NeuroImage: Clinical 41 (2024) 103556

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Large-scale effective connectivity analysis reveals the existence of two mutual inhibitory systems in patients with major depression

Jia Wang [a], Baojuan Li [a], Jian Liu [b], Jiaming Li [a], Adeel Razi [c], Kaizhong Zheng [d], Baoyu Yan [e], Huaning Wang [f,*], Hongbing Lu [a,*], Karl Friston [c]

[a] School of Biomedical Engineering, Fourth Military Medical University, Xi'an, Shaanxi 710032, China
[b] Network Center, Fourth Military Medical University, Xi'an, Shaanxi 710032, China
[c] The Wellcome Trust Centre for Neuroimaging, University College London, Queen Square, London WC1N 3BG, UK
[d] Institute of Artificial Intelligence and Robotics, Xi'an Jiaotong University, Xi'an, Shaanxi 710049, China
[e] Air Force Hangzhou Special Service Nursing Center, Hangzhou, Zhejiang 310000, China
[f] Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi 710032, China

A R T I C L E I N F O

Keywords:
Major depression
Effective connectivity
fMRI
Brain networks
Rational brain
Emotional/sensory brain

A B S T R A C T

It is posited that cognitive and affective dysfunction in patients with major depression disorder (MDD) may be caused by dysfunctional signal propagation in the brain. By leveraging dynamic causal modeling, we investigated large-scale directed signal propagation (effective connectivity) among distributed large-scale brain networks with 43 MDD patients and 56 healthy controls. The results revealed the existence of two mutual inhibitory systems: the anterior default mode network, auditory network, sensorimotor network, salience network and visual networks formed an "emotional" brain, while the posterior default mode network, central executive networks, cerebellum and dorsal attention network formed a "rational brain". These two networks exhibited excitatory intra-system connectivity and inhibitory inter-system connectivity. Patients were characterized by potentiated intra-system connections within the "emotional/sensory brain", as well as over-inhibition of the "rational brain" by the "emotional/sensory brain". The hierarchical architecture of the large-scale effective connectivity networks was then analyzed using a PageRank algorithm which revealed a shift of the controlling role of the "rational brain" to the "emotional/sensory brain" in the patients. These findings inform basic organization of distributed large-scale brain networks and furnish a better characterization of the neural mechanisms of depression, which may facilitate effective treatment.

1. Introduction

As a common mental disorder, depression affects more than 300 million patients worldwide (Smith, 2014) with a very high lifetime risk of 15–18 % (Malhi and Mann, 2018), representing one of the leading causes of disability (Friedrich, 2017). Although new antidepressant drugs, as well as various brain stimulation techniques – such as deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS) – have been introduced in the treatment of depression during the past few decades, the therapeutic efficacy seems to be quite limited, with a large portion of patients failing to respond or remit (Nemeroff, 2007) (Levkovitz et al., 2015). Furthermore, treatment response varies considerably among individuals. It remains unclear why some patients detained a full remission, while others failed to show response to the same treatment strategy. This question may only be answered when we are able to establish a better understanding of the neural substrates of this disorder.

Recent advances in non-invasive in vivo neuroimaging techniques have provided unprecedented opportunities to elucidate the neural pathways involved in depression (Goulden et al., 2012; Davey et al., 2015; Cheng et al., 2016; Manelis et al., 2016; Satterthwaite et al., 2015; Simmons et al., 2016; Kerestes et al., 2015; Meng et al., 2014; Ho et al., 2014; Li et al., 2013; Aizenstein et al., 2009; Kaiser et al., 2015). fMRI studies have consistently demonstrated that the human brain is organized into distinct large-scale functional networks and can be viewed as a triune architecture with the essential emotional part (Dalgleish, 2004; Damoiseaux et al., 2006; Smith et al., 2009). Several studies indicated the emotional system consist of the regions in subcortex——the

* Corresponding authors.
E-mail addresses: xskzhu@fmmu.edu.cn (H. Wang), luhb@fmmu.edu.cn (H. Lu).

https://doi.org/10.1016/j.nicl.2023.103556
Received 23 October 2023; Received in revised form 12 December 2023; Accepted 16 December 2023
Available online 18 December 2023

thalamus, hippocampus and amygdala——and the PFC, which mainly involve the salience network (SN) and the default mode network (DMN) (Dalgleish, 2004; Leerssen et al., 2023; Quidé et al., 2023). According to Marlin, et al (Dalgleish, 2004), applying the cognitive control to the emotional experience which combines the external sensors and brain emotional information can be regarded as the rational response to the stimulus or external messages. The process of rational control is mediated mainly by the central executive network (CEN), dorsal attention network (DAN), ventral attention network (VAN) (Corbetta and Shulman, 2002). Evidences have proved that networks such as the SN, DMN, CEN, DAN exhibit disrupted activity or connectivity in depressed patients (Ho et al., 2014; Menon, 2011; Lozano and Lipsman, 2013). For example, the SN, DMN exhibit increased activity or connectivity in depressed patients (Ho et al., 2015; Yu et al., 2019), while the DAN, VAN show reduced connectivity (Sacchet et al., 2016). From these studies, a new hypothesis has emerged which argues cognitive and affective dysfunction seen in depression may be caused by dysfunctional signal propagation within core brain networks that mediate sensory, motor, emotion, cognitive control, self-referential processing (Menon, 2011; Lozano and Lipsman, 2013). However, this hypothesis still awaits validation with empirical neuroimaging data from clinical depressed patients and appropriate modeling schemes.

Most resting state fMRI studies typically employ functional connectivity analysis to examine the level of activity in brain regions or the interactions between brain regions (Avissar et al., 2017; Li et al., 2022; Cui et al., 2018). While in terms of the directionality of connection, the functional connection is undirected connection that only shows the abnormal transmission of neural signals between brain regions, but cannot clearly explain the causal relationship between neural activities in brain regions (Cui et al., 2018; Di Plinio et al., 2018; Mitra et al., 2023). Dynamic causal modeling (DCM) is proposed by Friston et al. in 2003 (Friston et al., 2003) and is one of the most sophisticated and widely methods to analyze the causal interactions and directed information flow within brain networks (Friston et al., 2014). It is a nonlinear dynamic differential equation model that simulates neuron activity as a multi-input and multi-output model, and then inversely deduces the effective connectivity parameters of brain regions (Friston et al., 2014). To address the hypothesis, the current study investigated large-scale effective connectivity within and among eleven brain networks in patients with major depression using DCM (Razi et al., 2017).

Cognition and emotion largely depend on the organization and hierarchical architecture of distributed large-scale brain networks. Contemporary neuroscience studies suggest that different brain regions within an interacting system act in different ways, with some brain regions acting as system "controllers" (Bressler and Menon, 2010; Hanning et al., 2023). For healthy subjects, the CEN has long been identified as a control system in human brain which has the ability to mediate the activity of the visual system (Ruff et al., 2006), while the dorsal attention network was thought to be associated with top-down control of attention (Corbetta and Shulman, 2002). However, it remains unclear whether the hierarchical architecture of large-scale brain networks is disrupted in depression. Notably, hypoactivation of the dorsolateral prefrontal cortex (DLPFC) in the CEN and biased attention towards negative stimuli are prominent in depressed patients. These observations raise the possibility that the controlling role of the CEN and DAN may be disrupted in depressed patients. Owing to the ability of the large-scale effective connectivity analysis to furnish the directionality of brain connections, we therefore characterized the hierarchical architecture of large-scale brain networks in depression.

Here, we collected resting-state fMRI images from 75 healthy controls and 65 patients with major depressive disorder (MDD). Spectral DCM was used to quantify large-scale effective connectivity among 11 large-scale brain networks including the anterior and posterior DMNs, left and right CENs, SN, DAN, auditory network (AN), visual networks (VNs), sensorimotor network (SmN), and cerebellum. The hierarchical architecture of this whole brain effective connectivity network was then examined, and "controllers" were identified using a PageRank algorithm. Here, we report our finding of two mutual inhibitory systems – an "emotional/sensory brain" and a "rational brain" – in healthy and depressed patients. Both systems demonstrated excitatory intra-system connections and inhibitory inter-system influences. Compared with healthy controls, patients with MDD showed increased intra-system connections within the "emotional/sensory brain" and over-inhibition of the "rational brain" by the "emotional/sensory brain". In addition, the controlling role of the "rational brain" was impaired in MDD patients.

