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Research Paper

Connectivity model of the anatomic substrates and network abnormalities in major depressive disorder: A coordinate meta-analysis of resting-state functional connectivity

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ABSTRACT

Increasing data suggests major depressive disorder (MDD) involves abnormal functional connectivity within a variety of large-scale brain networks. However, due to the use of unstandardized parcellation schemes, the interactions between these networks and the specific neuroanatomic substrates involved requires further review. We therefore sought to conduct a meta-analysis of functional connectivity changes encountered in MDD using a detailed and standardized parcellation scheme. A literature search for relevant resting-state fMRI studies related to MDD in PubMed was conducted. BrainMap's GingerALE 2.3.6 extracted the relevant fMRI data for creation of an activation likelihood estimation (ALE). A sphere was placed at the MNI coordinate of each ALE cluster and seed origin point, and the Human Connectome Project (HCP) parcellation schema was projected on these spheres. The parcellations most present in the ALE were analyzed based on their associated functional network and/or subcortical area to identify abnormal pairs based on the ALE and seed origin parcellation. Ultimately, 483 subjects across 15 studies were analyzed, wherein areas of decreased or increased functional connectivity compared to healthy controls were identified. Our MDD model most commonly implicated increased default mode network (DMN)-central executive network (CEN) pairs, while decreased paired networks commonly included the DMN with other brain networks. All intra DMN-DMN connections and salience network (SN) pairs showed decreased functional connectivity, while all intra CEN—CEN functional connectivity were increased compared to controls. We hypothesize that our findings of abnormal connectivity between the DMN, CEN, and SN core cognitive networks may demonstrate the inappropriate allocation of cognitive resources and cognitive depletion believed to cause persisting rumination in depression. Despite previous claims, DMN connectivity was found to be generally decreased, and we propose its connectivity direction is dependent on its interacting network partner and the specific parcellations involved. While both of these hypotheses remain speculative and require further validation, our work provides a comprehensive and anatomically precise model to be refined in future studies focusing on the functional connectivity underlying MDD pathophysiology.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric disease that has a 12-month prevalence of above 10% of the population (Hasin et al., 2018) with deep social and societal burden, rendering patients unable to perform daily tasks and reducing productivity (Simon, 2003). MDD diagnosis is based on a constellation of behavioral symptoms according to the Diagnostic and Statistical Manual of Mental Disorders, which are not anatomically based and do not focus on a biological origin. Yet, much of our understanding of MDD relies on previous

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research that separately focuses on *behavioral* symptoms or *biological* abnormalities confined to single, isolated cortical regions. Fortunately, recent advancements in neuroimaging technologies and data-driven approaches, particularly in the field of connectomics, have begun to unify our understanding of the pathophysiology of MDD, suggesting the disturbance of multiple brain networks which are necessary for appropriate neuro-behavioral functions (M.F. Glasser et al., 2016).

It is increasingly clear that many mental illnesses, including depression, have aberrations in functional connectivity as a defining feature of the disease (Helm et al., 2018; Menon, 2011; Zheng et al., 2015). There have been numerous studies that have identified a variety of areas that demonstrate abnormal functional connectivity in MDD in resting-state functional magnetic resonance imaging (rsfMRI) studies, most of which are involved in higher-order networks that are strategically organized to facilitate normal cognitive functioning (Kaiser et al., 2016; Lai and Wu, 2014; Song et al., 2016; Wang et al., 2016; Yan et al., 2019; Zhang et al., 2016). By contextualizing the pathophysiological mechanisms of MDD within a brain connectome framework, we may begin to better understand popular cognitive theories of MDD, such as the dual processing theory of cognitive vulnerability, and the variable outcomes related to MDD treatments (Beevers, 2005; Forgas, 2000). However, while numerous brain networks have been implicated in the pathophysiology of MDD, such as the default mode network (DMN), the central executive network (CEN), and the salience network (SN), few studies have elucidated the dynamic interaction of these neural networks together in depressed patients in great detail (Wang et al., 2016; Zhou et al., 2020). Given that such data can be utilized to better understand and subsequently improve outcomes in treatments for depression, improved information on the depression connectome remains an important endeavor.

Previous research is however challenged in the reproducibility and generalizability of their findings of network abnormalities primarily due to the lack of anatomic specificity and the heterogenous methodology employed (Guo et al., 2013a; Kaiser et al., 2016; Lai and Wu, 2014; Ramasubbu et al., 2014). Recent data suggests that these limitations are particularly important when analyzing regions such as the left dorsolateral prefrontal cortex (DLPFC), which is common site of study and possible target for modulatory treatment in depression. While often treated as a single region in numerous studies, more recent work has demonstrated that the DLPFC can be functionally segregated into many distinct regions, each with distinct connections to different complex brain networks (M.F. Glasser et al., 2016). It has also been shown that a more granular approach using more detailed parcellation schemes may be necessary in targeting this region for optimal clinical response (Moreno-Ortega et al., 2020; Rosen et al., 2021). Together, such differences have prevented our successful creation of an accurate neuroanatomic model of depression and therefore limits our ability to study and treat MDD with reproducible results. We instead propose that the application of a more detailed and standardized anatomic framework, such as the Human Connectome Project Multimodal Parcellation Scheme, to the analysis of previous functional connectivity studies to produce a parcellation-based, connectomic framework would provide a unique opportunity to clarify our current understanding of the pathophysiology of this disease process (Zhou et al., 2020).

Here, we performed a systematic review and coordinate based-meta-analysis of resting state fMRI (rsfMRI) neuroimaging data from medication naïve, first episode MDD patients. Our goal was to identify common anatomical and network abnormalities that may underlie the functional aberrations present in MDD, discuss these findings in light of previous theories on depression (Beevers, 2005; Wang et al., 2016). We hypothesized that those living with MDD would demonstrated decreased functional connectivity within the DMN, as has been previously demonstrated, however wanted to investigate the changes in the interactions of each network compared to controls. We performed our analysis using the anatomically specific Human Connectome Project (HCP) parcellation nomenclature to provide more precise results within a common vernacular that future clinicians and researchers alike can refine and improve upon (Glasser, 2016; Kaiser et al., 2015). In this context, our findings may not only clarify our current understanding of abnormal functioning in MDD, but may also provide clinically actionable anatomic data that clinicians can immediately utilize for novel treatments requiring precise anatomical targeting, such as transcranial magnetic stimulation (TMS) (Fox et al., 2012; Moreno-Ortega et al., 2020).

2. Methods and materials

2.1. Literature search

We searched for relevant fMRI studies related to MDD in PubMed from January 2000 up to December 2018. Only PubMed was used as it provides free and comprehensive access to both Medline articles and beyond, which is sufficient to encompass neuroimaging studies. We used the following search algorithm: ("major depressive disorder" OR "major depression" OR depression) AND (fMRI OR "resting state functional MRI") AND (connectivity OR "functional connectivity"). Records were screened by two of the authors, independently, and full-text articles were reviewed and included in our analysis if they fulfilled the following search criteria: (1) peer-reviewed publication, (2) resting-state fMRI study examining depression, (3) based on whole-brain, voxel-wise imaging, (4) including standardized coordinate-based results in the Talairach or Montreal Neuroimaging Institute (MNI) coordinate space, (5) including at least one healthy human control cohort, (6) subjects were adults with first-time, medication-naïve MDD. Only English language studies were included. Records were excluded if they were performed on pediatric or non-human cohorts, cohorts previously treated for MDD, and on cohorts with psychiatric and non-psychiatric comorbidities. Fifteen papers met criteria for inclusion in this study (Fig. 1) (Buchanan et al., 2014; Guo et al., 2013a, 2013b, 2015a; Guo et al., 2015b; Kaiser et al., 2016; Lai and Wu, 2014; Peng et al., 2015; Ramasubbu et al., 2014; Sheline et al., 2010; Song et al., 2016; Tang et al., 2013; Wu et al., 2016; Yang et al., 2017; Zhu et al., 2018). The details of these studies are summarized in Table 1. Note that in instances where duplicate cohorts from distinct studies were included, these utilized different seed-regions, demonstrating distinct functional connectivity patterns. Similarly, in instances where the same study has been reported twice under both increased connectivity and decreased connectivity compared to controls, these refer to distinct brain regions which were highlighted.

2.2. Activation likelihood generation and identification of relevant cortical regions

In order to generate a summary of regions demonstrating increased or decreased functional connectivity compared to controls in the identified studies, we used BrainMap GingerALE 2.3.6 to create an activation likelihood estimation (ALE) from the MNI coordinates reported in the 15 studies (Eickhoff et al., 2012). All Talairach coordinates identified during literature review were converted to the MNI coordinate space using SPM Conversion in GingerALE. We subsequently performed a single study analysis using cluster-level interference in the MNI coordinate space (cluster level of 0.05, threshold permutations of 1000, uncorrected p-value of 0.001). The ALE coordinate data was displayed on an MNI-normalized template brain suing the Multi-image Analysis GUI (Mango) 4.0.1.

A code in Python was subsequently applied to identify the regions reported by Ginger ALE in the Human Connectome Project nomenclature. This code was developed by the above authors for the purpose of incorporating results from coordinate-based meta-analyses into the Human Connectome Project parcellation scheme, and has previously been used in several studies with great reproducibility. In brief, a sphere, 15 mm in radius, was placed at the MNI coordinate of each ALE cluster.

