Decreased inter-hemispheric connectivity in anterior sub-network of default mode network and cerebellum: significant findings in major depressive disorder

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Abstract

The issue of inter-hemispheric connectivity is an emerging new area in understanding the pathophysiology of depression. This study was designed to analyse the pattern of inter-hemispheric connectivity in patients with major depressive disorder (MDD). The resting-state functional magnetic resonance imaging (rsfMRI) was acquired in all enrolled patients and controls. We used a method of voxel-mirrored homotopic connectivity (VMHC) to estimate the significant differences in inter-hemispheric connectivity between 44 patients with first-episode medication-naïve MDD and 27 normal controls. The patients and controls were matched for age and gender. The patients with first-episode medication-naïve MDD showed lower VMHC than normal controls in bilateral medial frontal cortex, anterior cingulate and cerebellar posterior lobe. The strength of inter-hemispheric connectivity VMHC value was negatively correlated with clinical severity of MDD. From the results, we suggested that decreased inter-hemispheric connectivity in the anterior sub-network of the default mode network and the cerebellar posterior lobe might represent an emerging finding in the pathophysiology for MDD.

Key words: Anterior cingulate, cerebellar posterior lobe, major depressive disorder, medial frontal cortex, voxel-mirrored homotopic connectivity.

Major depressive disorder (MDD) is a major mental illness with significant influences on social and occupational function. It causes a lot of impact on economics and productivity. Additionally, a relatively high proportion of MDD patients might also enter a treatment-resistant phase (Souery et al., 2007). Due to the important consequences to society and on mental health it is therefore, important to understand the underlying pathophysiology of MDD. There are many scientific reports mentioning the structural and functional pathophysiology in the fronto-limbic network and default mode network (DMN) of patients with MDD (Lai et al., 2010; van Tol et al., 2010; Alexopoulos et al., 2012; de Kwaasteniet et al., 2013). The frontal-limbic and default mode network findings might be compatible with the initial ‘limbic-cortical-striatal-pallidal-thalamic tract’ hypothetical model for MDD (Sheline, 2000). In recent years, Sheline et al., proposed a new MDD model involving the DMN, which constituted of the ventromedial prefrontal cortex, anterior cingulate and the lateral parietal cortex. The DMN was involved in self-referential problems and negative ruminations, which also played a role in the pathophysiology of MDD (Sheline et al., 2009). The above results suggested that an emerging endophenotype in the pathophysiology of MDD might exist in resting and non-resting brain activities.

Apart from the above pathophysiological mechanism, inter-hemispheric functional connectivity in MDD is another field useful for understanding the psychopathology of MDD. It suggests that the brain’s commissural system, such as the corpus callosum or commissures, can mediate the inter-hemispheric interaction (Hopftman and Davidson, 1994). Past reports showed that ‘split-brain’ patients had deficits in selective, sustained attention, excessive vigilance towards external stimuli (Dimond, 1979a) and depletion of cognitive attention (Dimond, 1979b). Moreover, bi-hemispheric actions can also give the ability of each hemisphere to have competence in task demand and inter-hemispheric functional connectivity might maintain our ability for strategic deployment of attentional resources (Levy and Trevarthen, 1976;
Belger and Banich, 1992). The previous studies have shown the importance of inter-hemispheric interaction for cognitive and attentive ability.

For resolution of inter-hemispheric interaction, functional connectivity would be the translating candidate for this kind of message. Resting-state functional magnetic resonance imaging (RFMRI) is an important technique for acquisition of functional connectivity. It has been used to measure the intra- and inter-hemispheric functional connectivity (Hoptman et al., 2012). Recently, a concept called ‘voxel-mirrored homotopic connectivity’ (VMHC) has been reported, which represents the functional architecture for the synchrony of spontaneous events in each hemisphere (Salvador et al., 2005). VMHC might reveal some useful messages for hemispheric specialisation in cognitive and motor functions. It can be applied in investigation of the disease process (Stark et al., 2008).