2. Methods and materials

2.1. Subjects

A total of 65 patients were recruited from the Department of Psychiatry in Xijing hospital from 2014 to 2018. 75 healthy controls were also recruited via advertisement. The current study was approved by the Ethics Committee of Xijing Hospital of the Fourth Military Medical University and conducted in accordance with the Declaration of Helsinki. It has been registered with the ClinicalTrials.gov database (reference number: NCT01516931). All the participants provided written informed consent after a detailed description of the aims and procedure of the study. Sixty-five male and female subjects were diagnosed as MDD by trained psychiatrists according to the International Classification of Diseases, 10th revision (ICD-10), or Diagnostic and Statistical Manual for Mental Disorders IV. Severity of depression and anxiety symptoms were accessed by the 24-item Hamilton Rating Scale for Depression (HAMD-24) and the Hamilton Anxiety Rating Scale (HAM-A), respectively. All MDD patients were enrolled for 8 weeks of antidepressant therapy. Patients were mainly treated with venlafaxine, a small number of patients received fluoxetine hydrochloride, paroxetine hydrochloride, escitalopram oxalate, sertraline hydrochloride in combination with the disease. At the same time, some patients also used a combination of anti-anxiety drugs. Following 8 weeks of antidepressant treatment, all patients were given the second assessment of severity of depression and anxiety symptoms. Clinically, it can be regarded as treatment effective (responder) when the ratio of score declines in behavioral scale more than 50 %, conversely, the patient was defined as non-responder.

2.2. Image acquisition

MRI images were collected in Xijing hospital with a 3.0 Tesla GE Discovery MR750 scanner. Resting-state fMRI images were acquired using a gradient-echo echo planar imaging sequence. For each subject, we obtained 210 resting-state scans in 7 min with the following parameters: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, field of view = 24 × 24 cm^2, slice thickness = 3.5 mm, slices = 45, matrix = 64 × 64. The subjects were instructed to lie still in the scanner and stay awake with their eyes closed. They were also interrogated after the experiment to confirm that they did fell asleep during the experiment. A high-resolution T1-weighted structural image was also acquired using a BRAVO sequence (repetition time = 8.2 ms, echo time = 3.2 ms, flip angle = 12°, field of view = 24 × 24 cm^2, slice thickness = 1 mm, slice = 196, matrix = 512 × 512).

2.3. Data preprocessing

MRI images were preprocessed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and DPARSF (http://www.fil.ion.ucl.ac.uk/spm/ext/#DPARSF) (Chao-Gan and Yu-Feng, 2010). The first 10 scans of the fMRI images were discarded for magnetic saturation. Slice timing and motion correction was then performed. The motion can be corrected by a simple rigid body shift. Using a reference image (usually the first or middle scanned image), estimate six correction parameters by three translations in the X, Y, Z directions and three rotations around the X, Y, and Z axes, aligning each individual image with the reference image. The six parameters estimated are the head motion parameters. Subjects with head motion parameters greater than 3 mm or 3° are generally considered to have excessive head motion. The T1-weighted structural image was co-registered to the functional images and segmented into gray matter, white matter and cerebrospinal fluid (CSF). The deformation field was then estimated and used to normalize the functional images to the Montreal Neurological Institute template. Consequently, the normalized fMRI images were spatially smoothed by using a Gaussian kernel of 6 mm^3 FWHM.

2.4. Group independent component analysis

In order to obtain the coordinates of the regions of interest (ROIs) in each resting-state network, group independent component analysis (ICA) was performed using the Group ICA of fMRI Toolbox (https://mialab.mrn.org/software/gift/index.html). The preprocessed images were decomposed into 27 spatially independent maps (independent components, ICs). The number of the ICs was estimated using the minimum description length criteria (Li et al., 2007). The ICs that best fit the spatial patterns of typical brain networks reported in the literature – and our previous studies – were selected (Li et al., 2013; Smith et al., 2009; Petersen and Posner, 2012). Eleven resting-state networks were identified, with the spatial patterns provided in Fig. 2 and the coordinates of the ROIs in these networks provided in Table 2.

2.5. Effective connectivity analysis

2.5.1. Dynamic causal modelling

Dynamic causal modelling (DCM) was introduced to study directed influences from one brain region to another during task performance (Friston et al., 2003). The capacity of DCM to study the underlying directed (causal) and recurrent interactions among hidden neuronal states makes it apt for elucidating signal propagation among brain regions. The propagation of neural activity signals between different brain regions, that is, the coupling of signals, is known as effective connectivity (Friston et al., 2003). In DCM, the causal or explanatory variables that make up the traditional design matrix become inputs, and the interaction parameters between the variables are measures of effective connectivity (Friston et al., 2003). We extended traditional deterministic DCM and developed stochastic DCM for fMRI; which models causal interactions among regions at rest (Li et al., 2011; Li et al., 2012). Recently, spectral DCM for resting-state fMRI was introduced as a simpler and more efficient approach to estimate effective connectivity, based on observed cross spectra (Friston et al., 2014). The spectral DCM was proposed by Friston et al in 2014 based on deterministic DCM (Friston et al., 2014). The advantage is that the connection parameters are pushed back in the frequency domain, which is more efficient and the result is more accurate. The high computational efficiency of spectral DCM now makes it possible to study large-scale resting-state networks that may comprise many (e.g., 32–64) regions (Razi et al., 2017).

In this study, we aimed to investigate large-scale resting-state effective connectivity in patients with MDD using spectral DCM. The causal interactions among different regions were modeled using the neuronal model (Friston et al., 2014):

$$\dot{x}(t) = Ax(t) + v(t) \quad (1)$$

where $\boldsymbol{x}(t) = [\ x_1(t), x_2(t), \ldots x_n(t)]$ denotes the hidden neuronal states of n interacting regions. The elements of matrix A are the effective connectivity parameters that represent the strength of the causal effects of one region on another. Specifically, the element A_{ij} means the influence of region j to region i. Additionally, $v(t)$ models endogenous fluctuations driving the system at rest. This neuronal model is supplemented with hemodynamic state equations that model the transformation of neuronal states into observed BOLD signals $y(t)$ (Friston et al., 2014):

$$y(t) = g(x,\theta) + e(t) \quad (2)$$

here, g is a nonlinear function of neuronal state x and parameter θ, while $e(t)$ represents the observation noise. Spectral DCM replaces the time series with their cross spectra and calculates the expected cross spectra as (Friston et al., 2014):

$$\begin{aligned} g_y(\omega,\theta) &= |K(\omega)|^2 g_v(\omega,\theta) + g_e(\omega,\theta) \\ g_v(\omega,\theta) &= \alpha_v \omega^{-\beta_v} \\ g_e(\omega,\theta) &= \alpha_e \omega^{-\beta_e} \end{aligned} \quad (3)$$

$g_v(\omega,\theta)$ and $g_e(\omega,\theta)$ are the spectral density of the endogenous fluctuations and observation noise, while $|K(\omega)|$ is a function of matrix A in equation (1). For a given model m, the model evidence $p(g(\omega)|m)$ and the posterior density of the parameters $p(\theta|g(\omega),m)$ are estimated using a standard Variational Laplace scheme 35.

2.5.2. Regions of interest

To extract regional BOLD time courses, a general linear model was specified with the following variables as multiple repressors: 1) motion parameters estimated when preprocessing the fMRI data; 2) the mean signal from the white matter at each time point calculated from the segmented T1 images and the preprocessed resting-state fMRI images; and 3) the mean signal from the CSF at each time point. The ensuing SPM was then used to extract the time course from each ROI which is a 6 mm sphere centered on the peak voxels/local maxima of the clusters in each resting-state network (Table 1). For each ROI, subject-specific time courses were extracted from the fMRI images by summarizing the first principle component of the time courses of voxels within that ROI. The locations of the ROIs and the time courses from representative regions are shown in Fig. 2.

2.5.3. Parametric empirical Bayes

A fully-connected model – which posits bidirectional connections between any pair of ROIs – was first specified for each subject. Spectral DCM was used to estimate model parameters of the fully-connected model. The commonalities and differences in effective connectivity between the MDD group and the controls were investigated using a hierarchical or Parametric Empirical Bayes (PEB) model (Moler, 2011). PEB is a Bayesian method used to estimate the prior distribution of parameters. It combines the advantages of empirical Bayesian method and Bayesian method to improve the accuracy and reliability of parameter estimation. This method can perform parameter estimation without prior knowledge, and can improve the accuracy of estimation by updating the prior distribution continuously.

After model estimation at the first level, the parameter estimates from all the subjects were then modeled at the group level using a (Bayesian) General Linear Model. In the current study, three covariates were included in the (Bayesian) General Linear Model: a constant covariate (ones) model the commonalities in effective connectivity between groups, a second covariate model the group differences and the third covariate model the effects of gender.

Table 1
Demographic and clinical characteristics at baseline.