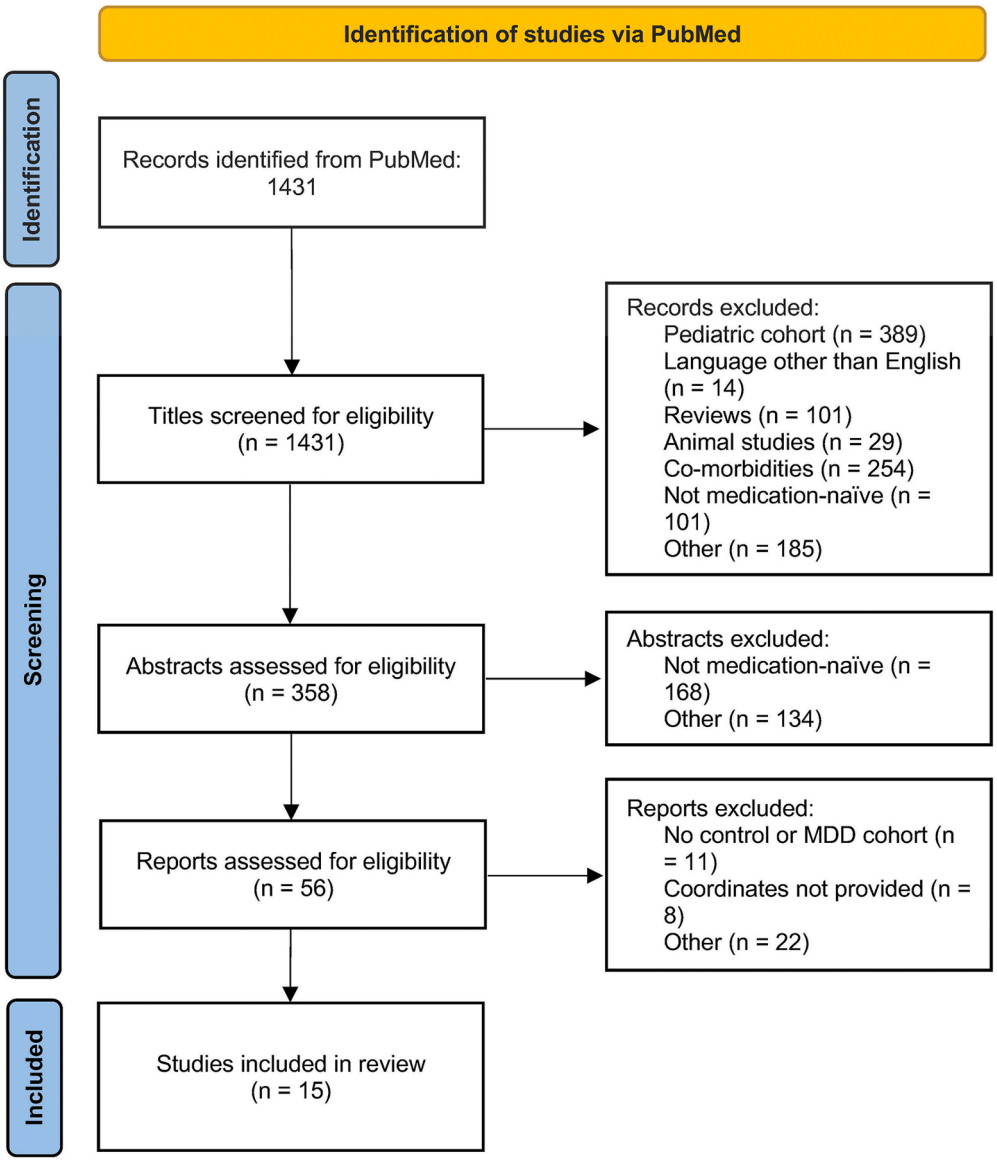

Fig. 1. PRISMA Flow diagram.

The sphere was then projected onto the HCP-MMP parcellation schema, which is also in MNI coordinates. The degree to which any local HCP parcellations fell within the ALE cluster was calculated as a percentage (percentage of the parcellation that falls within the ALE cluster). Any parcellation that had more than 10% of its volume within the ALE cluster was included in further analyses, described below. Pre-constructed ROIs of the HCP parcellations were also overlaid on the ALE and compared visually to ensure true overlap.

2.3. Meta-analysis comparisons

The seed regions reported in each study were used to demonstrate the origin of functional connectivity problems for each MNI point, creating a pair of HCP parcellations for each coordinate used in the meta-analysis. The MNI point of the seed regions were also converted into the HCP parcellation schema by the technique described above. Three studies used voxel-mirrored homotopic connectivity (VMHC) instead of seeding and, as such, were excluded from the pairs, as we could not demonstrate functional connectivity between two regions with the current methodology. From here, comparisons were made between the parcellations identified by the corresponding ALE, and parcellation pairs that were described by the studies. Only parcellation pairs that were seen in their corresponding ALE were used in the results. Each parcellation identified was then matched to its associated large-scale resting-state network or subcortical structure based on previously published network templates utilizing the HCP parcellation scheme (Briggs et al., 2018; O'Neal et al., 2021; Yeo et al., 2011).

3. Results

3.1. ALE regions and their corresponding parcellations

Our final analysis of fifteen fMRI experiments includes a total of 483 medication-naïve, adult patients with first episode MDD. Based on these patients, Fig. 2 demonstrates the ALE clusters of the decreased functional connectivity (Fig. 2a) and increased functional connectivity (Fig. 2b), compared to controls in each study. Following the overlap analysis described earlier, 46 parcellations of the Human Connectome Project parcellation scheme were found to overlap the fMRI data which are listed in Table 2. Comparison overlays between the HCP cortical parcellations and the ALE data for decreased (3A) and increased (3B) connectivity are shown in Fig. 3. As expected, there are a diverse range

Table 1
Studies used to generate the activation likelihood estimate (ALE) of decreased or increased functional connectivity in Major Depressive Disorder.

Increased or Decreased Functional Connectivity MNI Points	Study	Number of Participants	MNI Co-ordinates Used in the Meta-Analyses (x, y, z)		
Decreased	Guo et al., 2013a	24	−3	−15	9
			9	−6	9
			6	66	27
			−18	72	0
			−15	−15	9
			−9	72	15
			27	57	24
			−21	63	27
			21	30	27
			−27	54	24
			6	18	33
	Guo et al., 2015b	44	−33	36	−12
			−39	−57	15
			33	−9	0
			39	−84	18
			−45	12	−15
			39	−84	18
	Lai and Wu, 2014	44	9	30	12
			−9	30	12
			3	60	6
			−3	60	6
			6	−75	−39
			−6	−75	−39
	Ramasubbu et al., 2014	55	−54	18	−2
			−26	−30	62
			−12	0	16
			40	10	−6
			16	−44	62
			−56	−36	−4
			60	−8	−10
			58	8	−8
			2	−86	−6
			−14	−84	−20
			46	−74	−32
			−10	−38	−16
			34	2	8
			−12	0	16
			24	−82	10
			−16	−94	24
			48	−64	−32
	Yang et al., 2017	40	42	−66	30
			42	−69	54
			12	42	45
	Wu et al., 2016	19	−42	49	6
			39	36	21
	Song et al., 2016	28	−21	−63	−30
			27	−63	−33
			21	−27	−9
			−30	−12	−15
			30	18	−3
			−33	3	−3
			−27	−6	42
			42	0	42
	Peng et al., 2015	16	−9	−34	58
			−21	−31	58
			6	−19	52
			−33	−61	−11
			−33	−40	−20
			36	−55	−20
	Buchanan et al., 2014	20	32	54	38
			33	23	35
			49	25	36
	Tang et al., 2013	28	−51	42	−9
			−42	57	0
	Guo et al., 2013b	24	−66	−30	24
			−36	−15	−33
			51	0	−36
Increased	Guo et al., 2013a	24	−48	24	21
	Ramasubbu et al., 2014	55	38	8	66
			34	12	−24
			−34	10	−24
			−58	−2	−34
	Sheline et al., 2010	18	1	48	18
			−12	37	42
			7	38	36
			−21	15	46
			21	15	44
			−35	19	32
			−9	29	19
			9	26	19
			5	30	−2
			−5	−41	38
			−8	−5	15
			9	−56	19
			1	−57	38
			29	−34	−03
			−21	−32	−10
			−4	−72	32
	Zhu et al., 2018	47	51	−51	−6
			42	42	15
			44	−33	45
			27	−54	48
	Yang et al., 2017	40	18	−87	30
			3	−93	27
			−9	−75	48
			45	−75	39
			−30	−78	39
	Wu et al., 2016	19	−52	−17	38
			−45	−81	19
	Song et al., 2016	28	3	63	3
	Kaiser et al., 2016	100	32	−4	−2
			22	−28	−20
	Guo et al., 2015a	44	30	21	−21
			6	51	−9
			−54	−9	−12
	Guo et al., 2013b	24	33	−33	−3

of networks and individual cortical regions which are seen as abnormal connected in depressed patients. Therefore, the current study also characterized specific functional connectivity abnormalities between individual cortical regions by matching each parcellation to their associated brain network based on previous work (M.F. Glasser et al., 2016; Yeo et al., 2011).

3.2. Functional connectivity patterns identified

88 network pairs were identified as having abnormal connectivity. Of these pairs, 50 (57%) were hypoactive ("decreased") and 38 (43%) were hyperactive ("increased"), compared to the functional connectivity of each pair in controls. Specific networks, organized by their included HCP parcellations, can be visualized in Fig. 4. The DMN was the most commonly implicated network, involved in a total of 38 (43%) of the total pairings. As expected, the next most common cortical origin of functional abnormality was the CEN, as well as subcortical structures, both of which were involved in a total of 30 (34%) of the total pairings. These abnormal network trends are listed according to their frequencies listed in Table 3.

3.3. Decreased functional connectivity network pairs

The most commonly decreased paired networks included DMN-Subcortical (9/50, 18%), limbic-subcortical (8/50, 16%) and intra

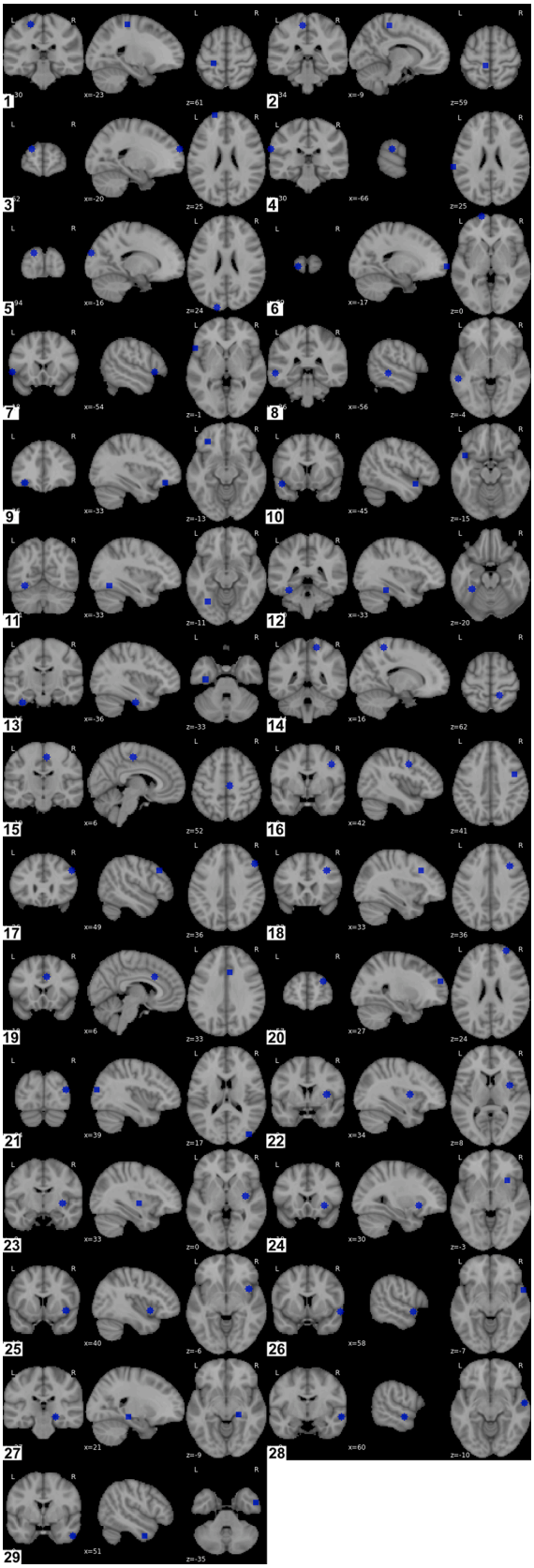

Fig. 2. Activation likelihood estimation (ALE) clusters of fifteen fMRI experiments including a total of 483 medication-naïve, adult patients with first episode MDD used in our meta-analysis. The three-dimensional ALE data are displayed on a brain normalized to the MNI coordinate space and a sphere was placed at the MNI coordinates of each ALE cluster with radius 15 mm. The ALE clusters of the decreased functional connectivity are shown in Fig. 1a and increased functional connectivity shown in Fig. 1b.

