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Research report

Frontal-insula gray matter deficits in first-episode medication-naïve patients with major depressive disorder

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ABSTRACT

Objective: This study is designed to investigate the gray matter volume (GMV) deficits in patients with first-episode medication-naïve major depressive disorder (MDD).
Methods: We enrolled 38 patients with first-episode medication-naïve MDD and 27 controls in this project. Voxel-based morphometry was used to compare GMV differences between two groups. Besides, the relationship between GMV of patients and the severity of clinical symptoms was estimated to confirm the role of GMV deficits in clinical symptoms. The correlation between total GMV and illness duration was also performed to elucidate the impacts of untreated duration on the GMV.
Results: We found that first-episode medication-naïve MDD patients had significant GMV deficits in bilateral superior frontal gyri, left middle frontal gyrus, left medial frontal gyrus and left insula. The GMV of patient group was negatively correlated with the severity of clinical symptoms and the illness duration.
Conclusion: A pattern of GMV deficits in fronto-insula might represent the biomarker for first-episode medication-naïve MDD.

1. Introduction

Major depressive disorder (MDD) is a kind of mental illness with a relatively high prevalence. It will cause deteriorations in social and occupational functions. The biomarker of brain structure in MDD is an intriguing issue and might reveal some important meanings for clinical symptoms and functions. Many scientists focus their interest in the pathophysiology of MDD. In the structural aspect, gray matter is an important factor to establish the pathological model for MDD.

Apart from traditional manual-based parcellation method in magnetic resonance imaging (MRI) studies, several semiautomatic methods are developed to avoid manual biases. A new methodology, optimized voxel-based morphometry (VBM), shows the stable quality for the study in gray matter volume (GMV) of many neuropsychiatric illnesses (Lai and Hsu, 2011; Lai et al., 2010; Lai and Wu, 2012; Sobanski et al., 2010). Recently several studies of voxel-based morphometry (VBM) showed fronto-limbic deficits in gray matter volume (GMV) of MDD patients (Abe et al., 2010; Lai and Hsu, 2011; Lai et al., 2010; Li et al., 2010; van Tol et al., 2010; Yuan et al., 2008). Abe et al. also found that GMV reductions in bilateral middle frontal gyri (MFG) of MDD patients and they suggested the existence of GMV deficits might constitute the fronto-limbic circuit model for pathophysiology (Abe et al., 2010). The gray matter reductions in superior frontal gyrus (SFG) would be associated with attention biases toward negative stimuli and predispose MDD patients to respond inappropriately to negative stress (Leung et al., 2009). Frontal-related GMV deficits in the MDD patients might contribute to neuropsychological impairments (Abe et al., 2010; Ballmaier et al., 2004b; Li et al., 2010; van Tol et al., 2010). The VBM study of van Tol et al. suggested that inferior frontal cortex may reflect specific symptom clusters for MDD (van Tol et al., 2010). The gray matter deficits of right medial frontal gyrus (MeFG) are also associated with depressive psychopathology and might be a part of structural deficit model of MDD (Vasic et al., 2008). Serro-Blasco et al. suggested that GMV deficits in SFG and MeFG would be associated with duration of illness (Serra-Blasco et al., 2013) These studies supported the existence of frontal-specific pattern of neuroanatomical deficits in patients with MDD.

Apart from frontal-specific GMV deficits, several other brain regions with GMV alterations or even volume increases have been reported in MDD. Frodl et al. reported that hippocampal GMV reductions would be an important marker of first-episode MDD patients (Frodl et al., 2002b) and would be associated with different genotypes of serotonin transporter polymorphism (Frodl et al., 2004; Frodl et al., 2008b). Even paradoxically, larger volumes of amygdala were found in first-episode patients with MDD (Frodl et al., 2002a; Frodl et al., 2003).

In this study, we planned to enroll first-episode medication-naïve MDD patients into our VBM study to clarify the GMV deficit

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pattern in MDD. According to the above VBM studies, we hypothesized that MDD patients might have GMV deficits in multiple frontal regions, such as SFG, MFG, MeFG, inferior frontal gyrus, and hippocampus or amygdala. We would also investigate the correlation between total GMV and MDD symptom severity. We hypothesized that there was a negative correlation between total GMV and depressive severity. The correlation between the illness duration and total GMV was also estimated. We hypothesized that a negative correlation would also exist between two parameters.

2. Method

2.1. Participants

The selection criteria for patients were as follows: (1) first-episode, medication-naïve patients with MDD diagnosis (DSM-IV criteria) made 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: Clinician Global Impression of Severity >4, Hamilton Rating Scales for Depression (HDRS) score >20, Hamilton Rating Scales for Anxiety (HARS) score <5, (4) no previous cognitive behavioral 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 MR scanning. The healthy controls had no psychiatric illnesses or significant medical illnesses. They were staff volunteers of Buddhist Tzu Chi Hospital, Taipei Branch. All participants signed the inform consents approved by the Institute of Review Board, Buddhist Tzu Chi Hospital, Taipei Branch. At the time of the MR imaging, none of the participants received psychotropic treatment of any kind. Handedness was determined by using the Edinburgh Inventory of Handedness (Oldfield, 1971).