Characteristics	Sample		*P*-value
	MDD patients (n = 43)	Healthy controls (n = 56)	
Age, Year, Mean (SD)	35.2 ± 11.2	32.1 ± 11.8	0.1721
Sex, (Female/Male)	30/13	26/30	0.02
Severity of depression (HAMD-24), Mean (SD)	23.4 ± 3.6	1.6 ± 3.7	<0.000
Severity of anxiety (HAM-A), Mean (SD)	18 ± 4.5	1.2 ± 1.8	<0.000

Table 2
The MNI coordinates of the ROIs included in the DCM analysis.

Resting-sate network	ROI	Brain region	MNI coordinates	IC
Default mode network1	DMN1	Cuneus_L	(0,-72,33)	IC1
Default mode network2	DMN2	Frontal_Sup_Medial_L	(−3,60,9)	IC11
Auditory network	AN1	Temporal_Sup_R	(60,-18,6)	IC14
	AN2	Temporal_Sup_L	(−60,-24,9)	IC14
Sensorimotor network	SMN1	Precuneus_L	(−3,-39,69)	IC18
	SMN2	Precentral_L	(−24,-24,69)	IC18
	SMN3	Precentral_R	(24,-21,69)	IC18
Salience network	SN1	Frontal_Mid_L	(-33,54,12)	IC26
	SN2	Frontal_Sup_R	(30,51,21)	IC26
	SN3	Cingulum_Ant_L	(−3,27,27)	IC26
Right CEN	CENR1	Frontal_Mid_R	(39,27,39)	IC15
	CENR2	Angular_R	(48,-60,39)	IC15
Left CEN	CENL1	Frontal_Mid_L	(−39,27,39)	IC8
	CENL2	Angular_L	(−51,-63,30)	IC8
Cerebellum	VERMIS	Vermis_10	(0,-45,-36)	IC19
Visual network 1	VN1	Calcarine_L	(0,-78,9)	IC3
Visual network 2	VN2	Cerebelum_Crus1_L	(−39,-72,-21)	IC9
	VN3	Occipital_Mid_R	(33,-81,15)	IC9
Dorsal attention network	DAN1	Frontal_Inf_Tri_L	(−51,21,21)	IC23
	DAN2	Frontal_Inf_Tri_R	(48,33,15)	IC23
	DAN3	Parietal_Inf_L	(-33,-69,42)	IC23
	DAN4	Angular_R	(36,-66,42)	IC23

2.5.4. "Controllers" identification

The PageRank (Kahneman, 2015) algorithm was then used to identify "controllers" in the effective connectivity networks of patients and healthy controls. The PageRank algorithm was originally used to identify important pages in the World Wide Web. The basic ideas behind this algorithm are: 1) a page is more important if more pages link to it; 2) a page is more important if other important pages link to it. In the current study, the PageRank algorithm was implemented using the Matlab software (centrality.m). For each subject, the PEB-updated connectivity parameters (GCM_updated.Ep.A) were extracted.[1] One-sample *t*-tests ($p < 0.05$) were then used to summarize the connectivity pattern for the control and patient group, respectively. Two subjects in the control group and one patient who demonstrated very high connectivity strength were considered as outliers and were excluded from further analysis. The "very high connectivity" was defined as the value of connectivity strength greater than $\mu + 3\sigma$ or less than μ-3σ, where μ is the sample mean and σ is the sample standard deviation. Subsequently, an adjacency matrix H was constructed for each group according to the results from one-sample *t*-tests. For each element H_{ij}, H_{ij} was set to 1 when the connection from the i_{th} ROI to the j_{th} ROI was significant (at the nominal level). Otherwise, H_{ij} was set to 0. PageRank algorithm was applied with the adjacency matrix H of each group, to identify "controllers" in the effective connectivity network.

3. Results

3.1. Demographic and clinical characteristics

Twenty-two patients were excluded from the current study. Detailed reasons for exclusion are shown in the Supplementary Fig. 1. The demographic and clinical characteristics of the remaining fifty-six healthy controls and forty-three patients were shown in Table 1. The mean age of the 43 patients with MDD was 35.2 years (SD = 11.2 years; range 17–61 years; 30 females), and they had an average HAMD-24 depression scale score of 23.4 (SD = 3.6) and average HAMA anxiety scale score of 18(SD = 4.5). The mean age of the 56 healthy controls was 32.1 years (SD = 11.8 years; range 19–61 years; 26 females). Their average HAMD-24 score and HAMA score was 1.6 (SD = 3.7) and 1.2(SD = 1.8), respectively. There were no significant baseline differences between healthy controls and MDD patients in age. However, there were significant baseline differences in sex, depression and anxiety symptoms ($p < 0.05$) (see Table 1).

3.2. Group independent component analysis

The group independent component analysis showed that the resting-state fMRI images were decomposed into 27 independent components. According to the results of the group independent component analysis, we chose 11 resting state networks and specified 22 ROIs for further DCM analysis. The spatial patterns of these resting-state networks are shown in Fig. 1. The MNI coordinates of the ROIs are shown in Table 2, while the locations of these ROIs and time courses from representative regions are displayed in Fig. 2.

3.3. Commonalities in effective connectivity

The commonalities (across diagnostic groups) in large-scale effective connectivity are shown in Fig. 3. Fig. 3(a), 3(b) and 3(c) depict excitatory connectivity, while Fig. 3(d), 3(e), 3(f) show inhibitory influences. According to Fig. 3, the 11 networks appear to form two distinct systems: DMN2, AN, SmN, SN, VN1, and VN2 formed the first system, with regions in these networks being tightly and positively connected. The DMN1, left CEN, right CEN, Cerebellum and DAN formed a second system, with excitatory influences among regions within this system (Fig. 3(a), (b), (c)). In addition to excitatory connections within each system, there was strong evidence for negative (inhibitory) influences between systems (i.e., a posterior probability of greater than 95 %, based upon the free energy bound on log evidence — or marginal likelihood — for models with and without the connections in question) (Fig. 3(d), 3 (e), 3(f)).

3.4. Altered effective connectivity in MDD

Fig. 4 illustrates the second effect in the PEB model, which modelled group differences in effective connectivity. Connections that were decreased in patients are shown in Fig. 4(a)-(c), while connections that were increased in patients are shown in Fig. 4(d)-(f). Individuals with MDD demonstrated reduced connectivity from DMN2 to DAN, from AN to left and right CEN, from SmN to DMN1 and CENs, from SN to DMNs and left CEN, from VNs to DMN1, SN and CENs, from DMN1 to SN and DAN, from right CEN to AN, from cerebellum network to AN and SN, from DAN to AN, SmN, SN and VN2. The majority of these connections were inter-system connections (Fig. 4(a), 4(b)). Fig. 4(c) showed the strength of the top 10 decreased connections in controls and patients with a violin plot. Two outliers – that demonstrated very high strength of connections in the control group – and one outlier in the patient group were excluded. MDD patients also showed increased connectivity from AN to SmN, SN, VN, and DAN, from SN to AN, VN and DAN, from CENs to VN and SmN, from VN2 to SmN, from DAN to DAN and right CEN. The majority of these connections were intra-system connections (Fig. 4(d), 4(e)). Fig. 4(f) reports the strength of the top 10 increased connections in controls and patients (with outliers excluded) with the violin plot.

3.5. "Controller" in large-scale effective connectivity networks

Fig. 5 shows the PageRank values of all the 22 ROIs in controls and patients. The "controllers" in the effective connectivity network for healthy controls are mainly regions in the second system in the CENs and DAN including CENR1(Frontal_Mid_R), CENR2(Angular_R), CENL1 (Frontal_Mid_L), DAN4(Angular_R), DAN3(Parietal_Inf_L). In addition, SMN3(Precentral_R) was also identified as a "controller" in healthy controls. However, the PageRank values of the CENs and the DAN were

[1] These updated parameters inherit empirical shrinkage priors from the between-subject or group level of the parametric or empirical Bayes model.