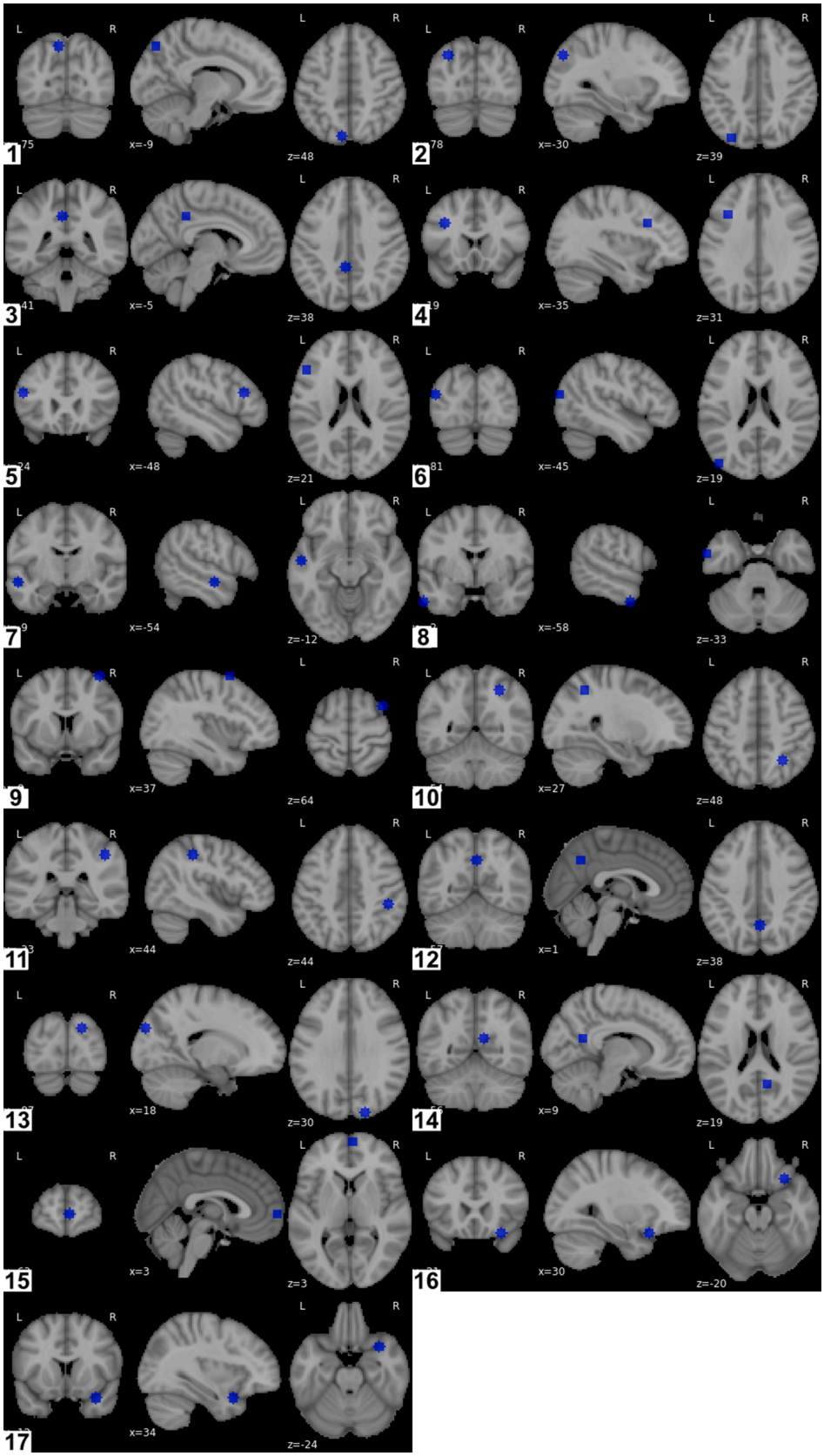

Fig. 2. (*continued*).

DMN-DMN (5/50, 10%) pairs. When assessing the connectivity pattern per network compared to their total amount of connections, the salience network demonstrated the most overall decreased connectivity (9/9 pairs, 100%), followed by the limbic system (22/28 pairs, 79%). The DMN demonstrated the majority of its negative connectivity originating from or going towards its core parcellations, mainly comprising the

Table 2
Included Human Connectome Project parcellations. List of HCP parcellations that had more than 10% of its volume within the activation likelihood estimation (ALE) cluster and was included in further analyses.

	Cluster ID	MNI (*x*, *y*, *z*)	HCP Parcellation Name	Percentage Overlap (%)
Decreased Functional Connectivity	1	−23 −30 61	L_3a	12.5210084
	2	−9 −34 59	L_5m	12.3126338
	3	−20 62 25	L_9a	17.4309314
	4	−66 −30 25	L_PFop	26.4018692
	5	−16 −94 24	L_V3A	27.1186441
	6	−17 69 0	L_10d	13.3531157
	7	−54 18 −1	L_FOP4	11.6037219
	8	−56 −36 −4	L_STSvp	23.6009732
	9	−33 36 −13	L_47m	31.1740891
	10	−45 12 −15	L_STGa	11.544544
	11	−33 −61 −11	L_VMV3	55.489022
	12	−33 −40 −20	L_VVC	17.445627
	13	−36 −16 −33	L_PeEc	17.8351784
	14	16 −44 62	R_5mv	10.7261825
	15	6 −19 52	R_24dd	20.315928
	16	42 0 41	R_PEF	36.1728395
	17	49 26 36	R_p9–46v	10.4500151
	18	33 23 36	R_8C	12.582297
	19	6 18 33	R_p32pr	12.4365482
	19	6 18 33	R_a24pr	42.0042644
	20	27 57 24	R_9–46d	15.7263958
	21	39 −84 17	R_V3CD	39.1684902
	22	34 2 8	R_MI	16.0740741
	22	34 2 8	R_FOP3	20.2247191
	23	33 −9 0	R_PoI1	12.4176858
	24	30 18 −3	R_AVI	12.9032258
	25	40 10 −6	R_PoI2	15.2747728
	26	40 10 −6	R_AAIC	17.1034483
	26	58 8 −7	R_A5	12.5965737
	27	21 −27 −9	R_PreS	29.4536817
	28	60 −8 −10	R_STSva	19.3604651
	29	51 0 −35	R_TE1a	13.9337049
Increased Functional Connectivity	1	−9 −75 48	L_POS2	17.6174497
	1	−9 −75 48	L_7Pm	13.8297872
	2	−30 −78 39	L_IPS1	17.2743056
	2	−30 −78 39	L_IP1	21.7504333
	3	−5 −41 38	L_31a	14.4168962
	3	−5 −41 38	L_d23ab	16.1557581
	4	−35 19 31	L_IFJa	12.3517787
	5	−48 24 21	L_IFSp	30.2889096
	6	−45 −81 19	L_PGp	24.2809735
	6	−45 −81 19	L_LO3	17.083947
	7	−54 −9 −12	L_STSda	13.7640449
	7	−54 −9 −12	L_STSva	26.8924303
	8	−58 −2 −33	L_TE1a	14.0841584
	9	37 8 64	R_i6–8	17.9087875
	10	27 −54 48	R_LIPv	24.9134948
	10	27 −54 48	R_LIPd	44.7427293
	11	44 −33 44	R_AIP	18.6451613
	12	1 −57 38	R_7m	26.984127
	13	18 −87 30	R_V3A	23.1067961
	14	9 −56 19	R_POS1	24.2558863
	15	3 63 3	R_10d	16.4568345
	16	30 21 −20	R_47s	32.2043969
	17	34 12 −24	R_Pir	13.8343296

anterior and posterior cingulate, and parietal regions. In particular, all of the intra DMN-DMN connections identified were negative (5/5, 100%). Similarly, most of the CENs decreased connectivity was confined to its *core* parcellations, mainly within the fronto-parietal regions, but also its *lateral* regions, extending into the temporal cortex. As predicted, when observing individual parcellations, the amygdala displayed the most negative connections based on its total connections identified (19/23, 83%). Compared to the right amygdala (6/8 pairs), the left amygdala was negatively connected more times (13/15 pairs) to other regions (Fig. 5A).

3.4. Increased functional connectivity network pairs

The increased paired networks most commonly included the CEN. These pairs consisted of DMN—CEN (8/38, 21%), intra CEN—CEN (5/38, 13%), and both CEN-Subcortical (4/38, 11%) and CEN-DAN (4/38, 11%). When assessing the connectivity patterns per network type, an obvious pattern was identified with the CEN network which mostly consisted of positive connections compared to its total amount of connections (24/30 pairs, 60%). Within this CEN network, the majority of increased functional connectivity was seen originating from or going towards its cingulate-insular parcellations. When observing individual parcellations, the most positively connected region based on its total connections identified included area left p24 (17/17, 100%). Area p24 is a posterior subdivision of area 24 located in the anterior cingulate gyrus just anterosuperior to the genu of the corpus callosum (Baker et al., 2018c; Sheline et al., 2010). Compared to the negative DMN-DMN connections described above, all intra CEN—CEN connections were positive (5/5, 100%) (Fig. 5B).

