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Original Article

ORIGINAL ARTICLE

Reconfiguration of Cortical Networks in MDD Uncovered by Multiscale Community Detection with fMRI

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Abstract

Major depressive disorder (MDD) is known to be associated with altered interactions between distributed brain regions. How these regional changes relate to the reorganization of cortical functional systems, and their modulation by antidepressant medication, is relatively unexplored. To identify changes in the community structure of cortical functional networks in MDD, we performed a multiscale community detection algorithm on resting-state functional connectivity networks of unmedicated MDD (uMDD) patients ($n = 46$), medicated MDD (mMDD) patients ($n = 38$), and healthy controls ($n = 50$), which yielded a spectrum of multiscale community partitions. we selected an optimal resolution level by identifying the most stable community partition for each group. uMDD and mMDD groups exhibited a similar reconfiguration of the community structure of the visual association and the default mode systems but showed different reconfiguration profiles in the frontoparietal control (FPC) subsystems. Furthermore, the central system (somatomotor/salience) and 3 frontoparietal subsystems showed strengthened connectivity with other communities in uMDD but, with the exception of 1 frontoparietal subsystem, returned to control levels in mMDD. These findings provide evidence for reconfiguration of specific cortical

functional systems associated with MDD, as well as potential effects of medication in restoring disease-related network alterations, especially those of the FPC system.

Key words: Antidepressant, Functional Connectivity, Graph Theory, MDD, Resting-state fMRI

Introduction

Many neuroimaging studies have demonstrated that major depressive disorder (MDD) is associated with altered functional and structural connectivity of distributed brain regions (Sheline et al. 2010; Zeng et al. 2012; Dutta et al. 2014; Korgaonkar et al. 2014; Gong and He 2015; Mulders et al. 2015). Altered connections include those mediating interactions within and between multiple brain systems supporting several specific functions, such as emotion, attention, cognitive control, and self-referential processing. Furthermore, the neuropathology of MDD involves disrupted interactions between different brain systems (Drevets 2001; Price and Drevets 2010). Therefore, MDD may be thought of as a "network disease," where a small local change may lead to global dysfunction expressed across the whole brain (Fornito et al. 2015).

The dysfunction of 3 systems are particularly relevant to MDD (Kaiser et al. 2015; Mulders et al. 2015): default mode (DM) system, frontoparietal control (FPC) system, and salience system. The DM system involved in self-referential process (Raichle et al. 2001; Greicius et al. 2003; Buckner et al. 2008) is related to pathological introspection of MDD patients like rumination (Zhu et al. 2017). The dysfunctional top–down control by FPC system (Corbetta and Shulman 2002; Fox et al. 2005) is associated with deficient cognitive control in depression (Stange et al. 2017). The salience system (overlapping with ventral attention system), supporting detecting and orientating to salient stimuli (Seeley et al. 2007), has a role in biased attention in MDD patients (Beevers et al. 2015). Moreover, abnormal interactions among these 3 systems have been observed in MDD patients (Manoliu et al. 2014; Kaiser et al. 2015; Mulders et al. 2015). Neurocognitive models of MDD suggested that imbalanced connectivity of FPC with DM and salience systems results in imbalanced control over introspection and external attention and furthermore affects mood regulation (Disner et al. 2011; Rayner et al. 2016). The triple-network model (Menon 2011), a common framework for multiple psychiatric disorders, also emphasizes that the deficient communication of these 3 core systems plays an important role in the psychopathology of psychiatric disorders. Thus, investigating the intrinsic organization and interactions of different functional systems in the brain network can help to identify preserved, dysfunctional, and compensatory subsystems in MDD and further help to understand the psychopathology of MDD, which may lead to targeted treatments.

Graph theory provides a useful tool to characterize the brain network (Sporns et al. 2005; Bullmore and Sporns 2009). The community structure is one of the most functionally relevant graph metrics to study the organization and interaction of functional systems in the brain network (Petersen and Sporns 2015). A community is a set of more densely interconnected nodes (or brain areas) within the set compared with between other sets (Fortunato 2010; Fortunato and Hric 2016; Sporns and Betzel 2016). The community structure (or modular organization) can delineate the functional segregation and integration of the whole-brain network. Researchers have identified community structure in both structural and functional networks in the healthy human brain (Chen et al. 2008; He et al. 2009; Meunier et al. 2009).

Identifying the community structure of the brain is also of great interest to clinical researchers because disrupted community structures were found in diverse brain disorders (Cary et al. 2016; Glerean et al. 2016; Lerman-Sinkoff and Barch 2016), including MDD (Bohr et al. 2012; Lord et al. 2012; Tao et al. 2013; Peng et al. 2014). Lord et al. (2012) detected community structure of functional network for individuals with unipolar depression. They found that superior regions in frontal and parietal cortex increased intercommunity connections, whereas inferior regions like occipital, temporal, and inferior frontal cortex increased intracommunity connections in patients. The participation indices (an index of how dense nodes are connected across multiple communities) of 15 nodes mainly located in frontal, parietal, and occipital cortex occupied top 25 informative metrics, which can identify patients from the healthy by machine learning. These findings indicate that the community structures are significantly reorganized in depressive patients by the alterations in widespread brain areas. However, they did not describe the specific alterations of the community structures in depression. Peng et al. (2014) reported different community structures between MDD group and the healthy controls (HC). They observed that an integrated community comprised the DM and FPC systems in the HC, but parts of this community belonging to the FPC system were separated in MDD group. Another community responsible for affective processing also split in MDD group. They suggested that these alterations might account for abnormal cognitive and affective processing in MDD. Tao et al. (2013) applied a reference community structure based on HC to first-episode MDD and resistant MDD patients and found widespread altered connections, mostly belonging to the attention system. These studies indicate that MDD-related alterations of functional connectivity underling altered community structures are distributed in different functional systems like the default, cognitive control, attention, and affective systems. This corresponds to the theoretical model. However, a limited number of studies on community structure in MDD reported inconsistent results, which calls for more investigations with solid methodology for robust identification of the neural alterations in MDD.