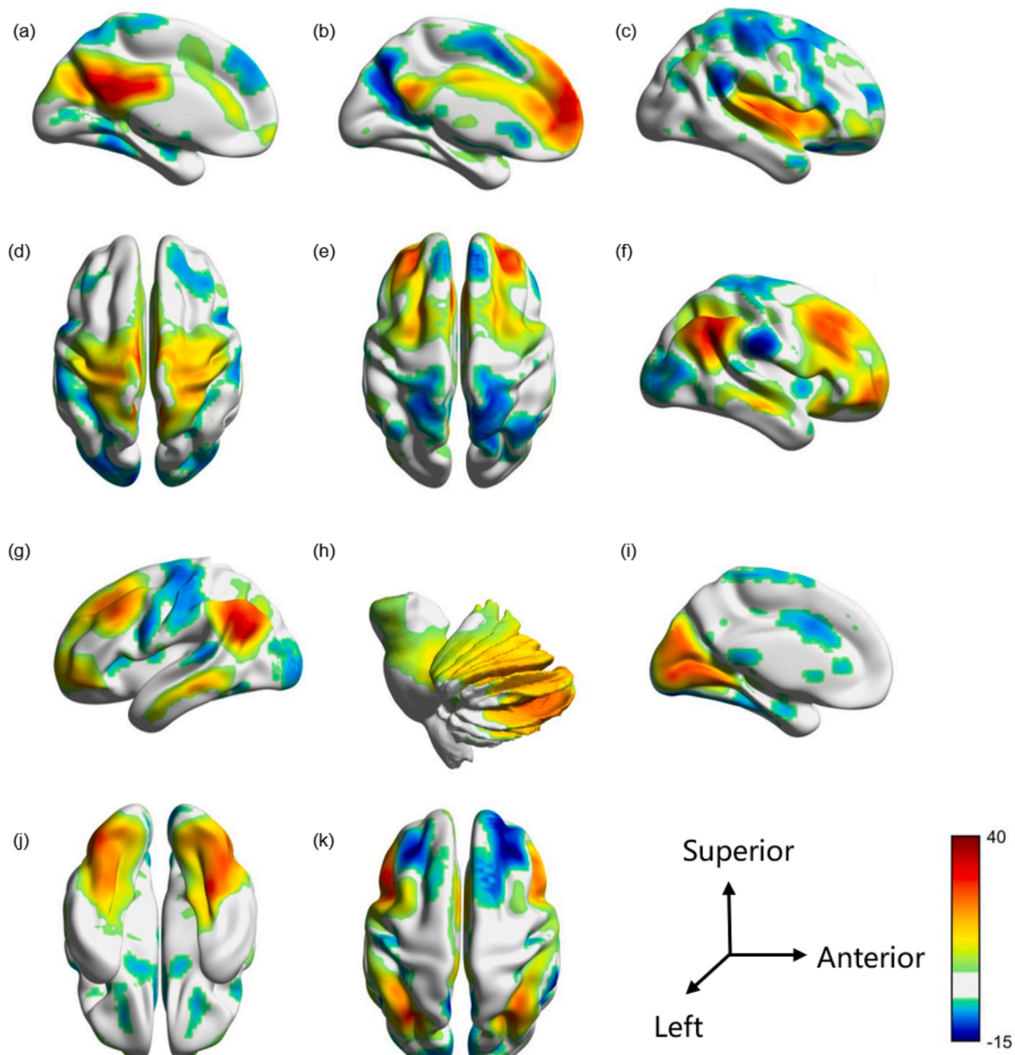

Fig. 1. The spatial patterns of resting-state networks. (a) The posterior default mode subnetwork(DMN1); (b)The anterior default mode subnetwork(DMN2); (c) The auditory network; (d) The sensorimotor network; (e) The salience network; (f) The right central executive network; (g) The left central executive network; (h)The cerebellum; (i) Visual network 1;(j) Visual network 2; (k) The dorsal attention network.

much lower in patients with MDD. In contrast, the PageRank values of networks in the first system including the anterior DMN, AN, SN and VNs were much higher in the patient group. In summary, the results from the PageRank analyses suggested that the resting-state effective connectivity network was controlled by CENs and DAN in healthy controls. However, the controlling role of these networks seemed to shift toward the emotional and sensory processing networks in the patients.

4. Discussion

In the current study, we quantified signal propagation between eleven large-scale brain networks in patients with MDD using DCM. Three main findings emerge from the current study: 1) according to the pattern of effective connectivity, we found that the 11 large-scale brain networks form two mutual inhibitory systems in healthy controls and patients with MDD. Both systems exhibited excitatory intra-system connectivity and inhibitory inter-system influences in the context of higher alpha power during eyes-closed resting state; 2) compared with healthy controls, patients with MDD exhibited increased intra-system connectivity and decreased inter-system connectivity; 3) the PageRank algorithm revealed a shift of the controlling role of the CEN and DAN to the DMN, SN, AN and VN in the patients.

4.1. Two mutual inhibitory systems in the brain

According to the effective connectivity patterns, the 11 resting-state networks formed two mutual inhibitory systems, with excitatory intra-system connections and inhibitory inter-system connections observed in both subject groups. We designated the first system as a “rational brain” since it mainly encompassed networks that were associated with cognitive control and attention such as bilateral CEN and the DAN. On the contrary, we would refer the second system as an “emotional/sensory brain”, since it mainly included networks (the DMN, AN, SmN, SN, VN1, and VN2) that were involved in processing of emotional and sensory stimuli. The results clearly showed the existence of two mutual inhibitory systems in controls and patients. Given that the patterns of the dynamic interactions among large-scale networks were essential for the emergence of cognition functions (Bressler and Menon, 2010), the results of the current study may provide novel insights into the brain’s functional architecture.

The excitatory connections among regions within the same system may furnish quick responses to accomplish specific tasks, while the inhibitory inter-system connections may reflect the antagonism between the “emotional/sensory brain” and “rational brain” (Agcaoglu et al., 2019). As noted by one of our reviewers, this kind of ‘antagonism’ may

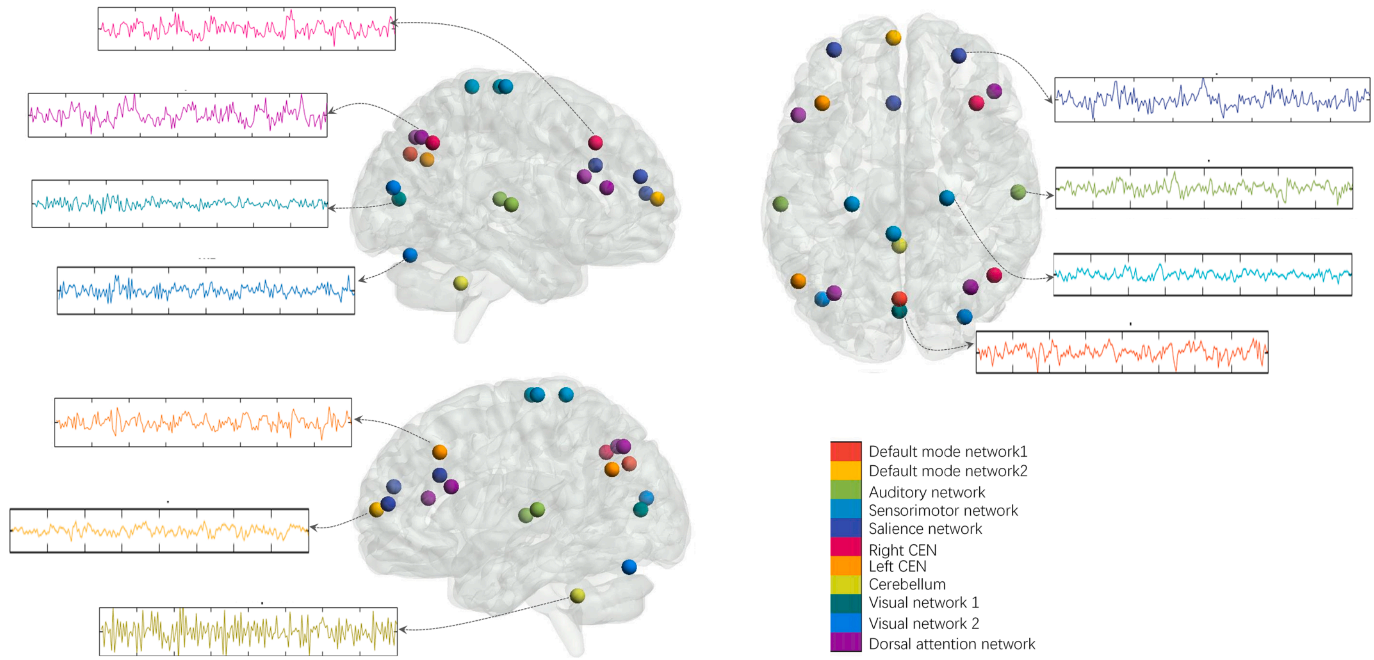

Fig. 2. The locations of the ROIs and the time course of a representative ROI for each of the large-scale networks. Nodes with the same color indicate that they belong to the same brain network, while nodes in different brain networks have different colors.

reflect an important aspect of functional integration; namely, the instantiation of attentional or intentional set. For example, when formulating functional integration in terms of hierarchical predictive coding, the mutual inhibition of 'emotional' and 'rational' systems may reflect the (reciprocal) selection of ascending afferents by the cognitive areas. In resting state fMRI — because the participants have their eyes closed — ascending afferents from the visual cortex to higher-order brain regions are attenuated; however, this attenuation itself rests on descending (cognitive control) predictions that the eyes are closed. Interestingly, in (Friston et al., 2014), the eyes closed condition increased the connectivity of the visual system with low level auditory and sensorimotor regions, which decreased when the eyes were open. This is consistent with notions of cognitive control that rest on (neuromodulatory) attenuation of gain (i.e., the precision) of ascending prediction errors (Parr and Friston, 2017; Kanai et al., 2015; Stange et al., 2017).