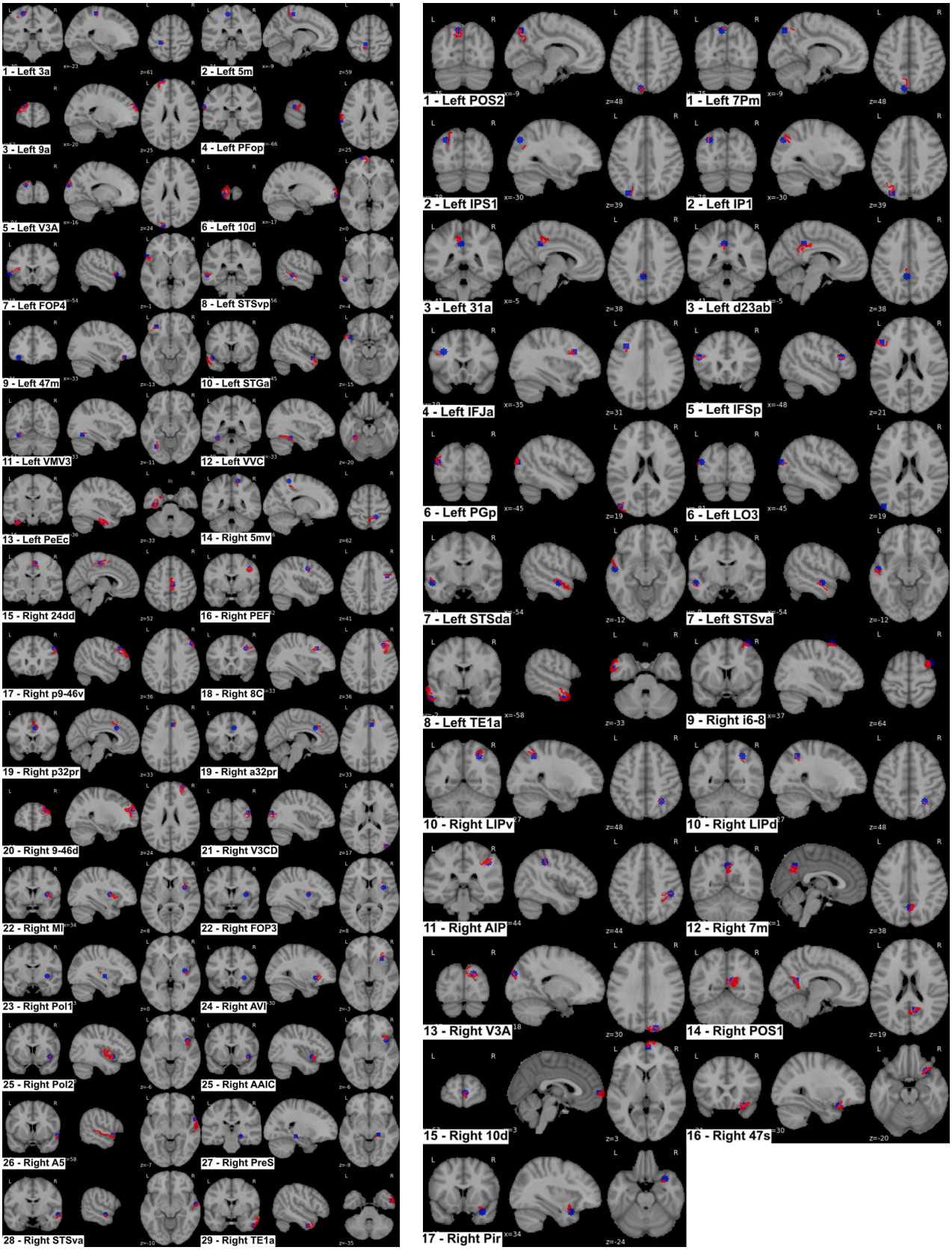

Fig. 3. Comparison overlays between cortical parcellation data (red) and the activation likelihood estimation clusters (blue) from Fig. 1. The spheres are projected onto the parcellation schema from the Human Connectome Project (HCP) which is also in MNI space. The equivalent HCP parcellation to that ALE cluster is the parcellation with the most overlap to the sphere. Parcellations and ALE clusters for decreased connectivity are shown in Fig. 2a and increased functional connectivity shown in Fig. 2b.

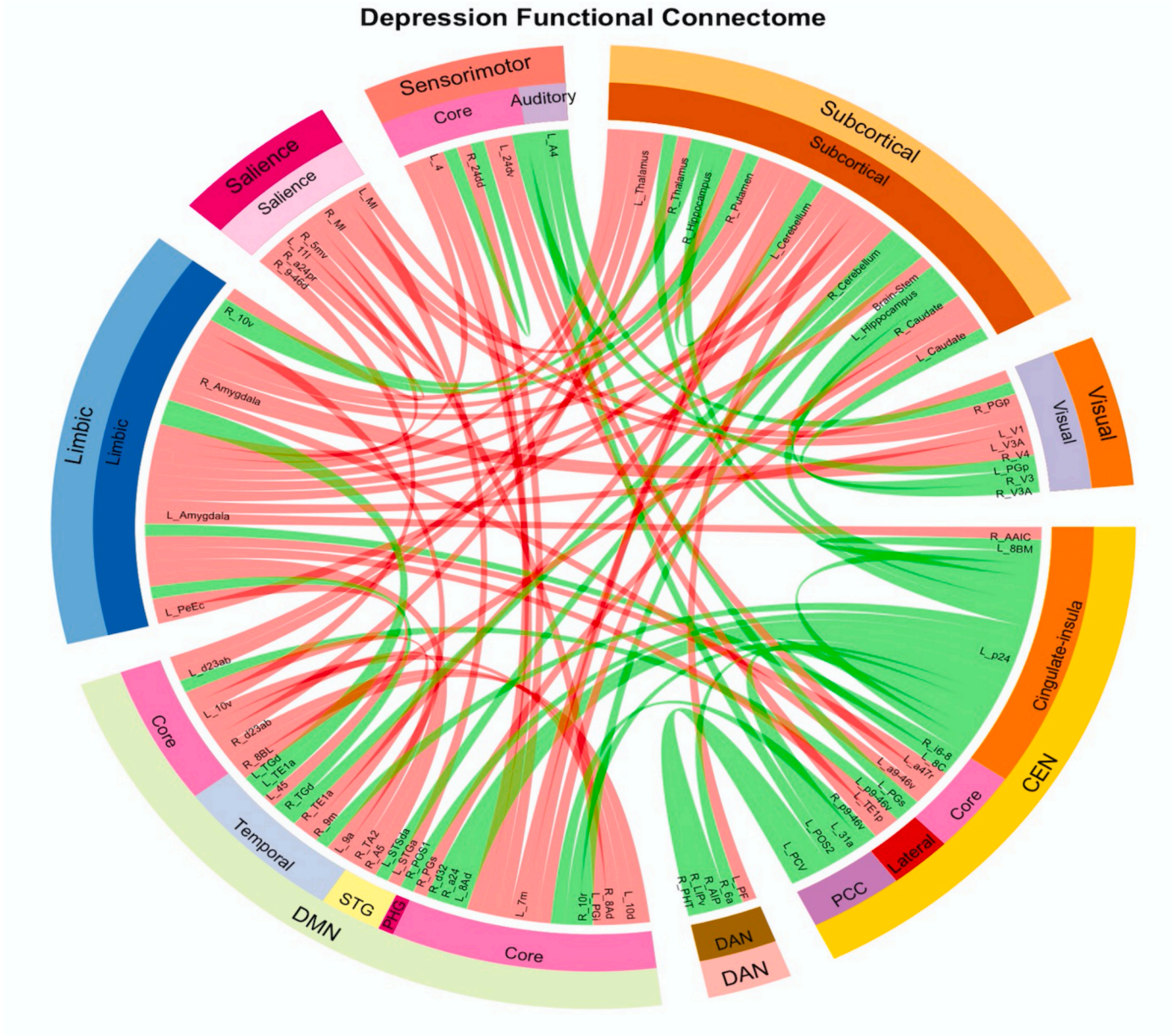

Fig. 4. MDD Functional Connectome. A simplified connectogram of abnormal functional connections in 483 medication-naïve, adult patients with first episode Major Depressive Disorder (MDD). Connections are grouped by their major brain network affiliation (outer layer) and further organized by the general location of the included Human Connectome Project (HCP) parcellations (inner layer). Individual fibers represent individual connections between two parcellations, which are seen as decreased (hypoactive) in red or increased (hyperactive) in green and highlighted further as individual diagrams in Fig. 4. When looing at general trends in abnormal network pairs, one can see that these pairs can generally be increased or decreased depending on the interacting partner, such as for the default mode network. However, all intra DMN-DMN and salience network (SN) connections were decreased, while all intra CEN—CEN and DMN—CEN connections were increased. Parcellation names are from the Human Connectome Project (M.F. Glasser et al., 2016).
Abbreviations: CEN, central executive network; DAN, dorsal attention network; DMN, default mode network; PCC, posterior cingulate cortex; PHG, parrahippocampal gyrus; STG, superior temporal gyrus.

4. Discussion

In the current study, we provide a map of the abnormal functional connectivity in medication naïve patients with major depressive disorder (MDD). Unsurprisingly, our results implicate large multi-network disturbances in MDD patients compared to healthy controls. In accordance with the previous literature, abnormal connectivity was identified between the core cognitive networks necessary for effective attentional and emotional processing in MDD patients, including the default mode network (DMN), central executive network (CEN), and salience network (SN). Previous reports generally suggest that 'hyperactive' DMN processing may underlie the cognitive vulnerability leading to depression (Beevers, 2005). However, our results suggest that this is not entirely the case. Instead, we propose that DMN connectivity, among other brain networks, can either be increased or decreased in MDD, depending on the interacting network. As such, our findings suggest a dynamic spectrum of the role of the core cognitive networks in MDD, possibly reflective of the previously proposed functional subsystems of certain networks (Andrews-Hanna et al., 2010; Buckner et al., 2008).

Our results add to the only other previous meta-analysis of abnormal functional connectivity in MDD patients (Kaiser et al., 2015). However, previous work has not clarified the connectivity profile of MDD in a level

Table 3
List of abnormal network pairs and their relative frequency in Major Depressive Disorder (MDD).

Decreased Pairs		*Increased Pairs*	
DMN-Subcortical	9	DMN—CEN	8
Limbic-Subcortical	8	CEN—CEN	5
DMN-DMN	5	CEN-Subcortical	4
DMN-Limbic	4	CEN-DAN	4
CEN-Limbic	4	DMN-Subcortical	3
DMN-Salience	3	DMN-Limbic	3
Limbic-Visual	3	Limbic-Subcortical	2
DMN-Sensorimotor	3	CEN-Sensorimotor(Auditory)	2
Salience-Limbic	2	Visual-Subcortical	2
Salience-Visual	2	Sensorimotor-Visual	2
CEN-Sensorimotor	2	Sensorimotor-Sensorimotor	1
Subcortical-Visual	1	Subcortical-Subcortical	1
DAN-Subcortical	1	CEN-Limbic	1
Salience-Salience	1		
Salience-Subcortical	1		
Limbic-Sensorimotor	1		

of granularity necessary for effective clinical translation. Extending past general descriptions of network connectivity, such as between the CEN-DMN, we provide our results down to the level of individual parcellations according to the established Human Connectome Project (HCP) parcellation scheme (Glasser, 2016). The clinical implications of abnormal MDD functional connectivity cannot be truly understood in complete accuracy without also discussing the precise individual parcellations implicated (Moreno-Ortega et al., 2020), all of which determine these general network trends. Our goal is to provide anatomically precise data that can be included in future work as additional covariates to study MDD pathophysiology.

