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Research report

The gray matter alterations in major depressive disorder and panic disorder: Putative differences in the pathogenesis

Chien-Han Lai [a,b,c], Yu-Te Wu [b,c,d,*]

[a] Department of Psychiatry, Cheng Hsin General Hospital, Taipei City, Taiwan, ROC
[b] Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei, Taiwan, ROC
[c] Institute of Biophotonics, National Yang-Ming University, Taipei, Taiwan, ROC
[d] Brain Research Center, National Yang-Ming University, Taipei, Taiwan, ROC

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ABSTRACT

Objective: This is a comprehensive study to establish a diagnosis-specific gray matter deficit model for major depressive disorder (MDD) and panic disorder (PD).
Method: We enrolled 53 patients with first-episode medication-naïve PD, 54 healthy controls and 53 patients with first-episode medication-naïve MDD in this study. They were age, handedness and gender matched. All participating subjects all received baseline structural scanning by the 3-Tesla magnetic resonance scanner. The optimized voxel-based morphometry was performed on the 3 groups of subjects and the ANOVA analysis was used to estimate the inter-group gray matter differences between each group.
Results: The PD group had higher gray matter volume than MDD group in the right medial frontal cortex and right temporal gyrus. The PD group had gray matter reductions in the right inferior frontal gyrus and right insula. The MDD group had gray matter reductions in bilateral medial frontal cortex, right superior frontal gyrus, right superior temporal gyrus and bilateral cerebellums.
Conclusion: The gray matter alterations of fronto-insula and fronto-temporo-cerebellum regions probably would be specific for PD and MDD respectively. In addition, the differences of gray matter volume in the fronto-temporal regions would be helpful to differentiate MDD from PD.

1. Introduction

The co-morbidity of major depressive disorder (MDD) and panic disorder (PD) reached high as 50–65% MDD prevalence in PD (Baldwin, 1998; Roy-Byrne et al., 2000). MDD also had moderating effects on the pattern of PD comorbidity (Biederman et al., 2005). The comorbidity PD and MDD would also increase the risk of suicidality (Brown et al., 2010; Diaconu and Turecki, 2007). The ambiguity of diagnosis due to co-morbidity indicated the necessity of comparing PD and MDD patients in brain pathophysiology, which might provide a method to delineate.

The structural differentiation of brain between MDD and PD is an issue which is not well-defined and clarified. Such comparison can provide us the evidence that MDD and PD are distinct diseases with different severity of structure alterations. It can help us establish the putative pathogenesis model to explain the different etiologies of two diseases. Furthermore, the complete survey of the structural differences in the MDD and PD can also provide us with the way to classify the two diseases by the severity of structural deficits. The gray matter volume (GMV) is an important index to evaluate the brain structure. In the past, just one study ever studied the GMV differences between the MDD and anxiety disorders. The results showed that reduced GMV of the rostral–dorsal anterior cingulate gyrus was a generic effect in depression and anxiety disorders. In addition, specific involvement of the inferior frontal cortex in MDD and lateral temporal cortex in anxiety disorders without comorbid MDD might provide a possible method to delineate between MDD and pure anxiety disorders (van Tol et al., 2010). However, the study suffered from the heterogeneity of anxiety disorders, which could lead to the possible bias and unspecific data for PD. Therefore we designed current study of voxel-based morphometry (VBM) to investigate the specific delineation between MDD and PD. In addition, we tried to establish the putative pathogenesis model specific for MDD and PD respectively.

The frontal-limbic regions are important structures for the

* Corresponding author at: Institute of Biophotonics, National Yang Ming University, No. 155, Sec. 2, Linong Street, Taipei, 112 Taiwan, Taiwan, ROC. Tel.: +886 2 28267000 × 7217; fax: +886 2 28201095.
E-mail addresses: stephenlai99@gmail.com (C.-H. Lai), ytwu@ym.edu.tw (Y.-T. Wu).

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GMV deficits in MDD (Sheline, 2000). 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). Frontal-related GMV deficits in the MDD patients might relate to the clinical symptoms and contribute to neuropsychological impairments (Abe et al., 2010; Ballmaier et al., 2004; Li et al., 2010; van Tol et al., 2010). The depressive psychopathology is also related to gray matter deficits in the right medial frontal cortex (MeFC) (Vasic et al., 2008). Serro-Blasco et al. suggested that GMV deficits in superior frontal gyrus (SFG) and MeFG would be correlated with duration of illness (Serra-Blasco et al., 2013) Our previous report of MDD also showed significant GMV deficits in bilateral SFG and MeFC of MDD patients (Lai and Wu, 2014). In addition, several meta-analysis study for depression revealed GMV alterations in the anterior cingulate cortex, frontal cortex, orbitofrontal cortex, hippocampus and striatum, which were involved in mood regulation. (Arnone et al., 2012; Bora et al., 2012; Wise et al., 2014) Therefore we hypothesized that MDD patients would have frontal-limbic GMV deficits.