4.2. Decreased inter-system connectivity and increased intra-system connectivity in MDD

Using DCM, we verified the hypothesis that signal propagation within core brain networks mediating sensory, motor, emotion, cognitive control, self-referential processing disrupted in MDD patients. Compared with healthy controls, patients with MDD demonstrated significantly decreased inter-system connectivity (Fig. 4a, 4b). The most notable differences were the reduction in the connections from several networks of the "emotional/sensory brain" including the AN, SmN, SN and VNs to the CENs of the "rational brain". Since the majority of these connections were negative in the patients representing inhibitory influences on the target region (Fig. 4c), reduced connections to the CENs would result in over-inhibition of the cognitive controls systems in the patients. This may explain hypo- activation and connectivity of the CENs consistently reported in patients with depression (Aizenstein et al., 2009; Baxter et al., 1989; Phillips et al., 2003). Studies have suggested that adaptive emotion regulation depends largely upon the effectively regulate of the SN by the CENs (Phillips et al., 2003; Pan et al., 2021). However, over-inhibition of the CEN appeared to further disrupt its competition with the "emotional/sensory brain" (Fig. 4d), with excitatory connections observed between these antagonistically coupled network in the patients (Fig. 4f). The results of the current study are consistent with the previous voxel-based functional connectivity results of the whole brain, that is, the areas in frontal-parietal, insula, and SmN in MDD patients showed significant functional connectivity abnormalities (Cui et al., 2018; Berlim et al., 2014). The effective connection further shows the direction of the abnormal signal transmission. Our results may explain the antidepressant action of rTMS (Noda et al., 2015); which normalized the activation of the CEN through repetitive transcranial magnetic stimulation of this network (Sheline et al., 2010). Interestingly, the patients seemed to regulate the activity of the SN by compensatory mechanisms through potentiated inhibitory influences from the DAN and cerebellum (Fig. 4a, 4b, 4c).

On the contrary, increased effective connectivity in the patients implicated primarily intra-system connections within the "emotional/sensory brain". Our findings concur with previous studies that have reported increased functional connectivity within this system. An early study by Sheline et al reported increased functional connectivity between the DMN and SN (Hamilton et al., 2015). Elevated DMN-SN functional connectivity was then confirmed by a *meta*-analysis study (Gotlib et al., 2004) and recently replicated with a large multisite dataset (Yu et al., 2019). In addition to increased connectivity of the SN, we found consistently elevated excitatory connectivity of the AN to SmN, SN and VNs in the patients, suggesting increased sensitivity of the extended emotional/sensory brain to external auditory stimuli. Disrupted large-scale effective connectivity patterns in the patients were also characterized by increased excitatory connections of the DAN. The connections from AN and SN to DAN and those from DAN to right CEN were elevated in the MDD group. This is in line with a recent study, which observed enhanced functional connectivity between the DAN and the CEN in patients (Yu et al., 2019). Elevated connectivity of the attention network may be associated with prominent negative attention bias in depression (Liu et al., 2019). In fact, stochastic DCM analysis of resting-state fMRI data from 216 healthy adolescents showed that stronger connectivity of the attention network was associated with higher self-reported depression (Badre, 2008). Thus, impaired effective connectivity patterns of large-scale networks were characterized by potentiated intra-system connections within the extended emotional/

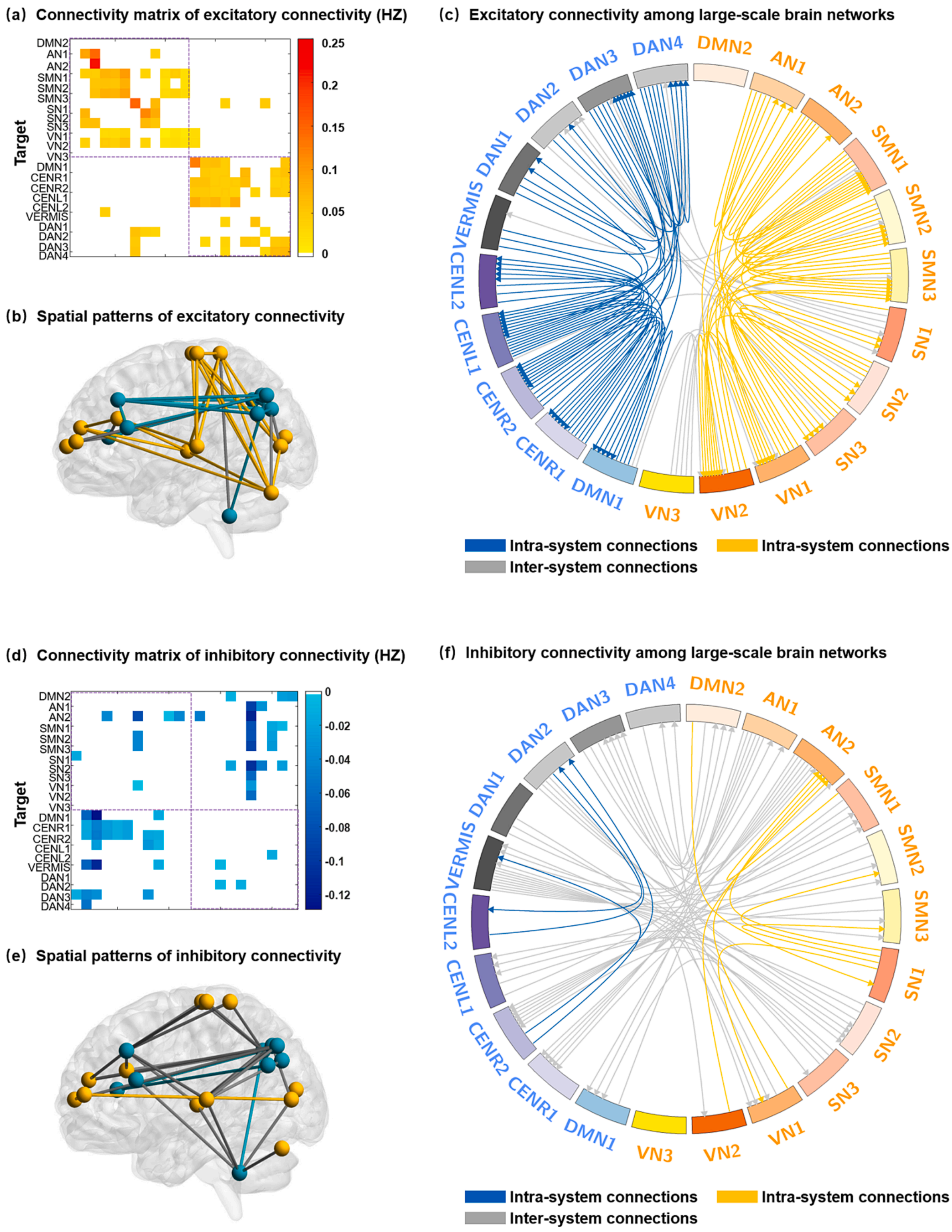

Fig. 3. Commonalities in large-scale effective connectivity in controls and patients with MDD. (a)-(c) Excitatory connectivity among large-scale brain networks, (d)-(f) Inhibitory influences among large-scale brain networks.

sensory brain that may result in increased sensitivity to external stimuli and hyperactivation of the emotional system, as well as over-inhibition of the extended rational brain by the extended emotional/sensory brain that may cause failure on top-down regulation of the emotion processing.