Previous studies have reported that antidepressant treatment modifies functional connectivity in distributed regions in MDD (Dichter et al. 2015; Gudayol-Ferre et al. 2015). Gudayol-Ferre et al. (2015) reviewed that antidepressant treatment mainly affected connectivity of portions of the DM and cortical–limbic networks. This suggests that the medication effect is widespread and complex, highlighting the need to examine its effect on the large-scale system level. Although these studies indicate that changes in functional network communities accompany MDD, none so far have 1) systematically examined the community structure of functional networks in both medicated and unmedicated MDD (uMDD), 2) addressed methodological problems with modularity maximization such as the resolution limit (Fortunato and Barthelemy 2007) and degeneracy (Good et al. 2010; Lancichinetti and Fortunato 2012), or 3) taken into account community partitions across multiple scales (Betzel et al. 2014b).

The primary aim of this study is to address these limitations, by examining changes in the community structure of

cortical functional networks in both uMDD and medicated MDD (mMDD), across multiple resolutions. To achieve this goal, we identified an optimal resolution parameter for each group based on the stability of the community structure against small changes in the resolution parameter, quantified as the variation of information (Meila 2003). We hypothesized that both MDD patient groups would exhibit altered community structure compared with that of HC group.

Materials and Methods

Participants

A total of 134 participants aged 18–65 years were included, containing 46 drug-naive MDD patients, 38 mMDD patients, and 50 age-, gender-, and education-matched HC participants (Table 1). No significant differences of age, gender, education, and head motion existed among the 3 groups. All participants were part of an ongoing depression research project, which was conducted by Southwest University, China. All the MDD patients were recruited from the psychiatric department of the First Affiliated Hospital of Chongqing Medical University and diagnosed with the Structured Clinical Interview of the DSM-IV by experienced psychiatric physicians. HC participants were screened without current or past Axis I or II disorder. All participants had 1) no neurological, organic brain diseases and other psychiatric disorders; 2) no family history of psychiatric disorders on their first-degree relatives; and 3) no physical contraindication for undergoing magnetic resonance imaging (MRI). The medicated participants had accepted antidepressant treatment before the MRI scan, in most cases including selective serotonin reuptake inhibitors including citalopram, escitalopram, fluoxetine, paroxetine, and sertraline; serotonin–norepinephrine reuptake inhibitors such as venlafaxine; serotonin antagonists and reuptake inhibitors such as trazodone; tetracyclic antidepressant such as mirtazapine; and tricyclic antidepressant such as amitriptyline and melitracen-flupentixol. All patients underwent assessment for depressive symptom by the 17-item Hamilton Rating Scale for Depression (HRSD) and the Beck Depression Inventory-II (BDI). The mMDD group had lower scores on BDI than the uMDD group, but there was no difference on HRSD and illness duration (Table 1). This study was approved by the Ethics Committee of Southwest University and First Affiliated Hospital of Chongqing Medical School. All participants provided informed written consent.

Image Acquisition

Magnetic resonance images were acquired from a 3 T Siemens TrioTim scanner. The resting-state functional images were obtained with an echo-planar imaging (EPI) sequence (volumes = 242, TR/TE = 2000/30 ms, flip angle = 90°, matrix = 64 × 64, thickness/gap = 3/1 mm, voxel size = 3.4 × 3.4 × 3 mm^3). The structural images were from a high-resolution, T1-weighted magnetization–prepared rapid gradient echo sequence (TR/TE/TI = 1900 ms/2.52 ms/900 ms, flip angle = 9°, matrix = 256 × 256, slices = 176, voxel size = 1 × 1 × 1 mm^3).

Table 1 Demographic information

	Unmedicated	Medicated	Control
Age (years)	39.46 (18–63)	39.77 (19–66)	40.4 (19–63)
Gender (male/female)	12/34	10/28	19/31
Education (years)	12.28 ± 3.55	11.13 ± 3.26	12.04 ± 4.11
meanFD (mm)	0.07 ± 0.04	0.06 ± 0.03	0.07 ± 0.03
BDI	23.82 ± 7.71**	18.86 ± 8.59**	—
HRSD	23.61 ± 4.33	23 ± 4.33	—
Duration (weeks)	106.11 ± 166.45	119.25 ± 132.45	—

**$P < 0.01$, obtained by 2-sample *t*-test.

Image Preprocessing

All the imaging data were preprocessed by using the Connectome Computation System pipeline (Xu et al. 2015), which provide a platform for processing multimodal images by integrating functions of analysis of functional neuroimages (Cox 1996), FreeSurfer (Dale et al. 1999; Fischl et al. 1999a), and FMRIB Software Library (Jenkinson et al. 2012). Structural MRI preprocessing included following steps of removing spatial noise by a nonlocal mean filtering (Xing et al. 2011; Zuo and Xing 2011) and then running recon-all command in FreeSurfer 5.1 to conduct brain extraction, structural segmentation, and surface reconstruction.

The preprocessing of functional images was completed by 1) removing the first 5 EPI volumes; 2) replacing temporal spikes; 3) slice timing correction; 4) head motion correction; 5) generating brain mask; 6) normalization of global mean intensity of 10 000; 7) nuisance variable regression (Fox et al. 2005; Lund et al. 2006) by regressing out mean signals from white matter, cerebrospinal fluid, Friston-24 head motion parameters (Friston et al. 1996; Yan et al. 2013) and the global mean signal; 8) band-pass filtering (0.01–0.1 HZ); 9) removing linear and quadratic trends; and 10) spatial smoothing with a 6-mm full-width at half-maximum filter. Functional images were coregistered to the native anatomical images by using boundary-based registration (BBR, Greve and Fischl 2009) and then were projected onto the *fsaverage* surface template and resampled to *fsaverage*5 surface (Fischl et al. 1999b). The global mean signal was removed in order to reduce physiological noise, such as movement and respiration (Power et al. 2014).

We performed quality control procedure on all imaging data to ensure the quality of preprocessing. First, visual inspection was conducted on screenshots of the following steps, including brain exaction, structural segmentation, surface reconstruction, and BBR-based functional images registration. Then, the mean frame-wise displacement (meanFD) was calculated as the head motion criterion (meanFD < 0.2 mm). All the participants included in the final study passed this criterion.