4.1. Abnormal connectivity between the core cognitive networks

The majority of abnormal connectivity found in the current study localized to the three canonical resting state networks, which can be thought of as the "core cognitive networks": CEN, DMN, and SN. In healthy individuals, the DMN is generally thought to alternate its activity with the CEN in an anticorrelated fashion, in which the DMN activates during passive states of mind while the CEN activates during goal-directed behavior and external attentional processing (Baker et al., 2018c; Sandhu et al., 2021). The SN network filters and processes specific stimuli, and then sends control signals to the DMN and CEN and mediates network switching between them based on the stimuli or goals presented (Menon and Uddin, 2010). However, abnormal connectivity within and between these core cognitive networks is thought form the underlying basis of the cognitive and affective dysfunctions in numerous psychiatric and neurological disorders, and specifically supports several well-known cognitive theories of MDD (Fig. 6) (Menon, 2011; Ren et al., 2020; Sheline et al., 2010; Zheng et al., 2015).

The *dual-processing theory of cognitive vulnerability* to depression suggests that incorrect control from an (1) effortful and attentional processing stream leads to the dominance of a (2) memory-based, implicit processing stream. Such an imbalance has been proposed to create a reinforcing cycle of negative, self-referential thought in MDD patients (Zhou et al., 2020). Increased DMN—CEN connections were the most common findings in the current study, which together with previous hypotheses may suggest DMN dominance over the CEN network leads to an introspective, persisting rumination (a narrow-associative negative thinking pattern) in MDD patients (Beevers, 2005; Buchanan et al., 2014; Davey et al., 2012; Sheline et al., 2010; Zhou et al., 2020; Zhu et al., 2018).

The CEN may not be able to correct such self-referential thoughts facilitated by the DMN because of abnormal saliency mapping from the SN. According to Menon's *triple network model*, abnormal SN connectivity can lead to inappropriate allocation of attentional resources between the CEN and DMN (Menon, 2011). In agreement with this second unifying theory, we found that the SN only displayed decreased connections in the current study regardless of its interacting partner, DMN or CEN, although most were with the DMN. However, it is important to note that other authors often include the amygdala as a node of the SN (Menon, 2011), while the current study considered this structure separately as part of a large limbic network. Nonetheless, as expected, we found that the amygdala also demonstrated abnormal connectivity to a number of similar networks (Ramasubbu et al., 2014).

4.2. Abnormal connectivity with the DMN and CEN depends on individual partners

While our findings of the abnormal connectivity between the core cognitive networks corroborates well with previous studies and likely forms much of the basis of many MDD processes, it is important to note that our results are in contrast to some of the previous literature concerning their specific connectivity to other networks (Kaiser et al., 2015). These differences are likely in part due to differences in topographical nomenclature, highlighting the importance of providing our results in a precise anatomic parcellation scheme. Many have mostly elucidated the depression connectome in the context of "DMN hyperactivity" and "CEN hypoactivity," while we instead argue that such descriptions are erroneous without providing further granularity based on the interacting network and on the individual cortical regions implicated.

4.2.1. The DMN

We found that the degree of DMN functional connectivity depends on the specific subsystems and individual parcellations involved, and generally intra-DMN connectivity was found to be decreased. In line with these results, it is important to note that the DMN is a highly complex amalgamation of cortical areas underlying diverse self-generated thoughts, highly based on the mental content its supporting. Therefore, many authors have proposed the anatomical subsetting of the DMN system into function-specialized systems and provides a framework that may best elucidate our contrasting results (Andrews-Hanna et al., 2010; Buckner et al., 2008).

Hannas et al. suggests that the DMN is composed of at least two distinct subsystems which converge on a core of cortical regions centered around the anterior medial prefrontal cortex and parts of the posterior cingulate cortex (Andrews-Hanna et al., 2010; Buckner et al., 2008). Indeed, our results suggest most of the increased DMN connections with the CEN originated to/from similar core DMN parcellations, supporting the possible strong, central role of the DMN in suppressing or draining CEN activity, leading to increased self-inflection (Menon, 2011; Zhou et al., 2020). One possible DMN subsystem, known as the a *medial temporal subsystem,* is preferentially engaged when an individual is making decisions about their own future based on episodic and autobiographical memories (Andrews-Hanna et al., 2010; Buckner et al., 2008). In agreement with this theory, many positive connections were identified as extending between many similar temporal regions of the DMN to deeper limbic structures associated with emotional processing. Given that DMN activity is strongly based on the type of self-generated mental thought it is facilitating, these connections may reflect a lack of emotional control on the negative thoughts in MDD patients concerning their future based on their previous negative experiences (Zhang et al., 2016). A second subsystem of the DMN, referred to as a *dorsal medial subsystem*, may exist for processes related to mentalizing, social cognition, and theory of mind. This subsystem includes regions of the dorsal medial prefrontal cortex, the temporoparietal junction, lateral temporal cortex, and the temporal pole. In this context, we found that many regions of the left superior temporal sulcus important for mentalizing in social interactions demonstrated decreased connections with regions of the limbic and SN network (Andrews-Hanna et al., 2010; Ramasubbu et al., 2014).

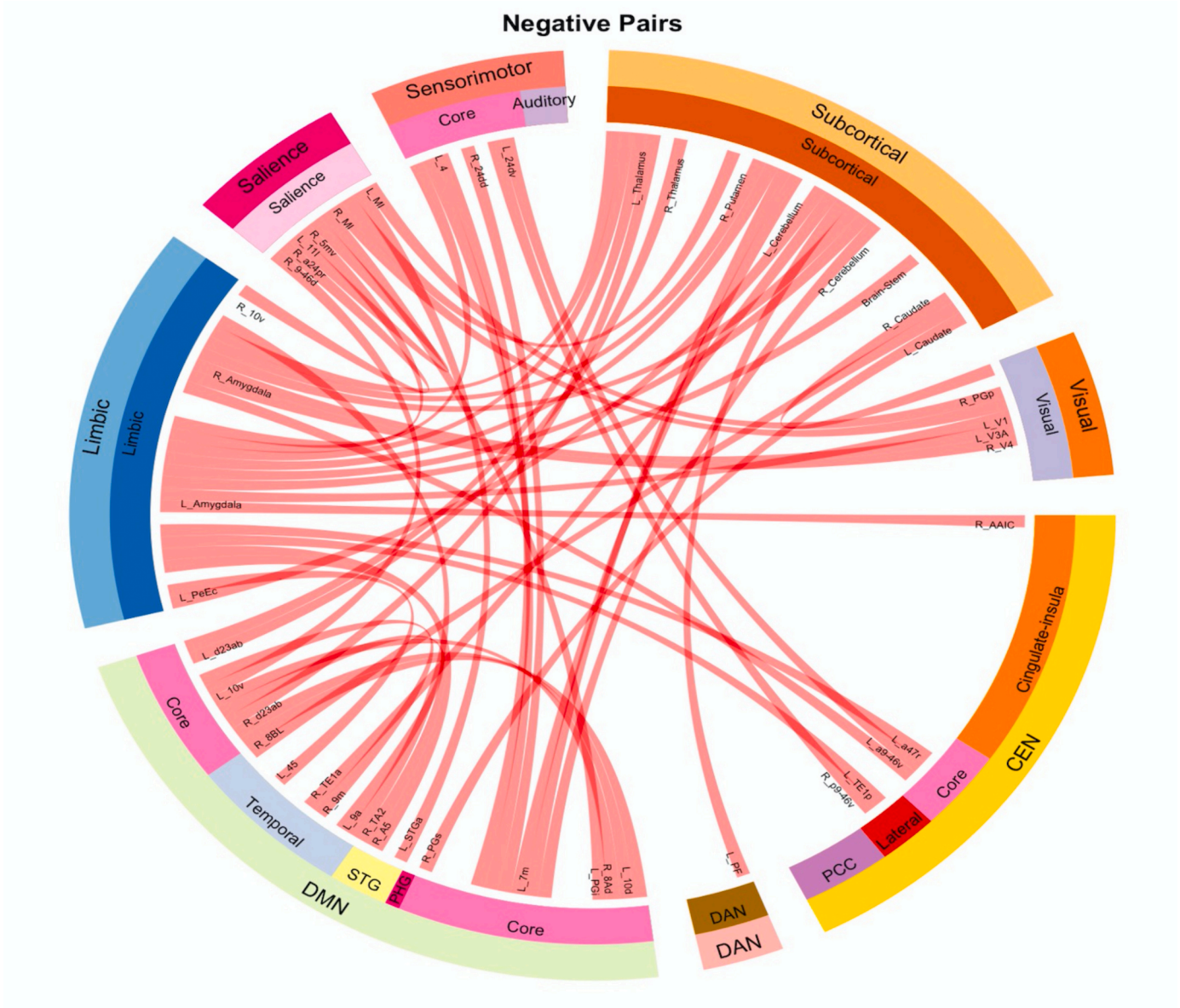

Fig. 5. Individual Decreased and Increased Connections in MDD. Simplified connectograms of abnormally decreased (A) and increased (B) functional connections in medication-naïve, adult patients with first episode Major Depressive Disorder (MDD). Connections are grouped by their major brain network affiliation (outer layer) and further organized by the general location of the included parcellations (inner layer). Individual fibers represent individual connections between two parcellations, which are seen as decreased (hypoactive) in red or increased (hyperactive) in green. In figure A, all salience network connections and all intra DMN-DMN connections between mostly core DMN regions are decreased. Connections with the amygdala are also commonly decreased. In Figure B, all intra CEN—CEN and DMN—CEN connections were increased. Parcellation left p24 demonstrated the most increased connections, primarily extending to the core of the DMN and subcortical structures. Area p24 is a posterior subdivision of area 24 located in the anterior cingulate gyrus just anterosuperior to the genu of the corpus callosum (Baker et al., 2018c; Sheline et al., 2010). Parcellation names are from the Human Connectome Project (M.F. Glasser et al., 2016).
Abbreviations: CEN, central executive network; DAN, dorsal attention network; DMN, default mode network; PCC, posterior cingulate cortex; PHG, parrahippocampal gyrus; STG, superior temporal gyrus.

Importantly, unlike previous studies (Kaiser et al., 2015), we found that most of the increased DMN connectivity was in the context of its *inter*-network dynamics, while the DMN *intra*-network connectivity was mostly decreased. However, it is important to remember that all regions or subsystems of the DMN still integrate and function together to support the goals of the network as a whole (Andrews-Hanna et al., 2010). Therefore, it is unsurprising to us that we found decreased intra DMN-DMN connections given that abnormal interactions within the DMN itself likely precludes normal DMN functioning in depressed patients all together. For instance, we found decreased connections between a number of core regions of the DMN with area right d23ab of the posterior cingulate cortex, a known hub in the DMN (Andrews-Hanna et al., 2010; Buckner et al., 2008). Imbalances in intra DMN-DMN connectivity may remove the self-regulation of its extra-network connections, possibly leading to increased connectivity with other important structures and increased negative emotional biases, such as via the increased connections we identified between temporal DMN regions and the amygdala and cerebellum (Anand et al., 2005; Guo et al., 2015a).