Zuo et al., introduced the first algorithm in the developmental trajectories and age-related changes in VMHC, which can be further applied in the research of psychiatric disorders (Zuo et al., 2010). There are several research reports of VMHC in the field of psychiatry, such as schizophrenia (Hopman et al., 2012; Guo et al., 2014a, b), MDD (Guo et al., 2013a, b; Wang et al., 2013), cocaine abuse (Kelly et al., 2011) and cannabis abuse (Orr et al., 2013). Previous reports in MDD showed an inconclusive pattern of VMHC results. Guo et al., showed decreased VMHC values in the bilateral posterior cingulate cortex and the medial prefrontal cortex (Guo et al., 2013a). They also identified that the lower VMHC values in calcarine cortex might represent a specific pattern for treatment-resistant MDD (Guo et al., 2013b). Another article reports a different network of VMHC deficits in the medial orbitofrontal gyrius, parahippocampal gyrus, fusiform gyrus, middle occipital gyrius and the cuneus (Wang et al., 2013). The inconsistent results suggest that the VMHC pattern in MDD still needs to be clarified.

In this study, we hypothesized that the VMHC values of MDD patients would probably be lower than those of normal controls. The VMHC deficits would occur within the DMN and might, mostly, be within the anterior sub-network of the DMN based on the self-referential hypothesis for MDD (Sheline et al., 2009). Additionally, the VMHC strength would be negatively correlated with the clinical severity of MDD.

Materials and method

Participants

The selection criteria for patients was as follows: (1) first-episode patients with a pure MDD diagnosis (DSM-IV criteria) as assessed by the Structured Clinical Interview for DSM-IV; (2) no co-morbid psychiatric illnesses or medical illnesses; (3) severity of MDD was at least moderate: measured by the Clinician Global Impression of Severity: score >4, Hamilton Rating Scales for Depression 17 items (HDRS): score >20, Hamilton Rating Scales for Anxiety (HARS): score <5; (4) no previous cognitive behavioural therapy or other psychotherapies; (5) medication-naïve (6) no abuse of or dependence on alcohol or other substances; and (7) no past history of claustrophobia or discomfort while receiving RFMRI scanning. The healthy controls had no psychiatric illnesses or significant medical illnesses. All participants signed the inform consent approved by the Institute Review Board, Buddhist Tzu Chi Hospital, Taipei Branch. At the time of the scanning, none of the participants in the control group received psychotropic treatment of any kind. Handedness was determined by using the Edinburgh Inventory of Handedness (Oldfield, 1971).

Structural MRI data acquisition

We obtained the MRI T1 image data to exclude structural bias and establish a study-specific template for our VMHC analysis. The structural MRI T1 imaging brain scans were obtained using a 3 T Siemens version scanner housed at the MRI Centre, National Yang Ming University. Scans with three-dimensional fast spoiled gradient-echo recovery (3D-FSPGR) T1WI (TR 25.30 ms; TE 3.03 ms; slice thickness=1 mm(no gap)); 192 slices; matrix=224×256; field of view: 256 mm; number of excitation=1) were performed.

RFMRI data acquisition and pulse sequence

Echo planar imaging (EPI) sequences were acquired in 20 axial slices (TR=2000 ms, TE=40 ms, flip angle=90°, field of view=24 cm; 5 mm thickness and 1 mm gap). The sequence duration was 300 s for each subject, 150 time points were acquired (voxel dimension: 64×64×20) at baseline in patients and controls. All the patients and controls were asked to relax and close their eyes and were instructed to move as little as possible during scanning. All the patients and controls reported that they were fully awake during MRI scanning.

