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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

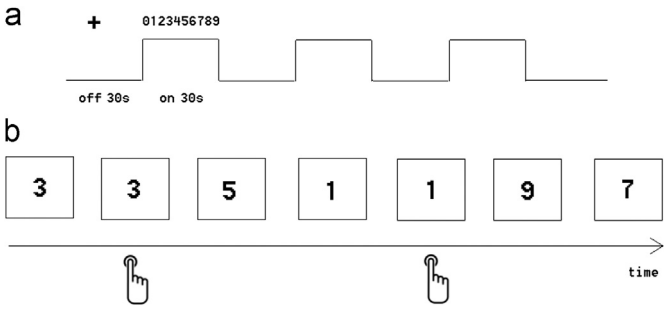

Fig. 1. Illustration of experiment design and the sequence of events in the one-back working memory task: (a) the structure of the whole experiment, with interleaving resting (fixation at the cross) and active task conditions (numbers 0 to 9); (b) the structure of a single block of the active condition.

the engagement of the anterior cingulate and dorso-lateral prefrontal regions in our activation map (Hartley and Speer, 2000). The participants responded when the number presented was the same as the preceding number and the participants withheld response when the numbers were different. Fifty percent of trials in each epoch required responses. The average inter-trial interval was 2 s, and the total number of trials was 45. The participant was instructed to focus on the central cross in the resting condition, and to make button presses to correct trials using the right index finger as a response. The experimental design is illustrated in Fig. 1. Each participant practiced the task for 10 min before the formal scanning experiment began. During the practice phase, each participant achieved a correct response rate above 90%.

2.2. fMRI data acquisition

Sequential T2*-weighted echoplanar images were acquired (Magnetom Trio with Tim, Siemens MRI Scanners; 3.0 T, 30 slices, 3.0 mm thick with 1 mm gap, TE 30 ms, TR 3.0 s, voxel size $3 \times 3 \times 4$ mm^3) for blood oxygenation level dependent (BOLD) effect. The slices covered the whole brain. Head movement was minimized during scanning by using a comfortable external head restraint. Seventy-five whole-brain images were obtained for around 3.5 min. The first five echoplanar volumes were not analyzed to allow for signal equilibrium. A T1-weighted structural image was obtained via 3D GRE pulse sequence for each participant to facilitate anatomical description of individual functional activity after co-registration with fMRI data.

2.3. fMRI data analysis

We used the Analysis of Functional Neuroimages software package (AFNI; http://afni.nimh.nih.gov/afni/) to analyze acquired fMRI data. Preprocessing included realignment (motion-corrected), slice time correction, and spatial normalization to standard stereotaxic space (voxel size $2 \times 2 \times 2$ mm; with respect to the Talairach coordinate system). The resulting movement parameters were checked and censored to ensure that motion did not exceed 4 mm in any plane. Scans were smoothed (Gaussian kernel full-width half-maximum, 8 mm) prior to analysis. For each participant, linear regression was used to model baseline drift (2nd order polynomial function) and residual motion artifact. The epochs of the active task condition were modeled as a block design, while the session effect was modeled in a separate column. Task-related brain activity was identified using the General Linear Model. Significant clusters were defined as contiguous voxels with $P < 0.025$ (corrected for multiple comparisons; family-wise error), voxel-wise threshold of 0.005, and a minimum volume of 160 μL (20 voxels). In each individual participant analysis, we constructed two contrasts: [1] active task minus resting (contrast *WR*) which would reveal the network of working memory and right index finger pressing response; and [2] resting minus active task (contrast R–W) which would reveal the midline and limbic structures resembling the default-mode network (for review, see Broyd et al., 2009). Differential brain activity of the PMDD and control groups was examined within the second-level analyses of the above contrasts using simple *t*-tests.

For the brain regions showing significant between-group differences, there exists an uncertainty regarding the contributing sources, e.g., neural nodes with activities showing "PMDD $W-R$" greater than "control $W-R$" could be partly attributed to reduced activities in "PMDD $R-W$" compared with "control $R-W$". Conversely, neural nodes derived by "control $W-R$" minus "PMDD $W-R$" could originate from enhanced activities in "PMDD $R-W$" compared with "control $R-W$". (Note: the condition of "control $R-W$" greater than "PMDD $R-W$" and the condition of "PMDD $R-W$" greater than "control $R-W$" are the same as the two aforementioned possibilities, respectively.) We thus constrained the between-group comparisons by taking the group results of the non-depressive controls as inclusive/exclusive masks. Again, the family-wise statistical threshold was set at $P < 0.025$, corrected, and the extent threshold was set at 20 voxels in the construction of masks and the group analyses. It was possible that the PMDD group mobilized extra resources, and hence activated brain regions outside the two inclusive masks, to facilitate the working memory task. We further constructed an exclusive mask by *F*-test of the $W-R$ contrast in the control group, which was equal to the union of the *t*-test results of both $W-R$ and $R-W$ contrasts. For each participant, we calculated the coefficients of the General Linear Model at all the brain regions showing significant between-group differences and the coefficients (at left amygdala, see Section 3) were further correlated with HDRS and HAM-A scores.