4.2.2. *The CEN*

Previous research generally suggests that the CEN, commonly also referred to as the fronto-parietal network, is mostly hypoactive in MDD

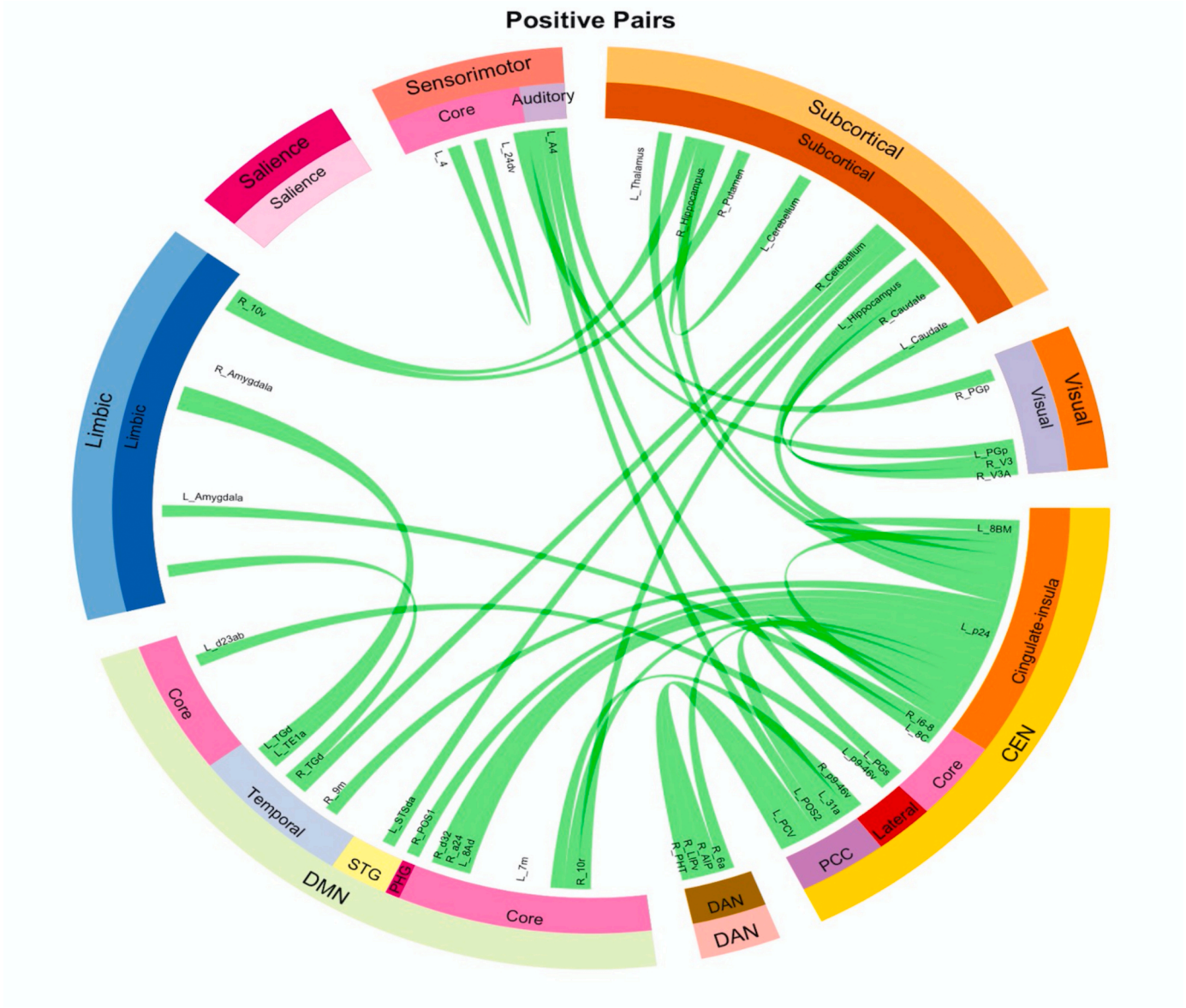

Fig. 5. (*continued*).

given its related known implications in top-down control of emotions and suppression of unpleasant thoughts in healthy individuals (Gagnepain et al., 2017; Li et al., 2018; Miller et al., 2018). As expected, some decreased connectivity was seen from the CEN, specifically in connections between the core and lateral/temporal parcellations of the CEN with the limbic and sensorimotor systems (Buchanan et al., 2014; Peng et al., 2015; Zhu et al., 2018). In depressed patients, these abnormal connections may reflect the lack of CEN-facilitated motor activity (Baker et al., 2018b; Vogt and Vogt, 2003), increased pain from recalling emotional, abnormal focus on autobiographical memories (Köhler et al., 2015), as well as decreased emotional processing (Guo et al., 2015a).

However, unlike previous connectivity-based studies, we found that the majority of abnormal processing from the CEN was in fact reflective of *hyperactive* connections even outside of its connectivity to the DMN. Increased connectivity was seen mostly with the cingulate-insular regions of the CEN, specifically associated with regions of the anterior cingulate and medial prefrontal cortex that extended to the DMN, subcortical structures, dorsal attention network (DAN), and also intra-CEN regions (Guo et al., 2015b; Yang et al., 2017; Zhu et al., 2018). In addition to the previously described hypotheses on increased CEN connectivity with the DMN, increased CEN connectivity with subcortical structures, such as the hippocampus, corroborate well with previous findings of increased focus on unpleasant memories in MDD patients (Guo et al., 2013a; Köhler et al., 2015; Song et al., 2016).

Interestingly, increased connectivity was identified specifically between CEN regions of the posterior cingulate cortex with regions in the DAN. While there remains conflicting results on such relationships with parietal nodes and the DAN (Fox et al., 2012; Mao et al., 2020), our results of increased connectivity to regions along the intraparietal sulcus within the DAN may support the increased attention depressed patients give to negative stimuli in the external environment (Allan et al., 2019; Kaiser et al., 2015; Mao et al., 2020; Zhu et al., 2018). For instance, the superior parietal lobule, including parcellations such as area AIP, has been described to have a transient role when shifting between attentive states (Behrmann et al., 2004; Zhu et al., 2018). Furthermore, area PCV, an anterior region of the precuneus, has been implicated in working memory as well as the recognition of emotional faces over neutral objects (Baker et al., 2018a; Cavanna and Trimble, 2006). Therefore, increased connectivity between the CEN and DAN via connections between these specific cortical regions (AIP-PCV) may facilitate known

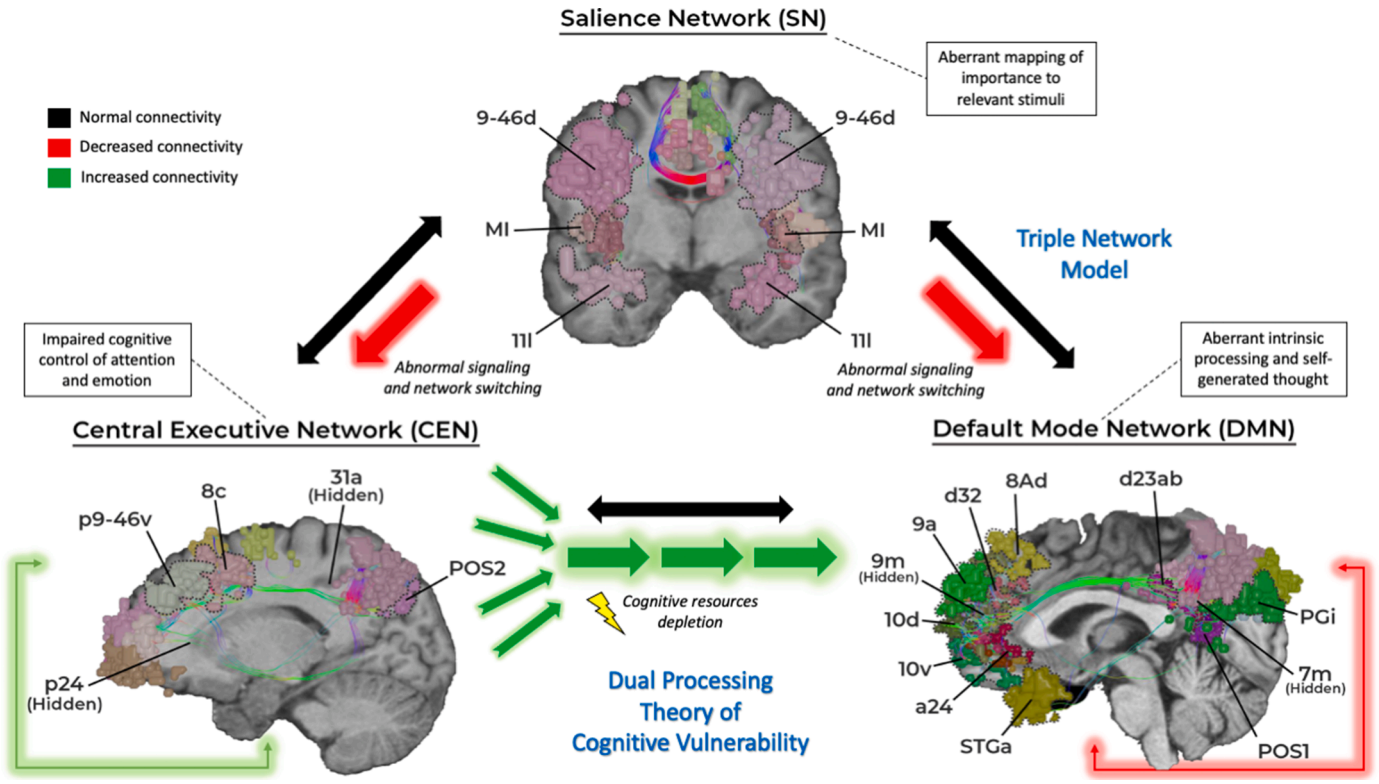

Fig. 6. Core Cognitive Networks in Depression. Abnormal connectivity within and between three canonical resting-state networks is thought form the underlying basis of many cognitive and affective dysfunctions and forms the basis of several well-known theories of depression that our data supports in great detail. These networks are the default mode network (DMN), central executive network (CEN), and salience network (SN) and can generally be thought of as the 'core cognitive networks'. *Theory one*: The dual-processing theory of cognitive vulnerability to depression includes a (1) *associative mode*, which involves implicit and effortless processing incorporating previously learned associations, and a (2) *reflective mode*, which involves effortful and attentional processing and is usually engaged when the associative mode is not being utilized (Beevers, 2005). As such, the DMN includes cortical regions known to facilitate this *associative* processing, while the CEN includes cortical regions involved in *reflective* processing. Increased negatively biased, self-referent associative processing (DMN) may develop the cognitive vulnerability to depression, unless corrected by reflective processing (CEN). According to our results and this theory, this network dynamic may be interrupted in depressed individuals as we found a number of specifically increased DMN—CEN connections, possibly reflecting the increased dominance of the DMN over CEN preventing corrective reflective processes. *Theory 2*: According to the triple network model, the SN is supposed to moderate the allocation of resources between the DMN and CEN (Menon, 2011). However, aberrant attributions of importance to specific stimuli and inappropriate SN-mediated switching may further exacerbate the abnormal DMN and CEN dynamics, leading to increased rumination and recurrent self-reflection (ie, increased DMN mediated activity)(Menon and Uddin, 2010). In agreement, we found only decreased SN connectivity with both the CEN and DMN.

mood-congruent processing biases seen in depressed individuals, such as with hyperactive processing of negative faces (Stuhrmann et al., 2011).