2.2. MR imaging procedure

2.2.1. Data acquisition:

The structural MR imaging brain scans were obtained using the 3T Siemens version scanners housed in the MR Center at the National Yang Ming University. Scans with three-dimensional fast spoiled gradient-echo recovery (3D-FSPGR) T1W1 (TR 25.30 ms; TE 3.03 ms; slice thickness$=1$ mm (no gap); 192 slices; matrix$=224\times256$; field of view: 256 mm; number of excitation$=1$; voxel size: $1\times1\times1$) were performed on the patients and controls at baseline.

2.3. VBM processing and statistical analysis:

After manually reorienting and centering the images on the anterior commissure, the processing of data was performed based on the optimized VBM approach. Structural MR images were also preprocessed with FSLVBM (http://www.fmrib.ox.ac.uk/fsl/fslvbm/, version 1.1) function of FSL (FMRIB Software Library; version 4.1.1) to compare the differences of GMV between patients and healthy controls. The theory of FSLVBM method consists of 4 following major steps. First, brain skull or other non-brain tissue was removed by "Brain Extraction Tool" to discard the confounding factors of nonbrain tissues in subsequent steps for analyzing. Second, FSL Automated Segmentaion Tool v4 performed tissue-specific segmentation to produce partial volume images of gray matter with more uniform intensity values with softer edges (Thomas et al., 2009). Then the images were aligned to Montreal Neurological Institute 152 template through the affine registration. The registered images were averaged and concatenated to establish a 4D self template of gray matter from all the participants in this study. Third, brain would be non-linearly registered to the study-specific template and all the registered images were visually inspected by Dr. Lai to check the quality of registration. After Jacobian modulation.of the warp field to compensate the non-linear transformation induced contraction or enlargement, all the modulated and segmented gray matter images were concatenated into a 4D multi-subject concatenated image. The modulated 4D image was smoothed by Gaussian kernels (sigma 3 mm in FSLVBM protocol, which approximately equal to Full Width at Half Maximum 7.5 mm) (Seidman et al., 2011). Besides, a gray matter mask was created by unsmoothed segmentations and unmodulated normalized segmentations. The FSL-VBM mask included voxels which met following criteria: minimum of gray matter probability larger than minimal threshold (0) and maximum of gray matter probability larger than maximal threshold (100 for FSL images). Smoothing 4D modulated image and gray matter mask were necessary for the following step of permutations. Fourth, a permutation-based non-parametric inference (Randomise function of FSL; http://www.fmrib.ox.ac.uk/fsl/randomise, version 2.1) was performed with gray matter mask and 4D image by Threshold-Free Cluster Enhancement (TFCE) method to compare two groups' GMV. Non-parametric computations were used due to the relatively small sample size and the method is comparable to multiple comparisons in random field theory (Nichols and Holmes, 2002). The randomise function used general linear model for permutations and we included global brain volume, age, gender, agoraphobia and duration of illness as covariates to control possible confounding factors. TFCE is a new method for finding clusters in data without having to define clusters in a binary way, which can avoid the bias related to the arbitrary threshold. Cluster-like structures were enhanced but the image remained fundamentally voxel-wise. This procedure would produce test statistic images and sets of *P*-value images. The neighborhood-connectivity parameters have been optimized and should be left unchanged to avoid edge effects of the border between gray matter and white matter. TFCE solved multiple comparisons by using a multi-threshold meta-analysis of random field theory cluster *P*-values. We used family wise error (FWE) to obtain results for continuous random processes to find *P*-values. "FWE-corrected" means that family-wise error rate is controlled. For the control of co-morbid agoraphobia in these patients, we included the agoraphobia as a covariate in the design matrix for TFCE analysis. Besides, we included global brain volume, age, gender and duration of illness as covariates in the design matrix to control these possible confounding factors. Statistical image after multiple comparisons was explored to find regions of GMV deficits. The statistics was performed by the TFCE method of FSL and the threshold was set as FWE corrected p value <0.05 with 5000 times of permutations for multiple comparisons (df$=63$) due to that we wanted to find the most significant regions with GMV differences. The statistical comparisons were performed in two-way style (patients vs. controls and controls vs. patients) to see the increments and decrements in GMV of patients with MDD.

A correlation between the scores of clinical rating scales (HDRS) and GMV in the general lineal model considering the voxel wise matrix with global brain volume, age and gender as covariates in design matrix of FSL correlation analysis would be performed (threshold: corrected $p<0.05$, multiple comparisons). This step could help us confirm which brain regions correlate with depression and which regions may be important in the physiopathology of the disorder. Besides, the correlation between untreated duration of illness and GMV with the same covariates (age, gender and global brain volume) was analyzed to elucidate the key characteristics of untreated duration in MDD.

Demographic data of patients and controls, such as age, HDRS scores and HARS scores, would be compared by nonparametric independent 2 sample t test (Mann–Whitney U test) with statistical threshold as $p<0.05$. The use of non-parametric comparison test was due to limited sample size of two groups. The genders and handedness of two groups were compared by Chi-Square test with $p<0.05$.