4.3. Shifting of the controlling role of the "rational brain" toward the "emotional/sensory brain"

The DCM analysis identified the pathways of signal propagation among distributed large-scale brain networks, which was then be used to further delineate the hierarchical architecture of these networks. In the current study, we paid special attention to putative "controllers" in the large-scale effective connectivity networks in healthy volunteers and MDD patients, respectively. The PageRank Algorithm revealed that the "controllers" in healthy volunteers were mainly nodes in the CEN, DAN and SmN (Fig. 5a). These findings are in line with previous studies that have identified the CEN and DAN as the "controllers" during cognitive control (Dosenbach et al., 2008), emotion regulation (Phillips et al., 2003) and attention control (Corbetta and Shulman, 2002). However, the controlling role of the CEN and DAN may be subverted in patients with MDD (Fig. 5b). The PageRank values of nodes in several networks

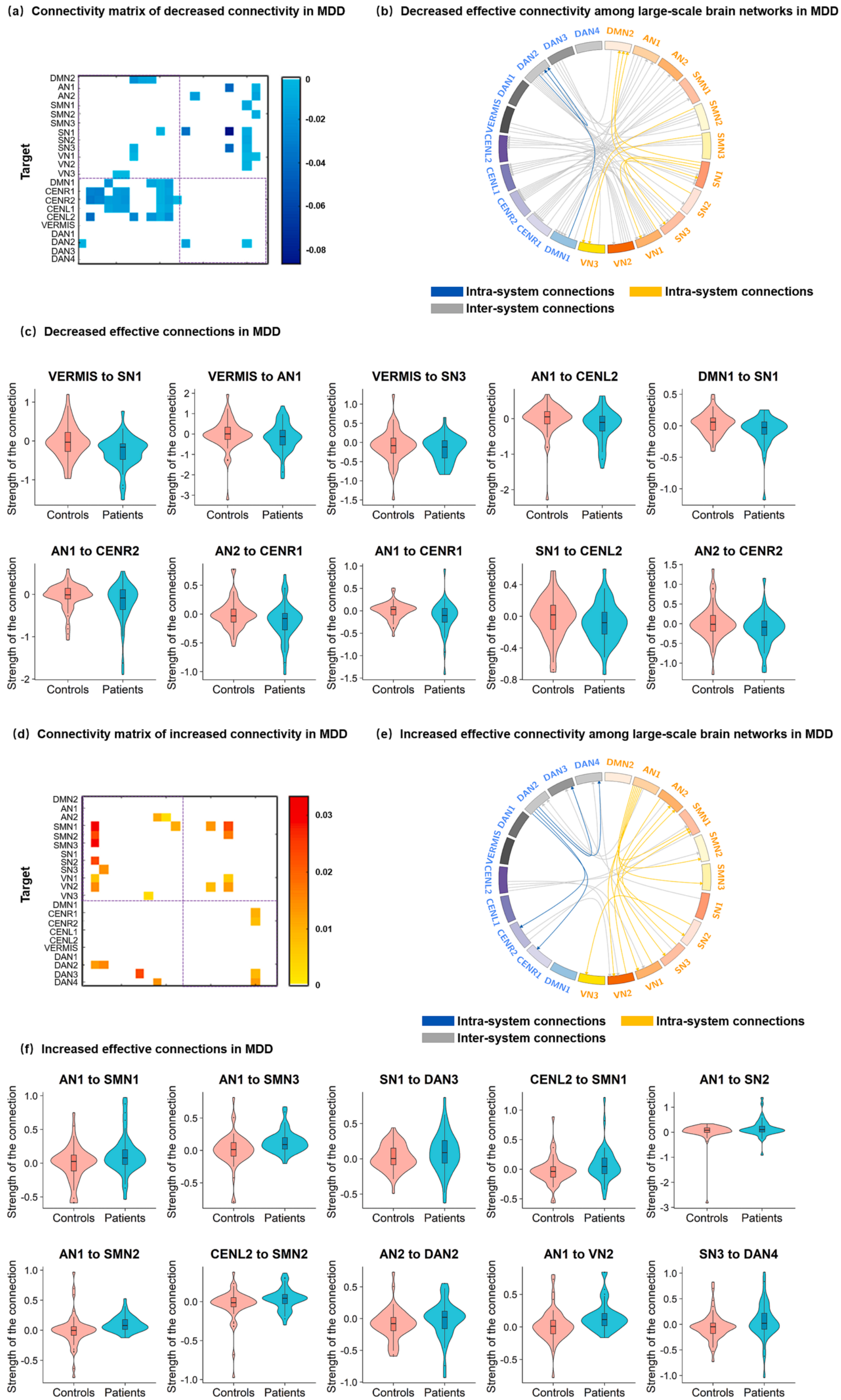

Fig. 4. Altered large-scale effective connectivity in patients with MDD. (a)-(b) Patterns of decreased connectivity in MDD patients. (c) Violin plot showing the strength of the top 10 decreased connections in controls and patients. (d)-(e) Patterns of increased connectivity in MDD patients. (f) Violin plot showing the strength of the top 10 increased connections in controls and patients.

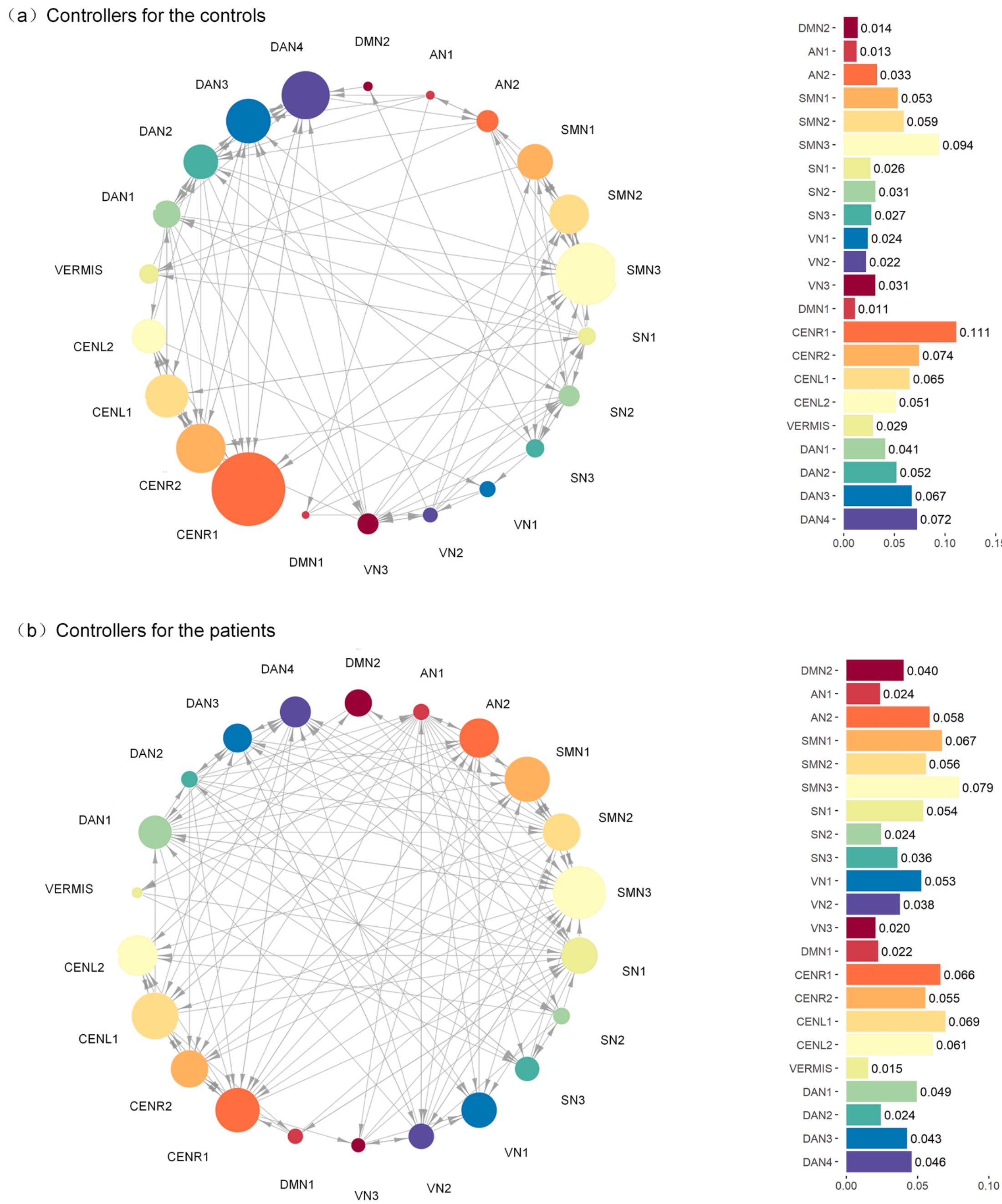

Fig. 5. The "controllers" in the effective connectivity networks of controls and MDD patients. (a) The "controllers" and the PageRank value of each node in healthy controls. The size of the node is proportional to its PageRank value. (b) The "controllers" and the PageRank value of each node in MDD patients.

of the "emotional/sensory brain" including the DMN2, AN, SN, VNs were increased, while the PageRank values of the networks such as the right CEN and DAN of the "rational brain" were decreased. The results suggested that the controlling role of the "rational brain" was shifted toward the "emotional/sensory brain" in the patients, which may result in insufficient cognitive control of emotion and other functions in these patients.