VMHC analysis by REST (Resting State FMRI Data Analysis Toolkit)

EPI data was pre-processed by DPARSF (Data Processing Assistant and Resting-State FMRI, version 2.2; State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, China.) (Chao-Gan and Yu-Feng, 2010) working with the Statistical Parametric Mapping 8 (SPM8) on the Matlab platform. The first ten time points were discounted in consideration of the instability of initial MRI signals and patient difficulty in adapting to the MRI. Subsequent images were; slice timed with the 20th slice as reference slice; realigned and normalised...
the pre-processed images were transformed to standard MNI spaces using EPI templates; and, re-sampled with 3 x 3 x 3 mm³, smoothing with Full Width at Half Maximum (FWHM) 4 x 4 x 4 kernel, to de-trend and filter data with residual signals within 0.01-0.08 Hz to discard the bias from high-frequency physiological noise and low-frequency drift. As all subjects’ head movements were less than 0.5 mm in translation and one degree in rotation (through obtaining the motion time courses of all subjects), no subject was excluded due to observed excessive motions. A study-specific MNI template was derived from segmented transformed images consisting of grey matter, white matter and cerebrospinal fluid in the MNI space. The filtered RFMRI data was registered (non-linear elastic registration) to this symmetric study-specific MNI template, which was created by voxel-based morphometry of T1 images. The estimated motion parameters were obtained for subjects and regressed on each voxel. The effects of ‘micro-movements’ and the nuisance correlation caused by head motions were removed by checking covariates in nuisance regressors in DPARSF (Power et al., 2012; Yan et al., 2013a). Several sources of spurious covariates were removed excepting global signals, due to control’s experimental design. No detectable motion time courses of all subjects, no subject was excluded due to observed excessive motions. An individual covariates of motion included Friston-24 parameter model (six head motion parameters, six head motion parameters – one time point before, and the 12 corresponding squared items) and group covariates of motion used the frame-wise displacement motion regression model (Yan et al., 2013b). Final output data after DPARSF pre-processing was then processed by REST (Resting State FMRI Data Analysis Toolkit, version 1.4; State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, China.) (Song et al., 2011) and VMHC data was subsequently produced. VMHC assumes symmetric morphology between hemispheres. The pre-processed images were transformed by applying RFMRI images to anatomical data. We then averaged an image with its left-right mirrored version to create identical mirrored hemispheres and RFMRI data was transformed to fit the new symmetrical anatomical image. VMHC was computed as the resting-state functional connectivity between any pair of symmetric inter-hemispheric voxels. For each subject, the Pearson correlation coefficient between each voxel’s residual time series and that of its symmetrical inter-hemispheric counterpart was performed. Correlation values were then Fisher-z transformed. The resultant values constituted the VMHC and were used for the group analyses. Because VMHC results were bilaterally identical or symmetric, we also used a unilateral hemisphere mask to confirm that our results were indeed found in one hemisphere (one-sided results).

### Statistics

The VMHC map was used for an independent two-sample t-test analysis function in the REST toolbox. The subsequent group comparison analysis between patients and controls was performed (second-level random effects model, independent two-sample t-test) using the following statistical criteria; uncorrected p < 0.00005, cluster>10 voxels, t-threshold: 3.65, surface connected theory. The statistical analysis also used age and gender as covariates to exclude possible influence. The same statistical threshold was applied for the results of the one-sided mask. To clarify the relationship between the clinical severity of MDD symptoms and VMHC values, a voxel-wise Pearson’s correlation was performed.

### Results

#### Demographic data

We enrolled forty-four patients with MDD and twenty-seven controls. There were no significant differences in all demographic parameters except HDRS scores between two groups (Table 1).

<table>
<thead>
<tr>
<th>Demographic Parameter</th>
<th>Patients (n=44)</th>
<th>Controls (n=27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age - yr (s.d.)</td>
<td>36.91 (5.31)</td>
<td>38.29 (11.80)</td>
<td>0.910, –0.113</td>
</tr>
<tr>
<td>Gender</td>
<td>F(23), M(21)</td>
<td>F(15), M(12)</td>
<td>0.553</td>
</tr>
<tr>
<td>Mean duration of illness - mth (s.d.)</td>
<td>4.68 (1.44)</td>
<td>0 (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Gender</td>
<td>R (44)</td>
<td>R (27)</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean HDRS (s.d.)</td>
<td>22.07 (2.29)</td>
<td>1.37 (0.88)</td>
<td>&lt;0.001, –7.07</td>
</tr>
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<td>Mean HARS (s.d.)</td>
<td>2.32 (1.05)</td>
<td>2.03 (1.01)</td>
<td>0.316, –1.003</td>
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<td>Mean educational - yr (s.d.)</td>
<td>15.70 (0.82)</td>
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- **Mean**: The mean value of a given parameter
- **s.d.**: Standard deviation
- **F**: Female
- **M**: Male
- **HDRS**: Hamilton Rating Scales for Depression
- **HARS**: Hamilton Rating Scales for Anxiety
- **N/A**: Not applicable
- **p**: p-value from significance testing

