS, AUD) is impaired in both mood and psychotic disorders might seem surprising, given it is seldom the focus of psychiatric brain imaging. The present meta-analytical results nonetheless indicate that connectivity alterations within motor and sensory networks as well as between them and neurocognitive networks are often reported, hence underscoring a lack of emphasis on such findings in the literature. This observation echoes recent calls to better promote research centered on motor and sensory systems in psychiatric neuroscience, as exemplified by the delayed inclusion of a domain dedicated to motor systems (Bernard and Mittal, 2015; Garvey and Cuthbert, 2017) and the suggestion to add a sensory processing domain (Harrison et al., 2019) in the Research Domain Criteria (RDoC) framework (Cuthbert and Insel, 2013). Motor abnormalities that include neurological soft signs, extrapyramidal symptoms (dyskinesia, parkinsonism) and catatonic phenomena, are observed in a wide range of disorders (Northoff et al., 2020; Peralta and Cuesta, 2017). Similarly, aberrant sensory processing and perceptual signaling are encountered in disorders other than SZ (Harrison et al., 2019; Javitt and Freedman, 2015; Javitt and Sweet, 2015). Accordingly, we observed several dysconnectivity patterns of motor (SMN) and sensory (VIS2, AUD) networks being shared by at least two disorders, in line with previous studies that reported transdiagnostic alterations of unimodal networks using fMRI (Elliott et al., 2018; Huang et al., 2020; Kebets et al., 2019; Tu et al., 2021; Xia et al., 2019). A notable result was however that, in some instances, there was more evidence for dysconnectivity of these networks (SMN, AUD) in SZ compared to BD and MDD. Gradients of impairments in connectivity that scale as a function of illness severity along the mood/psychosis cont have been reported before (Ma et al., 2020; Tu et al., 2021; Yange et al., 2018), and may account for more aggravated motor symptoms (Peralta and Cuesta, 2017) and the frequent presence of auditory hallucinations in SZ (Alderson-Day et al., 2015).

4.3. Strengths and limitations

The main strength of the present study lies in the use of text labels rather than stereotactic coordinates as the source of information for our meta-analysis (Costafreda, 2009; Radua and Mataix-Cols, 2012; Samartsidis et al., 2017). By doing so, a comprehensive inclusion of numerous prior studies that did not report coordinates was possible. Moreover, dysconnectivity patterns could be explored for the whole brain rather than focussing on a few selected networks of interest. The use of a whole-brain cortico-subcortical atlas that includes atypical auditory and language networks (Ji et al., 2019) further represents an improvement over previous meta-analyses. Besides, the manual extraction of text labels and subsequent automatic assignment to large-scale networks were shown to be reproducible. A future step will be to apply natural language processing algorithms to fully automatize the extraction of relevant papers and text labels (Jonnalagadda et al., 2015; Marshall et al., 2020), making our label-based meta-analytical approach an even more appealing alternative to traditional (coordinate-based) meta-analyses of brain imaging findings.

The systematic exploration of whole-brain connectivity comes at a cost. Multiple testing over all connections with sufficient statistical power can only be performed for a limited number of brain networks, not dozens or hundreds of local brain regions given the amount of available published studies. As aforementioned, networks such as the DMN or CON merge together distinct brain areas or subnetworks with distinct connectivity profiles and functions (Andrews-Hanna et al., 2010; Uddin, 2015), and are thus likely to be differentially impacted by psychopathology (Brandl et al., 2019; Sha et al., 2019). In addition, we adopted a conservative approach where a brain area corresponding to a text label could only be assigned to a single network, which it maximally overlapped with. The complexity of small regions with multimodal integration zones that in fact belong to multiple networks (e.g., the thalamus; Giraldo-Chica and Woodward, 2017) was thus ignored. For the same reason, the inferior frontal gyrus and amygdala were not respectively assigned to the LAN and ORA in our analysis, as one would have expected (Cavelti et al., 2018; Li et al., 2018). This may account for the lack of significant findings in these networks, despite past evidence of their roles in language disturbances associated with thought disorder and verbal hallucinations in SZ (Cavelti et al., 2018; Du et al., 2021) or emotional dysregulation across mood and psychotic disorders (Ho et al., 2019; Li et al., 2018; Upthegrove et al., 2017). As additional research in the field accumulates, we are hopeful that future label-based meta-analyses will be able to provide finer-grained assessments of functional brain dysconnectivity in psychiatric disorders.

5. Conclusions

Using a novel meta-analytical approach, we explored the relatedness of functional brain dysconnectivity patterns across three major psychiatric disorders. In line with prevailing models of psychopathology, transdiagnostic abnormal connectivity among core higher-order neurocognitive networks was highlighted. More surprisingly, lower-order (motor, visual, auditory) networks were also affected across disorders, however revealing gradients of impairment from mood to psychotic disorders. These findings underscore the role that motor and sensory processes play in the etiology of major psychiatric disorders and thus call for dedicated research on this topic (Garvey and Cuthbert, 2017; Harrison et al., 2019).

Ethical statement

The article does not involve any human subject.

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CRediT authorship contribution statement

Stéphanie Grot: Conceptualization, Investigation, Formal analysis, Writing – original draft. **Salima Smine:** Software, Formal analysis. **Stéphane Potvin:** Investigation, Writing – review & editing. **Maëliss Darcey:** Investigation. **Vilena Pavlov:** Investigation. **Sarah Genon:** Writing – review & editing. **Hien Nguyen:** Methodology, Software, Writing – original draft. **Pierre Orban:** Conceptualization, Formal analysis, Writing – original draft, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2024.110950.

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