3. Results

3.1. Demographical information and behavioral results

The PMDD and control groups are comparable in age, education level (years) and MMSE score. The mean age, education level and MMSE score of depressive patients and non-depressive controls are 65.1 (S.D. 4.9) vs. 64.8 (S.D. 4.2), 7.6 (S.D. 2.7) vs. 8.6 (S.D. 2.4) and 26.1 (S.D. 2.0) vs. 27.3 (S.D. 1.6), without significant statistical difference. No between-group difference of gender distribution is noted, either (F/M were 3/11 and 5/9 for PMDD and control groups). The averaged pre-treatment HDRS score is 18.5 (S.D. 3.8, minimum 14, maximum 27) and the averaged episode number of depression occurrence is 1.3. The treatment duration of the PMDD group is 1.48 years (minimum 7 months, maximum 26 months). There are marked differences in the HDRS and HAM-A scores between the PMDD group (HDRS: mean 16.1, S.D. 5.8, minimum 11, maximum 26; HAM-A: mean 17.1, S.D. 6.6, minimum 9, maximum 29) and the control group (HDRS: mean 2.8, S.D. 2.0; HAM-A: mean 6.1, S.D. 3.1) at scanning. Among the 14 PMDD patients, two have HAM-A scores above 25; however, they do not fit the diagnostic criteria of generalized anxiety disorder because the time requirement of 6 months is not met. The performance of the PMDD group is inferior to that of the control group on the Trail-making Test and the WCST. Demographic, neuropsychological evaluation and clinical information are summarized in Table 1. The prescribed psychotropic medications included anti-depressants (paroxetine × 6, escitalopram × 3, mirtazapine − 2, duloxetine − 2, venlafaxine − 1) and mild tranquilizers. The correlation between the severity of depression (HDRS) and anxiety (HAM-A) in PMDD is significant, with correlation coefficient 0.863 ($P < 0.001$). Behaviorally, the performance on the working memory task is also comparable between the PMDD patients and non-depressive controls; the correct response rate 88.3% (S.D. 9.8%) vs. 90.7% (S.D. 8.7%) and the reaction time 899.4 ms (S.D. 128.1 ms) vs. 842.7 ms (S.D. 97.2 ms), with the respective *P* value 0.506 and 0.199 (d.f. 26).

3.2. Functional imaging results

3.2.1. Activation maps of one-back working memory task

The contrast of $W-R$ reveals widespread activation in both PMDD and non-depressive control groups. For the control group, the neural nodes showing significant activity encompass bilateral, superior, middle and inferior frontal gyri, precentral cortex, medial frontal and anterior cingulate regions, superior and inferior parietal lobules, lentiform nuclei, thalamus, cerebellum and several visual associative cortices; see Table 2 and Fig. 2.

3.2.2. Deactivation maps of one-back working memory task

For the control group, the brain regions showing reduced activity in the one-back working memory task relative to the resting condition are similar to but extend beyond the reported default-mode network (for review, see Broyd et al., 2009). The deactivation map indicates the brain regions that show higher activity during the resting state, i.e., several midline and limbic structures, including superior and medial frontal cortices, superior, middle and temporal gyri, posterior cingulate,

Table 1
Demographic, neuropsychological, and clinical information of depressive patients and non-depressive controls.

Depressive patients	Non-depressive controls			
Number	14	14	*t* value	*P* value (d.f.=26)
Age (yr)	65.1 (4.9)	64.8 (4.2)	0.166	0.870
Education (yr)	7.6 (2.7)	8.6 (2.4)	−1.296	0.206
HDRS	16.1 (5.8)	2.8 (2.0)	8.086	<0.001
HAM-A	17.1 (6.6)	6.1 (3.1)	5.651	<0.001
MMSE	26.1 (2.0)	27.3 (1.6)	−1.769	0.089
Trail making task (s)	82.1 (28.8)	52.1 (17.9)	3.309	0.0032
WCST (%)	26.4 (11.0)	18.8 (5.8)	2.295	0.0300
–	–	–	χ^2 value	*P* value (d.f.=1)
Gender (F/M)	3/11	5/9	0.700	0.678
Handedness (R/L)	14/0	14/0	–	

The parametric variables were expressed as mean (S.D.).
The threshold of *P* value was set at 0.05, two-tailed.
HDRS: Hamilton Depression Rating Scale.
HAM-A: Hamilton Anxiety Scale.
MMSE: Mini-mental State Examination.
WCST: Wisconsin Card Sorting Test; perseverative error rates are compared.

parahippocampal gyri, uncus, subcallosal area, caudate head and amygdala; see Table 3 and Fig. 2 for details.