### Table 1. Demographic data of participating patients and controls

n, number; s.d., standard deviation; F, female; M, male; HDRS, Hamilton rating scales for depression; HARS, Hamilton rating scales for anxiety; N/A, not applicable; p, Sig (from Mann-Whitney U test for nonparametric independent 2-sample t-test); df, degree of freedom.
Table 2. The areas of VMHC differences between patients with MDD and normal controls

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI coordinate x, y, z</th>
<th>Cluster voxels</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ACC</td>
<td>9, 30, 12</td>
<td>24</td>
<td>Uncorrected p&lt;0.00005, peak intensity: 4.3671</td>
</tr>
<tr>
<td>Left ACC</td>
<td>−9, 30, 12</td>
<td>24</td>
<td>Uncorrected p&lt;0.00005, peak intensity: 4.3671</td>
</tr>
<tr>
<td>Right MeFC</td>
<td>3, 60, 6</td>
<td>27</td>
<td>Uncorrected p&lt;0.00005, peak intensity: 4.3817</td>
</tr>
<tr>
<td>Left MeFC</td>
<td>−3, 60, 6</td>
<td>27</td>
<td>Uncorrected p&lt;0.00005, peak intensity: 4.3817</td>
</tr>
<tr>
<td>Right CePL</td>
<td>6, −75, −39</td>
<td>21</td>
<td>Uncorrected p&lt;0.00005, peak intensity: 4.9833</td>
</tr>
<tr>
<td>Left CePL</td>
<td>−6, −75, −39</td>
<td>21</td>
<td>Uncorrected p&lt;0.00005, peak intensity: 4.9833</td>
</tr>
</tbody>
</table>

MNI, Montreal Neurological Institute; ACC, anterior cingulate cortex; MeFC, medial frontal cortex; CePL, cerebellum posterior lobe.

VMHC alterations in patients with MDD

Patients with MDD had significantly lower VMHC values in the bilateral anterior cingulate cortex (ACC), medial frontal cortex (MeFC) and cerebellar posterior lobe (CePL) (uncorrected p<0.00005, voxel threshold: 10) (Table 2, Table 3 and Fig. 1). There was no significantly higher VMHC in any region of MDD patients when they were compared with normal controls (uncorrected p<0.5, voxel threshold: 5). The voxel-wise Pearson’s correlation results showed that the VMHC values were negatively correlated with HDRS scores in the bilateral ACC of patients with MDD (uncorrected p<0.00005, r = −0.65).

Discussion

In this study we found the VMHC alterations in the anterior sub-network of DMN (ACC and MeFC) and the cerebellum (CePL) of patients with MDD. The VMHC values were also negatively correlated with clinical severity of MDD symptoms in this patient group. These results are both consistent and conflict with previous VMHC reports in MDD (Guo et al., 2013a, b; Wang et al., 2013). In previous reports our study found alterations in the medial prefrontal cortex and medial orbitofrontal cortex (Guo et al., 2013a; Wang et al., 2013). However, the results of ACC and CePL were inconsistent with these reports. The findings of Guo et al., were not just within the anterior sub-network of the DMN. Their results also showed significant differences in VMHC in the posterior cingulate cortex belonging to the posterior sub-network of DMN (Guo et al., 2013a). Another study by Guo and colleagues on treatment-resistant MDD showed lower VMHC values in the calcarine cortex, fusiform gyrus, hippocampus, superior temporal gyrus, middle cingulum and pre-central gyrus, which were not replicated in our results. In addition, Guo et al., found no significant differences in VMHC values in any brain region of MDD patients when compared to healthy subjects (Guo et al., 2013b) whereas our study showed VMHC alterations specific to the anterior sub-network of DMN. In addition, we found another region, CePL, which has never been mentioned in previous VMHC reports of MDD. The results highlighted the potential differences between previous reports and revealed a possible pattern for the pathophysiology of MDD.

