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Abnormal neural activity in partially remitted late-onset depression: An fMRI study of one-back working memory task

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ABSTRACT

Only half of the geriatric patients with major depressive disorder (MDD) can reach full remission after treatment of half a year. This study was designed to examine the neural responses in the partial responders of late-onset MDD. We used 3-Tesla functional magnetic resonance imaging to assess the patterns of cerebral activation/deactivation in the performance of a one-back version of the *n*-back working memory task. We recruited 14 major depressive patients who reached partial remission after at least half a year of pharmacological intervention, compared with 14 non-depressive controls. There were no significant between-group differences in the demographical profiles and working memory performance, which was true for both accuracy and reaction time. Brain masks encompassing the neural responses of activation/deactivation were constructed from the non-depressive controls. The depressive group shows enhanced activities at left middle frontal and left parietal regions, and reduced deactivation at several temporal regions and left amygdala within the masks. Besides, the depressive group activates extra neural nodes at middle frontal and middle temporal regions outside the masks. The neural responses in the left amygdala are significantly correlated with the severity of depression and comorbid anxiety. The loss of deactivation in the left amygdala and the temporal areas in cognitive endeavor may be related to the refractoriness to treatment.

1. Introduction

The World Health Organization announced that major depression is a leading cause of disability which decreases quality of life and causes marked impairment in occupational and social functioning (Lopez and Murray, 1998). Although most patients with major depressive disorder (MDD) experience improvement after treatment, long-term outcome remains unsatisfactory (Gayetot et al., 2007). Many depressive patients fail to attain or maintain a symptom-free state even after years of treatment (for review, see Tranter et al., 2002). MDD patients with partial treatment response, compared with their counterparts experiencing full remission, carry a higher relapse rate and higher risk of cardiovascular/cerebrovascular events. Such a picture is also applicable to the geriatric population. It has been estimated that, after receiving treatment for 6 months, only 50% of geriatric depressive patients achieved remission and the partial responders were much more likely to encounter a relapse (Steffens et al., 2003).

The patients in a currently depressed state or in a state of remission. There seems to be a trend in brain-imaging studies carried out under resting conditions (i.e., without a task) for depression to be characterized by reduced and enhanced metabolism at dorsal prefrontal regions and ventral prefrontal/limbic regions, respectively, with the pattern reversed after successful treatment (for review, see Taylor and Liberzon, 2007). The prefrontal cortex participates in regulation of mood, cognition and behavior, and has been implicated in the pathophysiology of MDD. Many neuropsychological studies thus have adopted tasks demanding working memory and/or executive function that engage the fronto-parietal and fronto-striatal networks as a surrogate to explore prefrontal dysfunction in mood disorder. During working memory challenges to adult MDD, depression is associated with hyperactivation of the prefrontal network, while remitted depression is associated with partial restoration (Harvey et al., 2005; Matsuo et al., 2007; Rose et al., 2006), leaving enhanced activity at cingulate regions in the euthymic state (Schöning et al., 2009). Given a substantial proportion of MDD patients are resistant to treatment

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or are partial responders, it is surprising that very few studies investigated the neural correlates of the subgroup of MDD who show partial response to treatment (PMDD). Recently, Ruchsow et al. used electroencephalography to explore the response monitoring and control processes in the PMDD group (Ruchsow et al., 2008). They found that partially remitted depression was associated with reduced Nogo-P3 responses. The actual neural characteristics of PMDD warrant more studies for clarification.

This study used a working memory task that has been widely applied in adult MDD to investigate the neural characteristics of old-age PMDD. Whether geriatric depression is a discrete clinical entity or an extension of adult depression to older age is still debated (Laks and Engelhardt, 2010). Since evidence has suggested that early- and late-onset geriatric depression might represent two distinct clinical syndromes (Baldwin and Tomenson, 1995; Krishnan, 1991), we restricted our research sample to late-onset PMDD patients who received free-dosing psychotropic treatment for at least half a year. It has been reported that compared with depression in younger patients, geriatric depression is associated with greater impairment of cognitive performance (Fountoulakis et al., 2003). Alexopoulos et al. showed that cognitive dysfunction is associated with chronicity, recurrence and relapse in geriatric depression (Alexopoulos et al., 2000). Among the types of cognitive impairment reported, executive dysfunction is of particular concern in late-onset depression, which has been developed into depression-executive dysfunction syndrome and has been characterized as an important indicator of resistance to conventional pharmacotherapy (Alexopoulos, 2003; Alexopoulos et al., 2008). The executive process is known to be one of the key compartments of the integrated model of working memory (Baddeley and Della Sala, 1996). Accordingly, our selection of a working memory task to investigate PMDD not only is justified by its significance in the pathogenesis of depressive disorder but also is relevant to the underlying mechanism of refractoriness to treatment.