Functional Network Construction

The whole-brain surface was parceled into 114 regions derived from a previously established functional parcellation of 17 networks (Yeo et al. 2011). Functional connectivity can be estimated from intrinsic spontaneous activity of brain regions (Biswal et al. 1995; van den Heuvel and Hulshoff Pol 2010), by computing the Pearson correlations of time series from all pairs of regions. For each subject group, the connection matrices obtained from each subject were averaged into a single group matrix used to detect network communities.

Community Detection

We used a multiscale community detection technique to identify the community structure of a large-scale functional network for each group (Fig. 1). One widely used strategy is to maximize connections within each community while minimizing connections between communities (Newman and Girvan 2004; Rubinov and Sporns 2010; Sporns and Betzel 2016). To achieve this, we maximize the quality function:

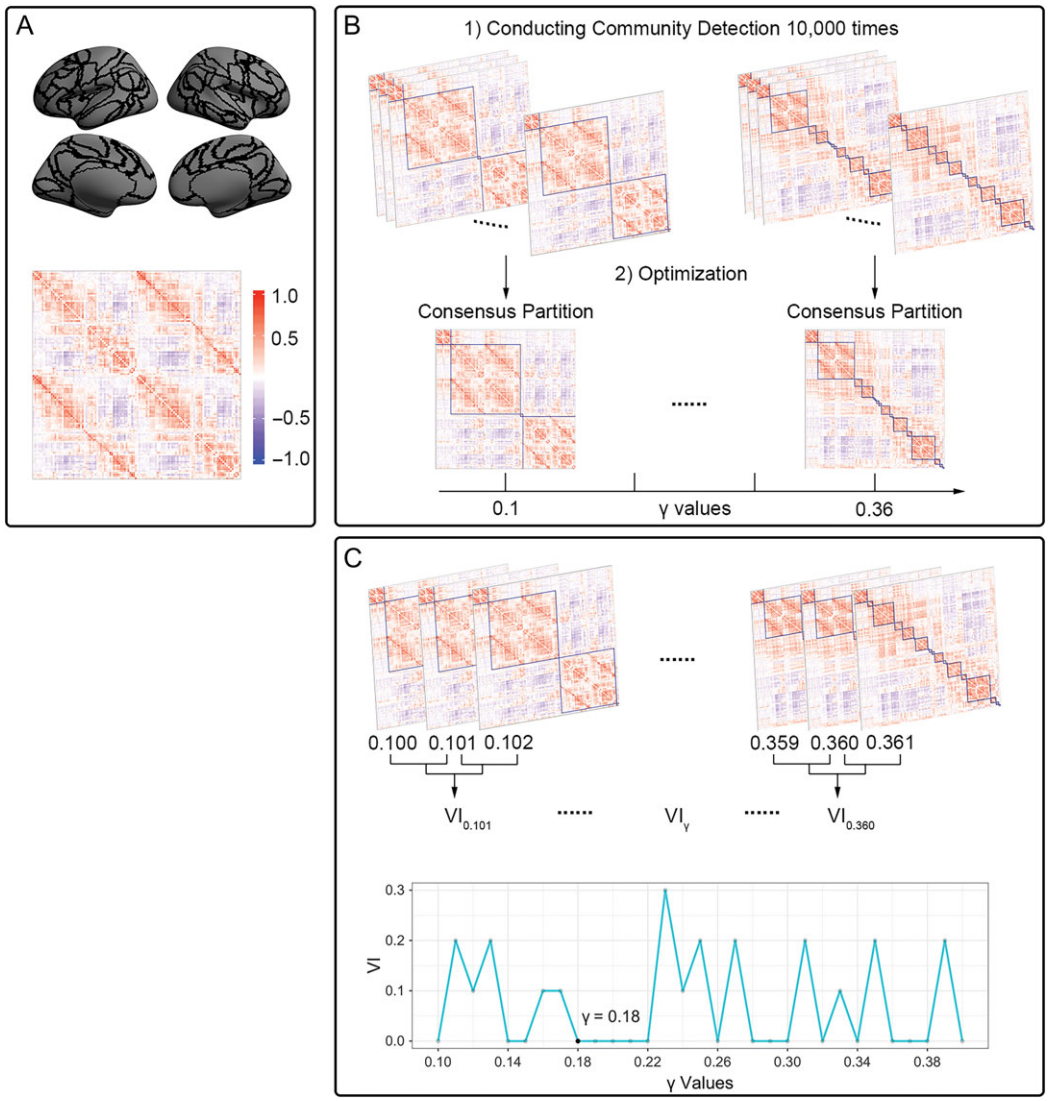

Figure 1. Multiscale community detection schematic. (A) The whole-brain surface comprised 114 parcels. A weighted adjacency matrix of functional connectivity of 114 brain regions was constructed for each subject. The matrices of subjects in each group were averaged into a single group-level matrix as the functional network. (B) The multiscale community detection was applied on each group matrix across a range of resolution parameter values. For each resolution parameter γ, 1) we repeated community detection 10 000 times and 2) finally obtained a single consensus community structure. (C) We chose the optimal γ based on the resolution stability, by calculating the averaged variation of information (VI) between the partition of each γ and its two contiguous neighbors ($\gamma_{(i-1)}$ and $\gamma_{(i+1)}$). Then, we targeted the broadest range of continuous γ values for which the VI remained equal to zero. For example, in the bottom plot, $\gamma = 0.18$ is chosen as the optimal.

$$Q(\gamma) = \frac{1}{2m} \sum_{ij} [A_{ij} - \gamma] \delta(g_i, g_j)$$

$A = [A_{ij}]$ is a weighted and signed functional connectivity matrix where A_{ij} represents the connection weight between node i and j estimated by Pearson correlation coefficient between 2 regional time series. g_i is the assignment of the node i to a community. Modularity maximization is subject to a "resolution limit"; that is, it is unable to detect communities smaller than a given scale (Fortunato and Barthelemy 2007; Fortunato and Hric 2016). Here, we included a tunable resolution parameter γ to mitigate this problem (Reichardt and Bornholdt 2006). By adjusting the value of γ from low to high, one can detect few large-size communities to more numerous small-size communities, which also corresponds to the "constant Potts model" (Traag et al. 2011) suitable for networks based on correlation matrices (MacMahon and Garlaschelli 2015).