ACC is an important region for the pathophysiology of MDD from a structural viewpoint (Lai et al., 2010; Pizzagalli, 2011; Lai, 2013) and a functional viewpoint (Greicius et al., 2007; Fitzgerald et al., 2008; Mannie et al., 2008; Sheline et al., 2009; Pizzagalli, 2011; Liu et al., 2012; Connolly et al., 2013). The meta-analysis of voxel-based morphometry study revealed that ACC would be the most consistent for grey matter deficits in MDD (Lai, 2013). In the first RFMRI study of DMN, patients with MDD had increased functional connectivity between the subgenual ACC and thalamus (Greicius et al., 2007). It suggested the existence of a disordered sub-network within the DMN in MDD. Liu et al., found that MDD patients would have lower coherence-based regional homogeneity in right ACC and MeFC (Liu et al., 2012), in agreement with our VMHC results. Zheng et al., proposed a possible classification method to identify the resting-state brain activities in MDD, including the DMN, with the ACC with a higher discriminative power in classification and diagnosis (Zeng et al., 2012). Another RFMRI study in MDD also showed that abnormal function connectivity of ACC and MeFC was associated with ruminations and self-referential thoughts, which contribute to the emotional and cognitive distortions in MDD (Zhu et al., 2012). Connolly et al., found that aberrant functional connectivity between ACC and frontal gyri would correlate with dysfunction of salience attribution and executive control in patients with MDD (Connolly et al., 2013). A study of the resting blood flow of the brain also showed that MDD is associated with decreased resting blood flow in right ACC and MeFC, which also showed inverse correlations with clinical severity of depression (Monkul et al., 2012). Pizzagalli suggested that rostral ACC might play a key role in treatment outcomes due to its hub position in DMN. He also hypothesized that elevation of rostral ACC activities could be helpful for fostering adaptive self-referential processing and recalibrating the relationship between
DMN and the cognitive control network (Pizzagalli, 2011). Higher activity in ACC and MeFC relates to increased thoughts of hope and aspiration (Johnson et al., 2009). The decreased inter-hemispheric connectivity in bilateral ACC may reflect disturbances in the control of self-referential thoughts, cognitive control, emotional regulation and emotional re-appraisal (Sheline et al., 2009). However, further investigation of the possible pathophysiological mechanism of VMHC decrease in ACC and its clinical implications is warranted.

Fig. 1. Significantly lower VMHC values in MDD. The patients with MDD had alterations in VMHC when compared with normal controls. The VMHC alterations were found in bilateral ACC (subfigure a), MeFC (subfigure b) and CePL (subfigure c). The one-sided results showed similar clusters in the right ACC, right MeFC (subfigure d) and right CePL (subfigure e). ACC, anterior cingulate cortex; MeFC, medial frontal cortex; CePL, cerebellum posterior lobe.
As for findings in MeFC, these should be compatible with the limbic-cortical model proposed by Sheline (2000). In a similar model suggested by Seminowicz, the MeFC is an important component within the limbic-cortical circuit, which can differentiate between treatment responders and non-responders (Seminowicz et al., 2004). MeFC is also the core structure for the processing of self-referential thoughts and maladaptive ruminations in depression. The lower activities in MeFC and ACC may be related to a decrease in both adaptive thinking and positive thoughts, such as hopes and aspirations (Johnson et al., 2009). In the extended self-referential network, the MeFC also cooperate with ACC in the processing of self-referential thoughts (Lemogne et al., 2009). The individualised and clinically relevant stimulus may induce activations in MeFC with ACC and limbic-subcortical structures, respectively (Kessler et al., 2011). The cognitive control ability of McF and ACC could be important regulators for the excessive emotional responses and ruminations of limbic-subcortical structures (Kessler et al., 2011).