Elsewhere, the unexpected intra-CEN activity may be partly explained by other CEN parcellations identified which are similarly involved in attention, such as area 31a of the PCC. While "hypoactive CEN connectivity" is generally proposed to explain the decreased attentional control seen in depressed individuals, they may still express increased cognitive control concerning certain negative stimuli and therefore increased connectivity between related cortices is unsurprisingly to us (Kaiser et al., 2015; Zhu et al., 2018).

4.2.3. Improved anatomic precision may clarify inter-network abnormalities and treatment outcomes

The HCP nomenclature provides individual surface-based parcellations that can localize to different networks, and these parcellations can be targeted separately with focal treatments that each induce different outcomes in MDD often despite their spatial proximity (Moreno-Ortega et al., 2020; Rosen et al., 2021). For instance, the dorsolateral prefrontal cortex (DLPFC) was subdivided by the HCP into 13 regions of interest. As such, the DLPFC includes many regions that are each separately contained within the DMN, CEN, and even SN networks (Sheline et al., 2010). Recent evidence from a large RCT comparing rTMS with sham treatment for depression demonstrated that the clinical response to rTMS was related to the accuracy in targeting two closely located HCP parcellations of the DLPFC, which each modulated different networks. When targeting area 8Av, the DMN was modulated and most of these patients were non-responders to rTMS stimulation. Differently, targeting a slightly more anterolateral frontal target, area 46, modulated the CEN and/or SN systems and this was more commonly seen in responders to rTMS stimulation treatment (Rosen et al., 2021). Such stark differences despite the spatial proximity between these parcellations implore the need for reporting results in more precise nomenclature. Within our study, we identified numerous abnormally connected regions slightly adjacent to the preferred rTMS responder target mentioned above (area 46) in the central portion of the dorsolateral prefrontal region. These regions each participated in a mix of decreased or increased DMN, CEN and even SN networks. We discuss these regions specifically in the supplementary material, but in general these findings highlight possible reasons behind the variable outcomes seen in focal treatments for variety of psychiatric illnesses, including depression (Riva-Posse et al., 2014), that focus on vague craniometric targets and in turn may modulate different, unexpected networks. The DLPFC, among other regions, remains an incredibly complex and increasingly evolved cortical area that is previously poorly understood in terms of its connectivity. With future refinement, our results can begin to inform decisions on connectomic-targeted treatments for MDD with improved precision (Fox et al., 2012, 2013; Rosen et al., 2021; Siddiqi et al., 2020).

4.3. Limitations

Coordinate-based meta-analyses allow the procurement of large amounts of reported data that complex computational algorithms can analyze to identify relevant ROIs with less bias (Eickhoff et al., 2012; Ren et al., 2020; Sandhu et al., 2021). However, such meta-analytic approaches are inherently limited by the quality of the reported literature. We attempted to overcome this by utilizing rigorous selection criteria, but this may have introduced additional selection bias that can influence the results of the current study. Furthermore, we utilized strict, cluster-level corrected statistical inferences on our included neuroimaging data to generate precise ALE maps to determine relevant ROIs to depression (Eickhoff et al., 2012), but this too may have introduced sampling bias given the lack negative data not reported by previous authors. Therefore, while our study presents the most anatomically precise coordinate-based meta-analysis on the current topic to the best of our knowledge, our findings should be interpreted cautiously for their clinical relevance to therapeutic options that may differ on an individual patient basis.

5. Conclusions

As expected, we found increased DMN—CEN connectivity and decreased SN connectivity with all network pairs suggesting abnormal interactions within the core cognitive networks responsible for appropriate control of attentional processing and self-generated thoughts based on the internal and external environment. However, compared to previous work, we found that DMN connectivity varied depending on its interacting network partner, and generally intra-DMN connectivity was decreased while intra-CEN connectivity was increased. Importantly, nearly all of the network connectivity relationships depended on which specific brain parcellation was involved within a particular network, highlighting the need to also interpret connectomic trends based on precise brain parcellations involved. As such, these findings provide a cortical model of depression with anatomically precise and clinically actionable information that may be refined in future studies.

Disclosures

Dr. Sughrue and Dr. Doyen are co-founders of Omniscient Neurotechnologies. Isabella Young, Onur Tanglay, Hugh Taylor, Lewis Crawford, and Peter Nicholas are employees of Omniscient Neurotechnology. No products directly related to this were discussed in this paper. All other authors have no financial interests or potential conflicts of interest.

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CRediT authorship contribution statement

Isabella M. Young: Investigation, Formal analysis, Writing – original draft. **Nicholas B. Dadario:** Investigation, Writing – original draft. **Onur Tanglay:** Investigation, Writing – review & editing. **Emily Chen:** Data curation. **Brennan Cook:** . **Hugh M. Taylor:** Visualization, Software. **Lewis Crawford:** Visualization, Writing – review & editing. **Jacky T. Yeung:** Writing – review & editing, Investigation. **Peter J. Nicholas:** Software. **Stéphane Doyen:** Supervision, Methodology. **Michael E. Sughrue:** Conceptualization, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jadr.2023.100478.

References

Allan, P.G., Briggs, R.G., Conner, A.K., O'Neal, C.M., Bonney, P.A., Maxwell, B.D., Baker, C.M., Burks, J.D., Sali, G., Glenn, C.A., Sughrue, M.E., 2019. Parcellation-based tractographic modeling of the dorsal attention network. Brain Behav. 9, e01365.

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., Mathews, V.P., Kalnin, A., Lowe, M.J., 2005. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biol. Psychiatry 57, 1079–1088.

Andrews-Hanna, J.R., Reidler, J.S., Sepulcre, J., Poulin, R., Buckner, R.L., 2010. Functional-anatomic fractionation of the brain's default network. Neuron 65, 550–562.

Baker, C., Burks, J., Briggs, R., Conner, A., Glenn, C., Manohar, K., Milton, C., Sali, G., McCoy, T., Battiste, J., O'Donoghue, D., Sughrue, M., 2018a. A Connectomic atlas of the human cerebrum—Chapter 8: the posterior cingulate cortex, medial parietal lobe, and Parieto-Occipital sulcus. Oper. Neurosurg. 15.

Baker, C.M., Burks, J.D., Briggs, R.G., Conner, A.K., Glenn, C.A., Manohar, K., Milton, C. K., Sali, G., McCoy, T.M., Battiste, J.D., O'Donoghue, D.L., Sughrue, M.E., 2018b. A connectomic atlas of the human cerebrum-chapter 8: the posterior cingulate cortex, medial parietal lobe, and Parieto-Occipital sulcus. Oper. Neurosurg. (Hagerstown) 15, S350–S371.

Baker, C.M., Burks, J.D., Briggs, R.G., Stafford, J., Conner, A.K., Glenn, C.A., Sali, G., McCoy, T.M., Battiste, J.D., O'Donoghue, D.L., Sughrue, M.E., 2018c. A connectomic atlas of the human cerebrum-chapter 4: the medial frontal lobe, anterior cingulate gyrus, and orbitofrontal cortex. Oper. Neurosurg. (Hagerstown) 15, S122–S174.

Beevers, C.G., 2005. Cognitive vulnerability to depression: a dual process model. Clin. Psychol. Rev. 25, 975–1002.

Behrmann, M., Geng, J.J., Shomstein, S., 2004. Parietal cortex and attention. Curr. Opin. Neurobiol. 14, 212–217.

Briggs, R.G., Conner, A.K., Baker, C.M., Burks, J.D., Glenn, C.A., Sali, G., Battiste, J.D., O'Donoghue, D.L., Sughrue, M.E., 2018. A connectomic atlas of the human cerebrum-chapter 18: the connectional anatomy of human brain networks. Oper. Neurosurg. (Hagerstown) 15, S470–S480.

Buchanan, A., Wang, X., Gollan, J.K., 2014. Resting-state functional connectivity in women with Major Depressive Disorder. J. Psychiatr. Res. 59, 38–44.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. The Year in Cognitive Neuroscience 2008. Blackwell Publishing, Malden, pp. 1–38.

Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129, 564–583.

Davey, C.G., Yucel, M., Allen, N.B., Harrison, B.J., 2012. Task-related deactivation and functional connectivity of the subgenual cingulate cortex in major depressive disorder. Front. Psychiatry 3, 14.

Eickhoff, S.B., Bzdok, D., Laird, A.R., Kurth, F., Fox, P.T., 2012. Activation likelihood estimation meta-analysis revisited. Neuroimage 59, 2349–2361.

Forgas, J.P., 2000. Managing moods: toward a dual-process theory of spontaneous mood regulation. Psychol. Inq. 11, 172–177.

Fox, M.D., Buckner, R.L., White, M.P., Greicius, M.D., Pascual-Leone, A., 2012. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol. Psychiatry 72, 595–603.

Fox, M.D., Liu, H., Pascual-Leone, A., 2013. Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. Neuroimage 66, 151–160.

Gagnepain, P., Hulbert, J., Anderson, M.C., 2017. Parallel regulation of memory and emotion supports the suppression of intrusive memories. J. Neurosci. 37, 6423–6441.

Glasser, M.F., Coalson, T.S., Robinson, E.C., Hacker, C.D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C.F., Jenkinson, M., Smith, S.M., Van Essen, D. C., 2016a. A multi-modal parcellation of human cerebral cortex. Nature 536, 171–178.

Guo, W., Liu, F., Dai, Y., Jiang, M., Zhang, J., Yu, L., Long, L., Chen, H., Gao, Q., Xiao, C., 2013a. Decreased interhemispheric resting-state functional connectivity in first-episode, drug-naive major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 41, 24–29.