We used a Louvain algorithm implemented in a MATLAB software package (Blondel et al. 2008; Jutla et al. 2011) to perform community detection. We varied γ within a range from 0.1 to 0.4 in increments of 0.001. The limits of this range were chosen such that they retrieve community partitions with significantly lower (γ = 0.1) or higher (γ = 0.4) numbers of communities than are included in a standard resting-state network partition (Yeo et al. 2011). For each of 301 settings of the γ parameter, we performed community detection 10 000 times and then identified a single consensus partition from the agreement matrix (Lancichinetti and Fortunato 2012).

After deriving the consensus partition at each γ, we selected a single level of γ for further analysis. Prior work used stability as a criterion, by looking for a plateau in the number of

communities (Swanson et al. 2016) or by calculating the similarity of partitions across a range of γ values (Misic et al. 2016). Here, we adopted an approach similar to the latter criterion by defining the stability of γ across a small window at each point across the range. Specifically, we used the variation of information (VI) (Meila 2003) to evaluate the variability between different partitions computed under small variations of γ for multiscale resolution stability. First, we calculated the VI averaged between the partition of each γ and each of its two contiguous neighbors ($\gamma_{(i-1)}$ and $\gamma_{(i+1)}$). This measure represents the stability of the partition when γ is changed slightly. Then, we targeted the broadest range of continuous γ values for which the averaged VI remained equal to zero (Fig. 1), taken to represent the most stable partition across multiscale resolutions.

Network Properties

To further examine the connectivity patterns of each community and the relationship between communities, we compared each community's intracommunity and intercommunity connectivity strengths based on the community structure from HC as a reference. First, we averaged all the intracommunity functional connectivity between each pair of nodes within each community. Second, we averaged all intercommunity functional connectivity between each community and all other communities. Finally, we compared the averaged intracommunity and intercommunity connectivity among 3 groups.

Statistics

Permutation testing was used to assess differences of network properties between groups with 10 000 permutations and tested at significance level 0.05 for a 2-tailed test. Before permutation test, age, gender, and the meanFD were regressed out from each network metric as covariates. In order to control any putative differences in whole-brain connection strength and focus on community-specific connectivity, individual mean whole-brain connection strength was also regressed out as covariate. The False Discovery Rate (FDR) was used for multiple comparison correction at $\alpha = 0.05$ (Benjamini and Hochberg 1995; Genovese et al. 2002).

Results

Optimal Parameter of Resolution in Multiscale Community Detection

We identified the optimal resolution parameter γ for each group based on the resolution stability (see Materials and Methods). As a result, we identified the optimal γ as 0.238 for HC, 0.173 for uMDD, and 0.181 for mMDD (Fig. 2).

Community Structures

The community structure of functional network of each group is shown in Figure 3. Figure 4 illustrates the community assignment of each brain region in 3 subject groups. Overall, the decomposition of the functional network using our multiscale community detection method (and the optimal γ) was similar to previous functional parcellations (Power et al. 2011; Yeo et al. 2011); we compared our community structures with the 7 networks previously reported in Yeo et al. (2011) by calculating their mutual information (Fig. 3). For the 3 groups, we obtained a mutual information of 0.718 (HC), 0.650 (uMDD), and 0.710 (mMDD). Our community detection approach disclosed 12 communities in the HC, 9 communities in uMDD, and 10 communities

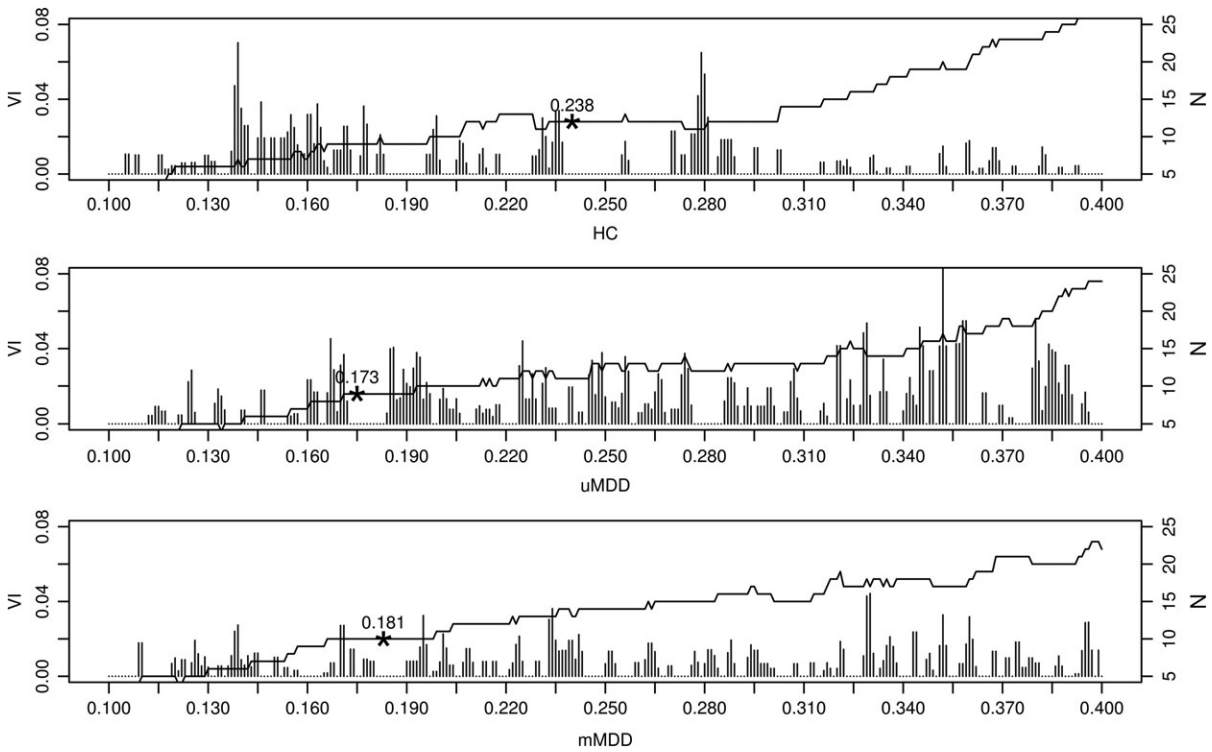

Figure 2. Selection of the optimal partition for each group. The plot illustrates the resolution stability VI value (shown as the histogram) and the number of communities (shown as the continuous line) obtained across a range of resolution parameter γ in 3 subject groups. For 3 groups, the optimal γ was marked in the plot, as 0.238 for the HC, 0.173 for uMDD, and 0.181 mMDD, for which the VI is equal to zero with the broadest range.