However, there are some limitations in our study. First, this is a preliminary study with a relatively small sample size. It would be nice to see future studies reproduce the findings in the current study, with multi-site large datasets. Second, the subjects were scanned with their eyes closed on MRI. It is reported that connectivity of visual systems to other networks exhibits significant differences between eyes opened and eyes closed (Friston et al., 2014). Our results need to be replicated on another dataset which subjects with their eyes opened when scanning. Finally, the large-scale networks we studied did not involve subcortical regions. The relationship between these two systems and our experimental results still needs to be further explored. In the future, we plan to study signal propagation across the whole brain, including subcortical regions, in patients with major depression.

To conclude, we delineated large-scale effective connectivity networks in patients with MDD, which revealed the existence of two mutual inhibitory systems: the "emotional/sensory brain" and "rational brain". Patients with MDD were characterized by increased intra-system connectivity and decreased inter-system connectivity. When analyzing the hierarchical architecture of these large-scale effective connectivity network, we found that the controlling role of the "rational brain" appeared to shift toward the "emotional/sensory brain" in the patients.

The findings of the current study provide novel insights into the neural mechanisms of depression.

CRediT authorship contribution statement

Jia Wang: Data curation, Formal analysis, Visualization, Writing – original draft, Validation. **Baojuan Li:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing, Investigation. **Jian Liu:** Data curation, Formal analysis, Visualization, Writing – original draft, Validation. **Jiaming Li:** Formal analysis, Methodology, Visualization. **Adeel Razi:** Conceptualization, Methodology. **Kaizhong Zheng:** Data curation, Formal analysis, Methodology. **Baoyu Yan:** Formal analysis, Supervision, Visualization. **Huaning Wang:** Data curation, Project administration, Resources, Supervision. **Hongbing Lu:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Karl Friston:** Conceptualization, Methodology, Writing – review & editing.

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.

Data availability

Data will be made available on request.

Acknowledgments

This study was funded by the National Natural Science Foundation of China (61976248, 81301199, 81371478, 61503411), the National Key R&D Program of China (2016YFC1307100, 2017YFC0107400), Key Science and Technology Program of Shaanxi Province (2017ZDXM-SF-047)s Wellcome Principal Research Fellowship (Ref: 088130/Z/09/Z).

Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103556.

References

Agcaoglu, O., Wilson, T.W., Wang, Y.P., Stephen, J., Calhoun, V.D., 2019. Resting state connectivity differences in eyes open versus eyes closed conditions. Hum. Brain Mapp. 40, 2488–2498.
Aizenstein, H.J., Butters, M.A., Wu, M., Mazurkewicz, L.M., Stenger, V.A., Gianaros, P.J., Becker, J.T., Reynolds 3rd, C.F., Carter, C.S., 2009. Altered functioning of the executive control circuit in late-life depression: episodic and persistent phenomena. Am. J. Geriatr. Psychiatry 17, 30–42.
Avissar, M., Powell, F., Ilieva, I., Respino, M., Gunning, F.M., Liston, C., Dubin, M.J., 2017. Functional connectivity of the left DLPFC to striatum predicts treatment response of depression to TMS. Brain Stimul. 10, 919–925.
Badre, D., 2008. Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. Trends Cogn. Sci. 12, 193–200.
Baxter Jr., L.R., Schwartz, J.M., Phelps, M.E., Mazziotta, J.C., Guze, B.H., Selin, C.E., Gerner, R.H., Sumida, R.M., 1989. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch. Gen. Psychiatry 46, 243–250.
Berlim, M.T., van den Eynde, F., Tovar-Perdomo, S., Daskalakis, Z.J., 2014. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol. Med. 44, 225–239.
Bressler, S.L., Menon, V., 2010. Large-scale brain networks in cognition: emerging methods and principles. Trends Cogn. Sci. 14, 277–290.
Chao-Gan, Y., Yu-Feng, Z., 2010. DPARSF: A MATLAB Toolbox for "Pipeline" Data Analysis of Resting-State fMRI. Front. Syst. Neurosci. 4, 13.
Cheng, W., Rolls, E.T., Qiu, J., Liu, W., Tang, Y., Huang, C.C., Wang, X., Zhang, J., Lin, W., Zheng, L., Pu, J., Tsai, S.J., Yang, A.C., Lin, C.P., Wang, F., Xie, P., Feng, J., 2016. Medial reward and lateral non-reward orbitofrontal cortex circuits change in opposite directions in depression. Brain J. Neurol. 139, 3296–3309.
Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215.
Cui, X., Liu, F., Chen, J., Xie, G., Wu, R., Zhang, Z., Chen, H., Zhao, J., Guo, W., 2018. Voxel-wise brain-wide functional connectivity abnormalities in first-episode, drug-naive patients with major depressive disorder. Am. J. Med. Genet. B Neuropsychiatr. Genet. 177, 447–453.
Dalgleish, T., 2004. The emotional brain. Nat. Rev. Neurosci. 5, 583–589.
Damoiseaux, J.S., Rombouts, S.A., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F., 2006. Consistent resting-state networks across healthy subjects. PNAS 103, 13848–13853.
Davey, C.G., Whittle, S., Harrison, B.J., Simmons, J.G., Byrne, M.L., Schwartz, O.S., Allen, N.B., 2015. Functional brain-imaging correlates of negative affectivity and the onset of first-episode depression. Psychol. Med. 45, 1001–1009.
Di Plinio, S., Ferri, F., Marzetti, L., Romani, G.L., Northoff, G., Pizzella, V., 2018. Functional connections between activated and deactivated brain regions mediate emotional interference during externally directed cognition. Hum. Brain Mapp.
Dosenbach, N.U., Fair, D.A., Cohen, A.L., Schlaggar, B.L., Petersen, S.E., 2008. A dual-networks architecture of top-down control. Trends Cogn. Sci. 12, 99–105.
Friedrich, M.J., 2017. Depression Is the Leading Cause of Disability Around the World. J. Am. Med. Assoc. 317, 1517.
Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. Neuroimage 19, 1273–1302.
Friston, K.J., Kahan, J., Biswal, B., Razi, A., 2014. A DCM for resting state fMRI. Neuroimage 94, 396–407.
Friston, K., Schwartenbeck, P., FitzGerald, T., Moutoussis, M., Behrens, T., Dolan, R.J., 2014. The anatomy of choice: dopamine and decision-making. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369.
Gotlib, I.H., Krasnoperova, E., Yue, D.N., Joormann, J., 2004. Attentional biases for negative interpersonal stimuli in clinical depression. J. Abnorm. Psychol. 113, 121–135.
Goulden, N., McKie, S., Thomas, E.J., Downey, D., Juhasz, G., Williams, S.R., Rowe, J.B., Deakin, J.F., Anderson, I.M., Elliott, R., 2012. Reversed frontotemporal connectivity during emotional face processing in remitted depression. Biol. Psychiatry 72, 604–611.
Hamilton, J.P., Farmer, M., Fogelman, P., Gotlib, I.H., 2015. Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. Biol. Psychiatry.
Hanning, N.M., Fernández, A., Carrasco, M., 2023. Dissociable roles of human frontal eye fields and early visual cortex in presaccadic attention. Nat. Commun. 14, 5381.
Ho, T.C., Connolly, C.G., Henje Blom, E., LeWinn, K.Z., Strigo, I.A., Paulus, M.P., Frank, G., Max, J.E., Wu, J., Chan, M., Tapert, S.F., Simmons, A.N., Yang, T.T., 2014. Emotion-Dependent Functional Connectivity of the Default Mode Network in Adolescent Depression. Biol. Psychiatry.
Ho, T.C., Connolly, C.G., Henje Blom, E., LeWinn, K.Z., Strigo, I.A., Paulus, M.P., Frank, G., Max, J.E., Wu, J., Chan, M., Tapert, S.F., Simmons, A.N., Yang, T.T., 2015. Emotion-Dependent Functional Connectivity of the Default Mode Network in Adolescent Depression. Biol. Psychiatry 78, 635–646.
Kahneman D: Thinking, fast and slow 2015.
Kaiser, R.H., Andrews-Hanna, J.R., Spielberg, J.M., Warren, S.L., Sutton, B.P., Miller, G. A., Heller, W., Banich, M.T., 2015. Distracted and down: neural mechanisms of affective interference in subclinical depression. Soc. Cogn. Affect. Neurosci. 10, 654–663.
Kanai, R., Komura, Y., Shipp, S., Friston, K., 2015. Cerebral hierarchies: predictive processing, precision and the pulvinar. Philos. Trans. R. Soc. Lond. B Biol. Sci. 370.
Kerestes, R., Harrison, B.J., Dandash, O., Stephanou, K., Whittle, S., Pujol, J., Davey, C. G., 2015. Specific functional connectivity alterations of the dorsal striatum in young people with depression. NeuroImage Clinical. 7, 266–272.
Leerssen, J., Aghajani, M., Bresser, T., Rösler, L., Winkler, A.M., Foster-Dingley, J.C., Van Someren, E.J.W., 2023. Cognitive, behavioral, and circadian rhythm interventions for insomnia alter emotional brain responses. Biol. Psych. Cognit. Neurosci. Neuroimag.
Levkovitz, Y., Isserles, M., Padberg, F., Lisanby, S.H., Bystritsky, A., Xia, G., Tendler, A., Daskalakis, Z.J., Winston, J.L., Dannon, P., Hafez, H.M., Reti, I.M., Morales, O.G., Schlaepfer, T.E., Hollander, E., Berman, J.A., Husain, M.M., Sofer, U., Stein, A., Adler, S., Deutsch, L., Deutsch, F., Roth, Y., George, M.S., Zangen, A., 2015. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psych. Off. J. World Psych. Assoc. 14, 64–73.
Li, Y.O., Adali, T., Calhoun, V.D., 2007. Estimating the number of independent components for functional magnetic resonance imaging data. Hum. Brain Mapp. 28, 1251–1266.
Li, J., Chen, J., Kong, W., Li, X., Hu, B., 2022. Abnormal core functional connectivity on the pathology of MDD and antidepressant treatment: A systematic review. J. Affect. Disord. 296, 622–634.
Li, B., Daunizeau, J., Stephan, K.E., Penny, W., Hu, D., Friston, K., 2011. Generalised filtering and stochastic DCM for fMRI. Neuroimage 58, 442–457.
Li, B., Wang, X., Yao, S., Hu, D., Friston, K., 2012. Task-dependent modulation of effective connectivity within the default mode network. Front. Psychol. 3, 206.
Li, B., Liu, L., Friston, K.J., Shen, H., Wang, L., Zeng, L.L., Hu, D., 2013. A treatment-resistant default mode subnetwork in major depression. Biol. Psychiatry 74, 48–54.