The complexity of the neural aberrancy of MDD has been widely acknowledged. Even fully remitted MDD (rMDD) is still associated with functional and structural abnormalities (Gemar et al., 2007; Takahashi et al., 2010; Victor et al., 2010; Yucel et al., 2009). If there were differential structural and functional responses between PMDD and other states, e.g., rMDD, it would not be straightforward to attribute whether the differences originated from PMDD, rMDD or both. On the other hand, if there were no noticed differences in neural activities between PMDD and rMDD, it would not guarantee that there is no neural aberrancy in PMDD. This preliminary study thus compared PMDD with healthy and matched controls. We adopted an inclusive/exclusive masking strategy to differentiate neural characteristics in PMDD with in three different contexts: first, whether the patients have more/less activation at the brain regions where they should activate; second, whether the patients have more/less deactivation at the brain regions where they should deactivate; and last, whether the depressive pathology affects the neural substrates not engaged in the working memory task as an indication of several possible neural mechanisms modulated by disease. The neural mechanisms could include adaptation, compensation, pharmaco-modulation, engagement of accessary pathways, recruitment of extra-resources, mobilization of cognitive reserve, psychiatric comorbidity, and so on. The deactivation map was expected to be similar to the default-mode network, which is active and deactivated in resting brain and during task performance, respectively (for review, see Broyd et al., 2009). Although still debated, the default-mode network is generally believed to encompass the precuneus, posterior cingulate cortex, medial prefrontal cortex, medial temporal lobe, and medial, lateral and inferior parietal cortices. Abnormality in the default-mode network has been reported in MDD (Broyd et al., 2009; Greicius et al., 2007; Grimm et al., 2009).

We predicted that PMDD would show different neural responses compared with those reported in acute or remitted depression. In addition to the prefrontal and parietal networks commonly activated in working memory tasks, we were particularly interested in the neural responses in the amygdala and subgenual cingulate, areas that have been regarded as indicators of treatment response (Drevets, 1999; Mayberg et al., 1997). For example, Saxena et al. reported that improvement in depressive symptoms was significantly correlated with lower pretreatment metabolism in the amygdala (Saxena et al., 2003), while Mayberg et al. demonstrated that pretreatment cerebral glucose metabolism in the rostral cingulate region differentiated treatment responders from non-responders (Mayberg et al., 1997). We expect to see aberrant neural responses in the amygdala and/or rostral cingulate in PMDD, which might contribute to the inadequate treatment response. We also conjecture that PMDD might recruit extra-neural resources to carry out working memory tasks.

2. Methods

2.1. Participants, experimental stimuli and tasks

A total of 14 patients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for major depressive disorder and 14 non-depressive controls were enrolled in this functional magnetic resonance imaging (fMRI) study (American Psychiatric Association, 1994). Other inclusion criteria for the depressive group included the following: age of onset of depression older than 50 years, score on the Mini-Mental State Examination (MMSE, Chinese version) above 24, and score on the 17-item Hamilton Depression Rating Scale (HDRS, maximum = 52) above 10 after treatment for at least half a year without experiencing full remission (Guo et al., 1988; Hamilton, 1960). In this study, PMDD was defined by DSM-IV diagnosis, HDRS score greater than 10, non-remission, and treatment duration for at least half a year. No psychosis complicated the depression course. The patients were recruited from the psychiatric clinics of Chang Gung Memorial Hospital, Taoyuan, and had no additional diagnoses on Axis I of the DSM-IV (including schizophrenia, generalized anxiety disorder, substance abuse, panic and obsessive compulsive disorders) or major medical and/or neurological disorders. Since anxiety is frequently accompanies geriatric depression, anxiety level was assessed with the Hamilton Anxiety Scale (HAM-A, maximum = 56) (Cairney et al., 2008; Hamilton, 1959; King-Kallimanis et al., 2009; Lenze et al., 2001). The non-depressive participants were screened to exclude a history or evidence of neurological, medical, or psychological disorder including substance misuse. All the recruited subjects scored zero on the Clinical Dementia Rating (CDR). Our selection of CDR of 0 and MMSE greater than 24 is to guarantee that our research participants were neither contaminated by degenerative diseases associated with depressed mood, nor sampled in a biased manner since mild cognitive impairment is common in late-onset/geriatric depression. The Trail-making Test (Delis–Kaplan Executive Function System™) and the Wisconsin Card Sorting Test (WCST; Psychological Assessment Resources) were administered to evaluate the capabilities of working memory. In the Trail-making Test, the subjects were required to link numbers from 1 to 16 amongst distractors consisting of letters from the English alphabet. The consumed time served as an index of working memory performance. In WCST, the percentage of perseverative errors was quantified from 128 trials. Written informed consent, approved by the Local Ethics Committee, was obtained for each participant. All the participants are right-handed.

Experimental stimuli consisted of Arabic numbers of 1 to 10 and a cross. The stimuli were positioned at the center of the monitor, subtending 5×5 degrees of visual angle. Each participant was instructed to fixate on the center of the monitor. All stimuli and instructions at the beginning of the formal experiment were presented to the participant using an LCD media projector via a screen that was viewed through a mirror box placed on the MRI head coil. A simple block design was constructed with two interleaved conditions: resting baseline condition and active task condition. The task was performed over one session and the first epoch was resting. Each epoch lasts 10 scans and there were four resting epochs and three active task epochs, with 70 scans in total. Our pilot experiment revealed that the task loading of two-back or three-back was too difficult for a substantial portion of the elderly depressives. The imaging paradigm of this preliminary study just focused on the one-back condition to enable comparable behavioral performance. Previous research has demonstrated that the one-back condition activates similar but fewer neural correlates and weaker neural responses than the two-back condition, with the cognitive load manifest as a parametric dose response in the fronto-parietal network (Braver et al., 1997; Ragland et al., 2002). The one-back condition relies on the capability of registration, maintenance and constant updating, making it different from attention alone. The executive operation in the one-back condition could originate from switching/inhibiting the targets in previous trails to the potential targets in ongoing trials, which is supported by