Our previous RFMRI study of antidepressant effects in MDD patients also suggested that MeFC regional homogeneity would be enhanced after remission of MDD symptoms, which also suggested the role of MeFC in MDD clinical symptoms and recovery (Lai and Wu, 2012). Monkul et al., reported that MDD is associated with a lower resting-state blood flow in ACC and MeFC with clinical severity inversely correlating with the resting-state blood flow in MeFC. Their study also proved the resting-state activities (an indirect indicator of resting-state blood flow) in MeFC is important in the pathophysiology of MDD (Monkul et al., 2012). Apart from the self-referential processing, emotion regulation and cognitive control, MeFC also can cooperate with ACC in the regulation of autobiographical memory and the retrieval of specific self-referential memory in patients with MDD (Young et al., 2013). The results from both Young et al., combined with our results suggests that the decreased VMHC in MeFC could be associated with disturbances in the limbic-cortical circuit and related dysfunctions in self-referential processing, emotional regulation, cognitive control and autobiographical memory retrieval.

Our study also found that patients with MDD had lower VMHC values in the CePL. However, from early lesion studies of the cerebellum, lesions in the posterior lobe may cause significant impairment in executive functions, spatial memory and emotional regulation. It may also link frontal and limbic structures, forming a network for the modulation of emotion and cognition (Schmahmann and Sherman, 1998). Meta-analysis of brain activities in depression also shows consistently lower activities in the cerebellum, ACC and MeFC (Fitzgerald et al., 2008). In a recent study by Stoodley et al., the role of the cerebellum in cognitive and affective control along with emotional regulation was replicated by the posterior lobe of the cerebellum (Stoodley and Schmahmann, 2010). Our previous structural study also showed that grey matter reduction in cerebellum plays a role in the pathophysiology of patients with MDD and panic disorder (Lai et al., 2010). A RFMRI study about regional homogeneity also showed different patterns in the MeFC and CePL of MDD patients compared with normal controls (Liu et al., 2012). Another RFMRI study also showed alterations in the amplitude of low frequency oscillations in the frontal cortex and cerebellum of MDD patients (Wang et al., 2012). The cerebellum is also a component of the classifying network for the recognition of patients with MDD. This network also includes the MeFC and ACC (Zeng et al., 2012). Peng et al., mentioned that the structural deficits of the cortico-limbic-cerebellum network may modify the traditional view point of the ‘fronto-limbic’ or ‘cortico-limbic’ model in the pathophysiology of MDD (Peng et al., 2013). The lower inter-hemispheric connectivity between bilateral CePL probably reflects functional disturbances of emotions and cognition within the cortico-limbic-cerebellum circuit.

Combining the literature and our results, we proposed a possible ‘DMN-cerebellum’ model specific in the inter-hemispheric connectivity of MDD. The VMHC model for MDD includes bilateral MeFC, ACC and CePL. The decreased inter-hemispheric coordination between bilateral ‘DMN-cerebellum’ could provide us with a new clue about the pathophysiology of MDD and may explain the dysfunction in emotion, cognition and self-referential processing ability.

Our study had several limitations. Firstly, it provided the VMHC functional data without structural deficits. Future studies with a multimodal imaging method, such as voxel-based morphometry and diffusion tensor imaging, can provide additional information about the structural aspects of MDD.
imaging, would help identify the unknown structural basis for VMHC alterations. The cross-sectional design of our study limits interpretation and, as such, a longitudinal study might be indicated. The VMHC results in our study were obtained during resting state and therefore, a task-oriented functional MRI study could provide a complementary view. Lastly, VMHC measures the inter-hemispheric connectivity haemodynamically and therefore, abnormal VMHC may be related to inter-hemispheric haemodynamic changes. However, whether VMHC can be used to detect early neuronal changes, or monitor disease progression in MDD, is still controversial.

Conclusion

To our knowledge, this is the only study that reports decreased VMHC in the anterior sub-network of DMN (ACC and MeFC) and CePL in patients with MDD. The inter-hemispheric coordination dysfunctions within this ‘DMN-cerebellum’ network could represent a new possible model for the understanding the pathophysiology of MDD.

Acknowledgments

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Statement of Interest

None.

References