Guo, W., Liu, F., Liu, J., Yu, L., Zhang, Z., Zhang, J., Chen, H., Xiao, C., 2013b. Is there a cerebellar compensatory effort in first-episode, treatment-naive major depressive disorder at rest? Prog. Neuropsychopharmacol. Biol. Psychiatry 46, 13–18.

Guo, W., Liu, F., Liu, J., Yu, M., Zhang, Z., Liu, G., Xiao, C., Zhao, J., 2015a. Increased cerebellar-default-mode-network connectivity in drug-naive major depressive disorder at rest. Medicine (Baltimore). 94, e560.

Guo, W., Liu, F., Xiao, C., Zhang, Z., Liu, J., Yu, M., Zhang, J., Zhao, J., 2015b. Decreased insular connectivity in drug-naive major depressive disorder at rest. J. Affect. Disord. 179, 31–37.

Hasin, D.S., Sarvet, A.L., Meyers, J.L., Saha, T.D., Ruan, W.J., Stohl, M., Grant, B.F., 2018. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiatry 75, 336–346.
Helm, K., Viol, K., Weiger, T.M., Tass, P.A., Grefkes, C., Del Monte, D., Schiepek, G., 2018. Neuronal connectivity in major depressive disorder: a systematic review. Neuropsychiatr. Dis. Treat. 14, 2715–2737.
Kaiser, R.H., Andrews-Hanna, J.R., Wager, T.D., Pizzagalli, D.A., 2015. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatry 72, 603–611.
Kaiser, R.H., Whitfield-Gabrieli, S., Dillon, D.G., Goer, F., Beltzer, M., Minkel, J., Smoski, M., Dichter, G., Pizzagalli, D.A., 2016. Dynamic resting-state functional connectivity in major depression. Neuropsychopharmacology 41, 1822–1830.
Köhler, C.A., Carvalho, A.F., Alves, G.S., McIntyre, R.S., Hyphantis, T.N., Cammarota, M., 2015. Autobiographical memory disturbances in depression: a novel therapeutic target? Neural. Plast. 2015, 759139-759139.
Lai, C.H., Wu, Y.T., 2014. Decreased inter-hemispheric connectivity in anterior sub-network of default mode network and cerebellum: significant findings in major depressive disorder. Int. J. Neuropsychopharmacol. 17, 1935–1942.
Li, B.J., Friston, K., Mody, M., Wang, H.N., Lu, H.B., Hu, D.W., 2018. A brain network model for depression: from symptom understanding to disease intervention. CNS Neurosci. Ther. 24, 1004–1019.
Mao, Y., Xiao, H., Ding, C., Qiu, J., 2020. The role of attention in the relationship between early life stress and depression. Sci. Rep. 10, 6154.
Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trend. Cogn. Sci. 15, 483–506.
Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 214, 655–667.
Miller, G.E., Chen, E., Armstrong, C.C., Carroll, A.L., Ozturk, S., Rydland, K.J., Brody, G. H., Parrish, T.B., Nusslock, R., 2018. Functional connectivity in central executive network protects youth against cardiometabolic risks linked with neighborhood violence. Proc. Natl. Acad. Sci. U. S. A. 115, 12063–12068.
Moreno-Ortega, M., Kangarlu, A., Lee, S., Perera, T., Kangarlu, J., Palomo, T., Glasser, M. F., Javitt, D.C., 2020. Parcel-guided rTMS for depression. Transl Psychiatry 10, 283.
O'Neal, C.M., Ahsan, S.A., Dadario, N.B., Fonseka, R.D., Young, I.M., Parker, A., Maxwell, B.D., Yeung, J.T., Briggs, R.G., Teo, C., Sughrue, M.E., 2021. A connectivity model of the anatomic substrates underlying ideomotor apraxia: a meta-analysis of functional neuroimaging studies. Clin. Neurol. Neurosurg. 207, 106765.
Peng, D., Liddle, E.B., Iwabuchi, S.J., Zhang, C., Wu, Z., Liu, J., Jiang, K., Xu, L., Liddle, P.F., Palaniyappan, L., Fang, Y., 2015. Dissociated large-scale functional connectivity networks of the precuneus in medication-naive first-episode depression. Psychiatry Res. 232, 250–256.
Ramasubbu, R., Konduru, N., Cortese, F., Bray, S., Gaxiola-Valdez, I., Goodyear, B., 2014. Reduced intrinsic connectivity of amygdala in adults with major depressive disorder. Front. Psychiatry 5, 17.
Ren, H., Zhu, J., Su, X., Chen, S., Zeng, S., Lan, X., Zou, L.Y., Sughrue, M.E., Guo, Y., 2020. Application of structural and functional connectome mismatch for classification and individualized therapy in Alzheimer disease. Front. Public Health 8, 584430.
Riva-Posse, P., Choi, K.S., Holtzheimer, P.E., McIntyre, C.C., Gross, R.E., Chaturvedi, A., Crowell, A.L., Garlow, S.J., Rajendra, J.K., Mayberg, H.S., 2014. Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression. Biol. Psychiatry 76, 963–969.
Rosen, A.C., Bhat, J.V., Cardenas, V.A., Ehrlich, T.J., Horwege, A.M., Mathalon, D.H., Roach, B.J., Glover, G.H., Badran, B.W., Forman, S.D., George, M.S., Thase, M.E., Yurgelun-Todd, D., Sughrue, M.E., Doyen, S.P., Nicholas, P.J., Scott, J.C., Tian, L., Yesavage, J.A., 2021. Targeting location relates to treatment response in active but not sham rTMS stimulation. Brain Stimul. 14, 703–709.
Sandhu, Z., Tanglay, O., Young, I.M., Briggs, R.G., Bai, M.Y., Larsen, M.L., Conner, A.K., Dhanaraj, V., Lin, Y.-H., Hormovas, J., Fonseka, R.D., Glenn, C.A., Sughrue, M.E., 2021. Parcellation-based anatomic modeling of the default mode network. Brain Behav. 11, e01976.
Sheline, Y.I., Price, J.L., Yan, Z., Mintun, M.A., 2010. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc. Natl. Acad. Sci. U. S. A. 107, 11020–11025.
Siddiqi, S.H., Taylor, S.F., Cooke, D., Pascual-Leone, A., George, M.S., Fox, M.D., 2020. Distinct symptom-specific treatment targets for circuit-based neuromodulation. Am. J. Psychiatry 177, 435–446.
Simon, G.E., 2003. Social and economic burden of mood disorders. Biol. Psychiatry 54, 208–215.
Song, Z., Zhang, M., Huang, P., 2016. Aberrant emotion networks in early major depressive disorder patients: an eigenvector centrality mapping study. Transl. Psychiatry 6 e819-e819.
Stuhrmann, A., Suslow, T., Dannlowski, U., 2011. Facial emotion processing in major depression: a systematic review of neuroimaging findings. Biol. Mood. Anxiety Disord. 1, 10.
Tang, Y., Kong, L., Wu, F., Womer, F., Jiang, W., Cao, Y., Ren, L., Wang, J., Fan, G., Blumberg, H.P., Xu, K., Wang, F., 2013. Decreased functional connectivity between the amygdala and the left ventral prefrontal cortex in treatment-naive patients with major depressive disorder: a resting-state functional magnetic resonance imaging study. Psychol. Med. 43, 1921–1927.
Vogt, B.A., Vogt, L., 2003. Cytology of human dorsal midcingulate and supplementary motor cortices. J. Chem. Neuroanat. 26, 301–309.
Wang, X., Ongur, D., Auerbach, R.P., Yao, S., 2016. Cognitive vulnerability to major depression: view from the intrinsic network and cross-network interactions. Harv. Rev. Psychiatry 24, 188–201.
Wu, X., Lin, P., Yang, J., Song, H., Yang, R., Yang, J., 2016. Dysfunction of the cingulo-opercular network in first-episode medication-naive patients with major depressive disorder. J. Affect. Disord. 200, 275–283.
Yan, C.G., Chen, X., Li, L., Castellanos, F.X., Bai, T.J., Bo, Q.J., Cao, J., Chen, G.M., Chen, N.X., Chen, W., Cheng, C., Cheng, Y.Q., Cui, X.L., Duan, J., Fang, Y.R., Gong, Q.Y., Guo, W.B., Hou, Z.H., Hu, L., Kuang, L., Li, F., Li, K.M., Li, T., Liu, Y.S., Liu, Z.N., Long, Y.C., Luo, Q.H., Meng, H.Q., Peng, D.H., Qiu, H.T., Qiu, J., Shen, Y. D., Shi, Y.S., Wang, C.Y., Wang, F., Wang, K., Wang, L., Wang, X., Wang, Y., Wu, X. P., Wu, X.R., Xie, C.M., Xie, G.R., Xie, H.Y., Xie, P., Xu, X.F., Yang, H., Yang, J., Yao, J.S., Yao, S.Q., Yin, Y.Y., Yuan, Y.G., Zhang, A.X., Zhang, H., Zhang, K.R., Zhang, L., Zhang, Z.J., Zhou, R.B., Zhou, Y.T., Zhu, J.J., Zou, C.J., Si, T.M., Zuo, X.N., Zhao, J.P., Zang, Y.F., 2019. Reduced default mode network functional connectivity in patients with recurrent major depressive disorder. Proc. Natl. Acad. Sci. U. S. A. 116, 9078–9083.
Yang, X.H., Tian, K., Wang, D.F., Wang, Y., Cheung, E.F.C., Xie, G.R., Chan, R.C.K., 2017. Anhedonia correlates with abnormal functional connectivity of the superior temporal gyrus and the caudate nucleus in patients with first-episode drug-naive major depressive disorder. J. Affect. Disord. 218, 284–290.
Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zollei, L., Polimeni, J.R., Fischl, B., Liu, H., Buckner, R. L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106, 1125–1165.
Zhang, S., Chen, J.M., Kuang, L., Cao, J., Zhang, H., Ai, M., Wang, W., Zhang, S.D., Wang, S.Y., Liu, S.J., Fang, W.D., 2016. Association between abnormal default mode network activity and suicidality in depressed adolescents. BMC Psychiatry 16, 337.
Zheng, H., Xu, L., Xie, F., Guo, X., Zhang, J., Yao, L., Wu, X., 2015. The altered triple networks interaction in depression under resting state based on graph theory. Biomed. Res. Int. 2015, 386326.
Zhou, H.X., Chen, X., Shen, Y.Q., Li, L., Chen, N.X., Zhu, Z.C., Castellanos, F.X., Yan, C.G., 2020. Rumination and the default mode network: meta-analysis of brain imaging studies and implications for depression. Neuroimage 206, 116287.
Zhu, J., Lin, X., Lin, C., Zhuo, C., Yu, Y., 2018. Selective functional dysconnectivity of the dorsal-anterior subregion of the precuneus in drug-naive major depressive disorder. J. Affect. Disord. 225, 676–683.