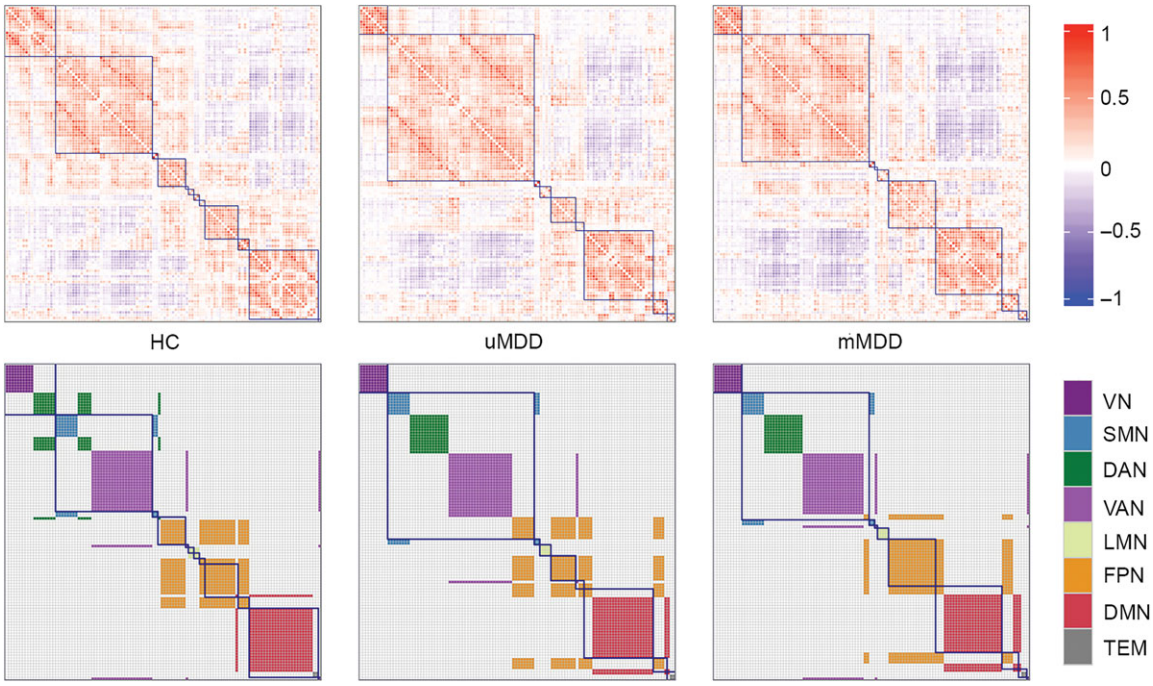

Figure 3. The community structures for 3 groups and the mapping with Yeo's 7 network. The upper panel shows community structures of functional networks of 3 groups. Twelve communities for HC, 9 communities for uMDD, and 10 communities for mMDD were separately identified. The bottom panel illustrates how our partitions compare with the 7 networks of Yeo et al. (2011), represented by 7 different colors. VN: visual network; SMN: somatomotor network; DAN: dorsal attention network; VAN: ventral attention network; LMN: limbic network; FPN: frontoparietal network; DMN: default mode network; TEM: TempPar (independent regions not belong to 7 networks).

in mMDD, and the community structures of both patient groups appeared similar to each other while differing from that of the HC group (Fig. 4). In addition, the mMDD group exhibited some new features of community structure that differed from the other two groups.

In particular, in the HC group, the communities we detected consist of visual association (VA), central (somatomotor/salience), FPC-A, FPC-B, FPC-C, and DM systems (ignoring small-sized communities with only 1 or 2 nodes). In contrast, the uMDD group showed that the VA and FPC-A systems have partly been fragmented, with parts merging with the central system (e.g., bilateral occipito-temporal sulcus, parieto-occipital gyrus, and superior parietal lobe from VA and bilateral posterior part of superior frontal sulcus, intraparietal sulcus, posterior part of inferior temporal gyrus, left inferior part of precentral sulcus, left anterior part of inferior frontal sulcus, and right posterior part of inferior frontal sulcus from FPC-A). FPC-B was split into 2 parts, one of which joined the DM system including the bilateral middle frontal gyrus and right angular gyrus. For the DM system, some regions including the bilateral superior temporal sulcus and the left inferior frontal gyrus formed an independent community, and the left posterior region of inferior parietal lobule combined with FPC-C. In addition, the bilateral medial orbital gyrus and temporal pole integrated into one community.

However, mMDD exhibited some new features of community structure in FPC-A and FPC-B that differed from the other 2 groups (Fig. 4). A part of FPC-A (including bilateral posterior part of inferior temporal gyrus, intraparietal sulcus, left posterior part of superior frontal sulcus, and left inferior frontal sulcus) and FPC-B (including bilateral posterior part of inferior temporal sulcus, lateral frontopolar cortex, middle part of medial superior frontal gyrus, left posterior middle frontal gyrus, and left anterior angular gyrus) combined together with bilateral posterior part of anterior cingulate cortex into an independent community. The right posterior region of inferior parietal lobule split from the DM system to join the FPC-C. In addition, some single nodes merging with other large communities in uMDD, like left orbital sulcus and right middle part of ACC, became independent in mMDD.