Liu, J., Xu, P., Zhang, J., Jiang, N., Li, X., Luo, Y., 2019. Ventral attention-network effective connectivity predicts individual differences in adolescent depression. J. Affect. Disord. 252, 55–59.
Lozano, A.M., Lipsman, N., 2013. Probing and regulating dysfunctional circuits using deep brain stimulation. Neuron 77, 406–424.
Malhi, G.S., Mann, J.J., 2018. Depression. Lancet 392, 2299–2312.
Manelis, A., Almeida, J.R., Stiffler, R., Lockovich, J.C., Aslam, H.A., Phillips, M.L., 2016. Anticipation-related brain connectivity in bipolar and unipolar depression: a graph theory approach. Brain J. Neurol. 139, 2554–2566.
Meng, C., Brandl, F., Tahmasian, M., Shao, J., Manoliu, A., Scherr, M., Schwerthoffer, D., Bauml, J., Forstl, H., Zimmer, C., Wohlschlager, A.M., Riedl, V., Sorg, C., 2014. Aberrant topology of striatum's connectivity is associated with the number of episodes in depression. Brain J. Neurol. 137, 598–609.
Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn. Sci. 15, 483–506.
Mitra, A., Raichle, M.E., Geoly, A.D., Kratter, I.H., Williams, N.R., 2023. Targeted neurostimulation reverses a spatiotemporal biomarker of treatment-resistant depression. PNAS 120.
Moler C: Chapter 7:Google PageRank. in Experiments with MATLAB, MathWorks, Inc.; 2011.
Nemeroff, C.B., 2007. Prevalence and management of treatment-resistant depression. J. Clin. Psychiatry 68 (Suppl 8), 17–25.
Noda, Y., Silverstein, W.K., Barr, M.S., Vila-Rodriguez, F., Downar, J., Rajji, T.K., Fitzgerald, P.B., Mulsant, B.H., Vigod, S.N., Daskalakis, Z.J., Blumberger, D.M., 2015. Neurobiological mechanisms of repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex in depression: a systematic review. Psychol. Med. 45, 3411–3432.
Pan, P., Wang, L., Wu, C., Jin, K., Cao, S., Qiu, Y., Teng, Z., Li, S., Shao, T., Huang, J., Wu, H., Xiang, H., Chen, J., Liu, F., Tang, H., Guo, W., 2021. Global functional connectivity analysis indicating dysconnectivity of the hate circuit in major depressive disorder. Front. Aging Neurosci. 13, 803080.
Parr, T., Friston, K.J., 2017. Working memory, attention, and salience in active inference. Sci. Rep. 7, 14678.
Petersen, S.E., Posner, M.I., 2012. The attention system of the human brain: 20 years after. Annu. Rev. Neurosci. 35, 73–89.
Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R., 2003. Neurobiology of emotion perception I: The neural basis of normal emotion perception. Biol. Psychiatry 54, 504–514.
Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R., 2003. Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biol. Psychiatry 54, 515–528.
Quidé, Y., Norman-Nott, N., Hesam-Shariati, N., McAuley, J.H., Gustin, S.M., 2023. Depressive symptoms moderate functional connectivity within the emotional brain in chronic pain. Bjpsych Open. 9, e80.
Razi, A., Seghier, M.L., Zhou, Y., McColgan, P., Zeidman, P., Park, H.J., Sporns, O., Rees, G., Friston, K.J., 2017. Large-scale DCMs for resting-state fMRI. Network Neurosci. (Cambridge, Mass). 1, 222–241.
Ruff, C.C., Blankenburg, F., Bjoertomt, O., Bestmann, S., Freeman, E., Haynes, J.D., Rees, G., Josephs, O., Deichmann, R., Driver, J., 2006. Concurrent TMS-fMRI and psychophysics reveal frontal influences on human retinotopic visual cortex. Curr. Biol. 16, 1479–1488.
Sacchet, M.D., Ho, T.C., Connolly, C.G., Tymofiyeva, O., Lewinn, K.Z., Han, L.K., Blom, E. H., Tapert, S.F., Max, J.E., Frank, G.K., Paulus, M.P., Simmons, A.N., Gotlib, I.H., Yang, T.T., 2016. Large-scale hypoconnectivity between resting-state functional networks in unmedicated adolescent major depressive disorder. Neuropsychopharmacology 41, 2951–2960.
Satterthwaite, T.D., Kable, J.W., Vandekar, L., Katchmar, N., Bassett, D.S., Baldassano, C. F., Ruparel, K., Elliott, M.A., Sheline, Y.I., Gur, R.C., Gur, R.E., Davatzikos, C., Leibenluft, E., Thase, M.E., Wolf, D.H., 2015. Common and dissociable dysfunction of the reward system in bipolar and unipolar depression. Neuropsychopharmacology 40, 2258–2268.
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. PNAS 107, 11020–11025.
Simmons, W.K., Burrows, K., Avery, J.A., Kerr, K.L., Bodurka, J., Savage, C.R., Drevets, W.C., 2016. Depression-Related Increases and Decreases in Appetite: Dissociable Patterns of Aberrant Activity in Reward and Interoceptive Neurocircuitry. Am. J. Psychiatry 173, 418–428.
Smith, K., 2014. Mental health: a world of depression. Nature 515, 181.
Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R., Beckmann, C.F., 2009. Correspondence of the brain's functional architecture during activation and rest. PNAS 106, 13040–13045.
Stange, J.P., Bessette, K.L., Jenkins, L.M., Peters, A.T., Feldhaus, C., Crane, N.A., Ajilore, O., Jacobs, R.H., Watkins, E.R., Langenecker, S.A., 2017. Attenuated intrinsic connectivity within cognitive control network among individuals with remitted depression: Temporal stability and association with negative cognitive styles. Hum. Brain Mapp. 38, 2939–2954.
Yu, M., Linn, K.A., Shinohara, R.T., Oathes, D.J., Cook, P.A., Duprat, R., Moore, T.M., Oquendo, M.A., Phillips, M.L., McInnis, M., Fava, M., Trivedi, M.H., McGrath, P., Parsey, R., Weissman, M.M., Sheline, Y.I., 2019. Childhood trauma history is linked to abnormal brain connectivity in major depression. PNAS 116, 8582–8590.