For the PD, fear circuit will play an important role in the pathophysiology, including frontal regions (de Carvalho et al., 2010; Gorman et al., 2000; Johnson et al., 2011). Several frontal-related GMV alterations in PD patients would suggest the alterations in the top-down regulation mechanism (Asami et al., 2009; Lai et al., 2010; Lai and Wu, 2012; Protopopescu et al., 2006; Roppongi et al., 2010; Sobanski et al., 2010; van Tol et al., 2010; Yoo et al., 2005). The inferior frontal gyrus (IFG) is correlated with the severity of PD symptoms (Yoo et al., 2005). In addition to frontal regions, the insula also will influence panic symptoms via the integration of multimodal sensory information (Asami et al., 2009; Graeff and Del-Ben, 2008; Uchida et al., 2008).

Finally, for the delineation between MDD and PD, we hypothesized that MDD patients would have more severe reductions in the GMV of fronto–limbic regions due to more severe affective impairments and dysfunctions in cognitive, social and occupational aspects (Beekman et al., 1997; Gatt et al., 2010; Graff-Guerrero et al., 2005; Judd et al., 1996; Naranjo et al., 2001; Souery et al., 2007).

2. Methods

2.1. Participants

None of the MDD patients had a history of panic or comorbid anxiety at the time of inclusion. In addition, none of PD patients had comorbid depression. All the MDD patients were met for the following criteria: (1) first-episode patients with a pure MDD diagnosis (DSM-IV criteria) made by the Structured Clinical Interview for DSM-IV; (2) 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; (3) no co-morbid psychiatric illnesses or medical illnesses; (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 PD group was enrolled according to the following criteria: (1) first-episode patients with a pure PD diagnosis (DSM-IV criteria) (2) The severity of PD was at least moderate: Clinician Global Impression of Severity >4, Quick Inventory for Depressive Symptoms-Self Rating 16-item version (QIDS-SR16) <9, Hamilton Rating Scales for Depression (HDRS) score <7, Hamilton Rating Scales for Anxiety (HARS) score >22, Panic Disorder Symptom Severity Scale (PDSS) >15, panic attacks of full blown symptom >4 times within previous 4 weeks before the baseline visit. The following criteria (3)–(7) was the same as the enrollment criteria (3)–(7) in MDD. The healthy controls had no psychiatric illnesses or significant medical illnesses. All patients and healthy subjects signed the informed consent that was approved by the three Institutional Review Boards at Taipei Tzu Chi Hospital, Cheng Hsin General Hospital and National Yang-Ming University according to the institute where they were recruited. The patients were enrolled at Taipei Tzu Chi Hospital and Cheng Hsin General Hospital. The controls were enrolled from Taipei Tzu Chi Hospital, Cheng Hsin General Hospital and National Yang-Ming University. At the time of the MR imaging, none of the participants in the control group received psychotropic treatment. Handedness was determined by using the Edinburgh Inventory of Handedness (Oldfield, 1971).

2.2. 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$=1$) were performed on the patients and controls at baseline.

2.3. VBM processing procedures

Structural MR images were 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 3 following major steps. First, brain skull or other non-brain tissue was removed to discard the confounding factors of non-brain tissues. Second, FSL Automated Segmentaion Tool v4 performed tissue-specific segmentation to produce partial volume images of gray matter (Thomas et al., 2009). The affine registered images were averaged and concatenated to establish a 4D self template of gray matter from all the subjects in this study. Third, brain would be non-linearly registered to self template and the quality of registration of brain to template was checked by Dr. Lai. All the Jacobian 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. Smoothing 4D modulated image and gray matter mask were necessary for the following step of permutations.

2.4. Statistical analysis

A permutation-based non-parametric inference (Randomize 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 of randomize function in FSL were used due to the relatively small sample size and the method was comparable to multiple comparisons in random field theory (Nichols and Holmes, 2002). For the main purpose of group comparisons, an ANOVA 1×3 factor analysis with group as the main random factor over all subjects. The randomize function used general linear model for permutations and