Intracommunity and Intercommunity Connectivity

To further determine the origin of the changes in the community structure in uMDD and mMDD patients, we examined intracommunity and intercommunity connectivity of each community based on the community structure of HC (see Materials and Methods for details). No significant differences of intracommunity connectivity among the 3 groups were found (Fig. 5). However, several communities in the uMDD group, including the central, FPC-A, FPC-B, and FPC-C systems, exhibited increased intercommunity connectivity compared with the HC (central, $P = 0.004$; FPC-A, $P = 0.002$; FPC-B, $P = 0.006$; FPC-C, $P = 0.040$; FDR corrected) and mMDD except FPC-A system (central, $P = 0.001$; FPC-B, $P = 0.007$; FPC-C, $P = 0.05$; FPC-A, $P = 0.086$; FDR corrected). Meanwhile, the mMDD group showed reduced intercommunity connectivity in the DM system compared with the other 2 groups (HC, $P = 0.003$; uMDD, $P < 0.001$; FDR corrected).

Discussion

Using a multiscale community detection approach, we identified the most stable community partitions of functional networks

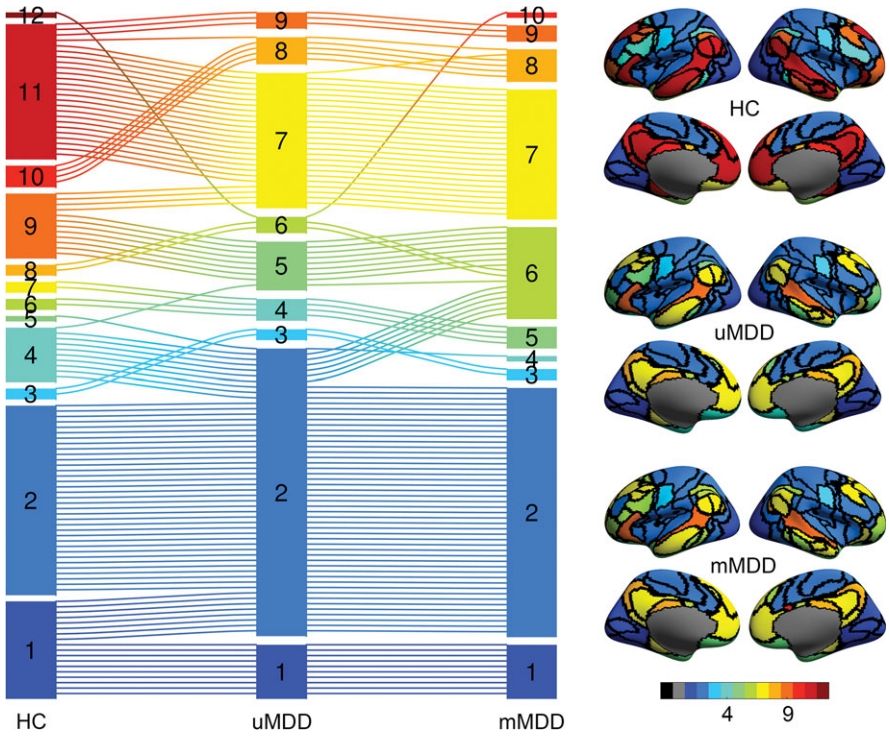

Figure 4. Community assignment of 114 brain regions. The left alluvial diagram (modified from https://github.com/mbojan/alluvial) illustrates changes of community assignments of brain regions across 3 groups. Each block represents a community and each line corresponds to a brain region. For example, comparing to HC, Community 1 fragmented to 2 parts, one of which joined Community 2 in uMDD and mMDD. The right image shows the brain surface mapping of community partitions. The color-coding is as same as the left diagram, corresponding to distinct communities. Major communities in HC includes (1) visual association (VA), (2) central system, (4) frontoparietal control-A (FPC-A), (9) frontoparietal control-B (FPC-B), (10) frontoparietal control-C (FPC-C), (11) DM system.

for each group. Importantly, we could delineate patterns of reorganization in the community structure of functional brain networks in MDD patients with or without antidepressant treatment. In particular, we observed disturbances in the community structure of VA and DM systems that were similar in uMDD and mMDD groups, while also identifying reconfigurations of the FPC subsystems that differed in the 2 patient groups. Moreover, further analysis of intracommunity and intercommunity connectivity revealed that changes in intercommunity connectivity mainly accounted for the observed changes in community organization in MDD patients. Specifically, in the uMDD group, the intercommunity connectivity in the central system and 3 FPC subsystems was stronger than both the HC and medicated patients (except the FPC-A system). The mMDD group additionally showed attenuated intercommunity connectivity in the DM system compared with the other 2 groups.

Multiscale Community Detection

Previous studies have demonstrated that structural and functional human brain networks are organized into a modular architecture (Hagmann et al. 2008; He et al. 2009; Meunier et al. 2009; Power et al. 2011). Functional communities are robustly identified with a variety of community detection methods (Sporns and Betzel 2016) and the resulting communities have been shown to correspond to functional brain systems that are coherently engaged in both rest and task conditions (Crossley et al. 2013; Bertolero et al. 2015). Thus, the community organization of large-scale human functional networks appears to reflect underlying neurobiological mechanisms, and variations in community structure may signal significant changes in the brain's functional capacities.

Although examining the community organization of human brain networks has been extremely fruitful for uncovering the organizing principles of the human brain, methodological limitations of community detection methods such as resolution limit and degeneracy of optimal solutions of community structure have so far remained largely unaddressed (Fortunato and Barthelemy 2007; Good et al. 2010; Lancichinetti and Fortunato 2012; Fortunato and Hric 2016). In the present study, we addressed some of these limitations by identifying an optimal resolution parameter γ associated with a highly stable community structure based on resolution stability measure for each group. The community structure of the control group was broadly similar to that identified in previous studies (Power et al. 2011; Yeo et al. 2011); yet, we found characteristic patterns of reconfiguration of functional networks, which differed among unmedicated and medicated patient groups.

Changes in Functional Networks in uMDD

We compared the community structure of MDD groups with the HC to locate disease-related changes in organization of functional networks. Notable differences were found in the composition of communities, especially in the DM, FPC-B, and VA systems. Each of them fragmented into 2 parts in the uMDD group compared with the healthy group. One segregated part of FPC-B joined the DM system, and one part of VA together with FPC-A joined the central system. This reconfiguration of community structure was associated with increased intercommunity connections, like the central system, 3 FPC subsystems in

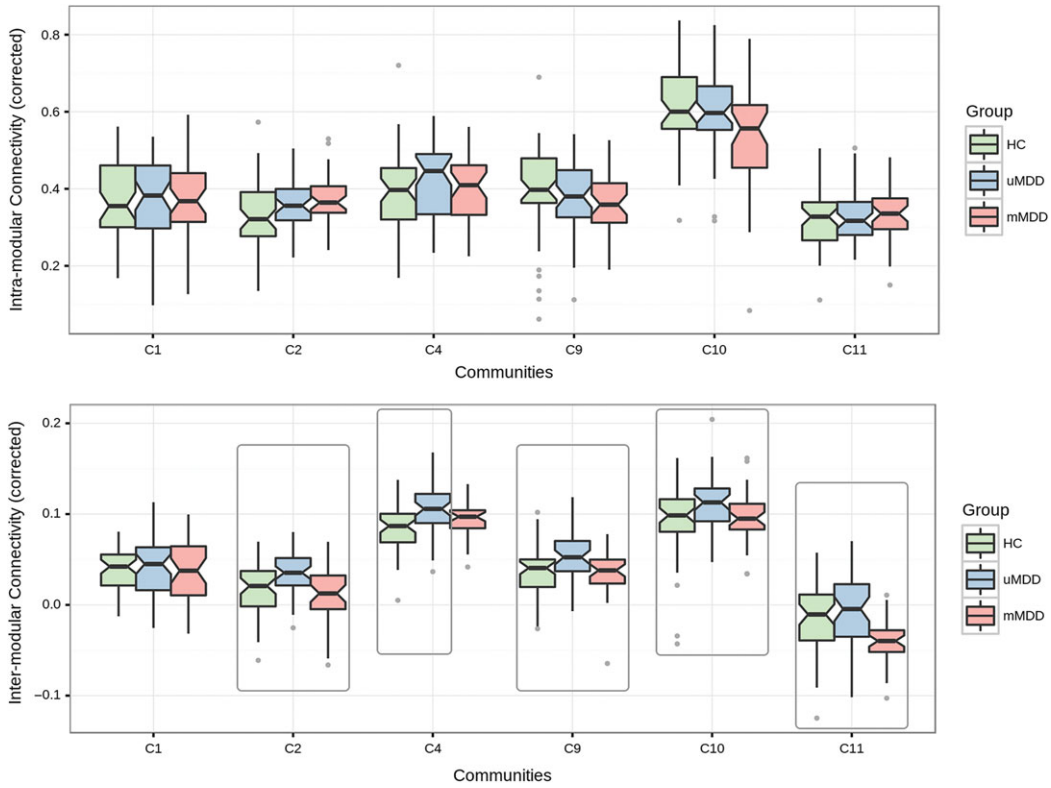

Figure 5. The intracommunity and intercommunity connectivity strengths. The intracommunity connectivity strength was quantified as the averaged functional connectivity between each pair of nodes within each community. The intercommunity connectivity strength was calculated as the averaged functional connectivity between the nodes within a community and all the other nodes outside the community. There was no significant difference in intracommunity connectivity among 3 groups. But significant differences were found in intercommunity connectivity (shown in rectangles of bottom panel). For C2 (central), C9 (FPC-B), C10 (FPC-C), uMDD showed increased intercommunity connectivity than the other 2 groups. For C4 (FPC-A), uMDD showed increased connectivity than HC. For C11 (DM), mMDD had lower connectivity strength than others. The gray dots represent outliers.

uMDD. These findings support the "hyperconnectivity hypothesis" of depression, which suggests that increased connectivity might be a biomarker of the mood disorder (Perrin et al. 2012). This is also consistent with a recent meta-analysis, which concluded that MDD involved imbalanced connectivity among functional networks, for example, DM, FPC, and attention networks (Kaiser et al. 2015).

The alterations of the DM, FPC, and central systems (overlap with salience system) have been widely reported in MDD (Mulders et al. 2015) and with high power for discriminating MDD from HC (Qin et al. 2015a, 2015b). Disturbed DM functional connectivity is related to excessive negative rumination in MDD (Zhu et al. 2017), which may underlie the negative internal processes occurring in MDD. The FPC system supports tasks/cognition control (Corbetta and Shulman 2002; Fox et al. 2005), which is suggested to be associated with maladaptive cognitive control in MDD, like controlling over attention and emotion (Joormann and Gotlib 2010; Joormann and Quinn 2014). The salience system (ventral attention system) is involved in detecting salient stimuli (Seeley et al. 2007), which is known to be affected in MDD (Peckham et al. 2010; Disner et al. 2011; Beevers et al. 2015). Our findings support the neurocognitive models of MDD, which propose that the symptoms of MDD can be attributed to disturbed connections of the FPC network with other networks involving attention, emotion, and internal mentation (Disner et al. 2011; Kaiser et al. 2015; Rayner et al. 2016). The imbalanced connectivity between FPC and DM results in the domination of self-focused introspection over external orientation. The disturbed connectivity between FPC and salience system causes the disruption of cognitive control of biased attention. Here, the altered community structure and increased connectivity of 3 FPC subsystems imply that FPC plays a vital role in the pathophysiology of MDD. Their separate recombination with the DM and central systems may reflect their different roles in abnormal control on emotional internal thought and external attention (Manoliu et al. 2014; Kaiser et al. 2015).

The central system (salience and somatomotor systems) showed stronger intercommunity connectivity in uMDD. This hyperconnectivity may explain the community recombination of the central system with parts of the VA system and the FPC-A system (Fig. 4). The shifted part of VA included the superior parietal, tempo-occipital sulcus, and parieto-occipital gyrus, are respectively in 2 visual processing pathways supporting cognitive processing of visual input, as the ventral and dorsal visual pathway (Goodale and Milner 1992). Studies suggested that altered occipital regions were related to negatively biased processing of visual inputs in uMDD (Graham et al. 2013; Cheng et al. 2016). Here, the recombination of the central system with a part of the VA system may reflect abnormal control of attention in visual processing in MDD, which lead to negative perception (Peckham et al. 2010; Zhou et al. 2010; Desseilles et al. 2011; Disner et al. 2011; Beevers et al. 2015; Tozzi et al. 2017). In addition, the somatomotor system has been found to be associated with depression severity in MDD, suggesting that it was related to abnormal pain processing (Tadayonnejad et al. 2015). The

dysfunction of somatomotor regions may be associated with physical symptoms like pain and fatigue in MDD (Bair et al. 2003). Together, hyperconnectivity of the central system may underlie nonemotional symptoms involving biased attention and somatosensation.

Effects of Medication on Network Topology of MDD

Several studies have reported that various kinds of antidepressants have heterogeneous effects on functional connectivity across the visual, DM, salience, and cognitive control networks (Dichter et al. 2015; Gudayol-Ferre et al. 2015; Wang et al. 2015). However, most of these studies investigated seed-based connectivity, without addressing the whole-brain system level. Using network analysis, we found that antidepressants affected the community structure mainly by modulating patterns of intercommunity connectivity, which more closely resembled those found in HC. In mMDD patients, decreased intercommunity connectivity appeared in almost all affected systems as opposed to increased intercommunity connections in unmedicated patients (except FPC-A), which may indicate normalization/restoration effects of medication. This normalization parallels recent findings showing that antidepressants can renormalize increased cortical thickness of widespread regions in depressive patients (Bansal et al. 2017) and could reduce increased functional connectivity of orbitofrontal cortex with distributed regions (Cheng et al. 2016). However, the community structure in medicated patients was largely the same as that of uMDD, except that FPC-A and FPC-B systems combined together. But the community structures of mMDD and the HC appear more similar to Yeo's network partition (Yeo et al. 2011). We speculate that antidepressants may contribute more to adaptive connectivity changes between communities rather than the general organization of the community structure.

A key finding of the antidepressant effect is that the FPC subsystems exhibited alterations in both community organization and connectivity. Previous studies have found that depression treatment could change functional connectivity of FPC (Aizenstein et al. 2009; Perrin et al. 2012; Liston et al. 2014). Perrin et al. (2012) found a reduced average global functional connectivity of dorsolateral prefrontal cortex after electroconvulsive therapy, which is consistent with our findings. Both the FPC and the DM systems exhibited reduced functional connectivity after antidepressant administration in healthy participants (McCabe et al. 2011; van de Ven et al. 2013). As we have shown that the FPC system is vital in the pathophysiology of MDD, we propose that it is also a potential therapeutic target of antidepressant medication. As the number of studies about the antidepressant effect on the FPC system is limited, further studies are needed.

A growing body of studies have reported altered connections by antidepressant treatment within DM system or between DM and other systems, like FPC system or limbic system, implying its prominent involvement in depression (Dichter et al. 2015; Gudayol-Ferre et al. 2015). Of note, in our findings, the intercommunity connectivity of the DM system in mMDD decreased below the level of the control group and uMDD. This may imply a compensatory mechanism of antidepressants on the DM system. In MDD patients, the connectivity of the DM system was associated with the antidepressant response (Pizzagalli 2011; Wang et al. 2015), and whole-brain connectivity of regions in the DM system can be reduced by the antidepressant (Fu et al. 2015; Wang et al. 2015). Its alteration of intracommunication and intercommunication is associated with MDD remission (Qin et al. 2015a, 2015b). However, some studies suggested that the normalization effect of antidepressants only took part in certain subsystems of the DM system (Li et al. 2013; Shen et al. 2015). Additional work is needed to provide more solid conclusions and interpretations regarding the role of antidepressants in modifying functional brain connectivity.

Limitations

Several limitations in the current study need to be noted. First, functional networks using only cortical regions are explored in this study. However, subcortical regions also play an important role in the pathophysiology of MDD (Heller 2016). Second, while other parcellations may be explored, our choice of a previously published parcellation based on data from 1000 participants (42) was based on its consistency with other canonical maps of brain functional systems (Power et al. 2011) and wide usage in the field (Baker et al. 2014; Betzel et al. 2014a; Yeo et al. 2015). Third, the antidepressant treatment is quite heterogeneous. The type of medication and treatment duration differs across subjects, which does not allow us to directly examine the effects of specific drugs or drug regimens on MDD. Previous studies have also incorporated diversely medicated patients because the subjects are patients that limits the sample size (Heller et al. 2013; Li et al. 2013; Qin et al. 2015a, 2015b; Gong et al. 2018). Studies comparing different medications have found similar effects on brain functional connections (Lisiecka et al. 2011; McCabe and Mishor 2011). In addition, many studies using different medications have found a convergent normalization effect on elevated functional connectivity, which are in line with our results. This suggests that there might be a general normalization effect across antidepressant treatments (Lisiecka et al. 2011; McCabe and Mishor 2011; Li et al. 2013; Wang et al. 2015; Fu et al. 2015; An et al. 2017). Thus, we included all the types of drugs to see if there is a general modulation effect of treatments. In order to characterize drug effects on functional connectivity more rigorously, longitudinal design with more uniform patient groups and drug treatments are needed in the future.

Conclusion

In the current study, we examined the community structure of cortical functional networks in uMDD, mMDD, and HC using a multiscale community detection method. Although uMDD and mMDD patients showed similar reorganization of community structure in VA and DM systems, the FPC subsystems, in particular, reconfigured differently in the 2 patient groups. uMDD patients were characterized by intercommunity connectivity increased in the central system and 3 FPC subsystems implicating altered communication among multiple large-scale systems, which appears partially restored or overly compensated in mMDD patients. Together, these findings provide a global picture of community structure alterations of cortical functional networks in uMDD and mMDD patients and suggest potential medication effects in restoring disease-related network alterations.

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