3.2.3. Between group differences in the activation map of working memory task

We compare the contrasts of $W-R$ in the PMDD and non-depressive control groups. Since the calculated between-group differences could have originated from differential activities in the activation ($W-R$) or deactivation ($R-W$) maps, we constrain between-group comparison with an inclusive mask to disambiguate the uncertainty. The inclusive mask is derived from the main effect of $W-R$ of the control group, the same as the brain map summarized in Table 2. The PMDD group shows enhanced activities at middle frontal cortex and parietal regions, including superior and inferior parietal lobules. The control group fails to show enhanced activities in any region of the inclusive mask; see Table 4 and Fig. 3.

3.2.4. Between group differences in the deactivation map of working memory task

We restrict the analysis of between-group differences in deactivation maps using an inclusive mask derived from the *R–W* contrast of the non-depressive control group, the same as the brain map summarized in Table 3. The PMDD group shows higher activity at the right superior and bilateral inferior temporal (polar) cortices and left amygdala (−25 −3 −22); see Table 4 and Fig. 3. The control group does not reveal enhanced activities in any region of this inclusive mask during the resting condition.

3.2.5. Between-group differences outside the activation/deactivation maps of the working memory task

We note that compared with the control group, the PMDD group does show differential brain activities outside the $W-R$ and $R-W$ contrasts of the control group (i.e., outside the mask derived from *F*-test), including middle frontal and middle temporal cortices; see Table 4 and Fig. 3 for details.

3.2.6. Neural responses and depressive/anxiety symptoms

The respective correlation coefficients between the beta coefficients at left amygdala and HDRS and HAM-A scores are 0.512 ($P=0.005$) and 0.536 ($P=0.003$), with the scatter plots and regression lines illustrated in Fig. 3. The respective mean beta coefficients of the PMDD group and the control group are 0.111 (S.D. 0.276; $P=0.111$, d.f.=13 when test value is zero) and −0.257 (S.D. 0.173; $P<0.001$, d.f.=13 when test value is zero) for the contrast $W-R$, indicating that the trend of amygdala deactivation disappeared in the PMDD gorup. When we perform similar analyses for all the regions showing between-group

Table 2
The activation map of one-back working memory task for the non-depressed controls (Task > Rest).

Brain area (Brodmann area/side)	Stereotaxic coordinates[a]			*Z* score	Cluster size
Superior frontal G (6/R)	14	1	52	5.12	262,912 [b]
Superior frontal G (6/L)	−23	−1	54	5.03	262,912 [b]
Middle frontal G (6/R)	34	−7	44	4.75	262,912 [b]
Middle frontal G (8,9/R)	33	40	34	3.82	262,912 [b]
Middle frontal G (6/L)	−41	−1	50	5.03	262,912 [b]
Middle frontal G (6,8,9/L)	−32	7	59	5.00	262,912 [b]
Middle frontal G (10/L)	−37	45	7	4.70	262,912 [b]
Inferior frontal G (9/R)	58	9	32	4.83	262,912 [b]
Inferior frontal G (10/L)	−38	47	1	4.89	262,912 [b]
Inferior frontal G (44,45,46/R)	46	7	26	3.97	262,912 [b]
Inferior frontal G (44,45,46,47/L)	−44	10	21	3.92	262,912 [b]
Precentral G (4,6/R)	45	−3	42	4.41	262,912 [b]
Precentral G (6,9/L)	−47	1	26	5.01	262,912 [b]
Precentral G (4,6/L)	−34	−10	50	5.61	262,912 [b]
Medial frontal G (6,8/R)	12	1	54	5.13	262,912 [b]
Medial frontal G (6,8/L)	−7	16	45	4.84	262,912 [b]
Anterior cingulate G (24/R)	7	19	41	5.01	262,912 [b]
Anterior cingulate G (24/R)	4	0	46	5.01	262,912 [b]
Anterior cingulate G (24/L)	−3	5	41	4.91	262,912 [b]
Para-cingulate (6,32/R)	8	16	42	5.00	262,912 [b]
Para-cingulate (32/L)	−8	8	44	5.26	262,912 [b]
Superior parietal lobule (7/R)	26	−57	39	5.27	262,912 [b]
Superior parietal lobule (7/L)	−23	−68	36	5.79	262,912 [b]
Inferior parietal lobule (39,40/R)	35	−64	31	5.75	262,912 [b]
Inferior parietal lobule (39,40/L)	−36	−56	46	5.50	262,912 [b]
Angular G (39/R)	32	−55	38	5.35	262,912 [b]
Suparmarginal G (40/L)	−35	−51	36	5.40	262,912 [b]
Precuneus (7/R)	6	−71	43	5.35	262,912 [b]
Precuneus (7/L)	−9	−69	47	5.41	262,912 [b]
Middle temporal G (37/R)	48	−35	−7	4.62	78,205 [c]
Middle temporal G (21/L)	−43	−53	−2	5.18	78,205 [c]
Middle temporal G (21/L)	−65	−21	−4	3.48	1771
Inferior temporal G (37/R)	48	−49	−13	4.33	78,205 [c]
Inferior temporal G (37/L)	−47	−66	1	4.37	78,205 [c]
Lingual G (17,18/R)	23	−59	4	3.85	694
Lingual G (17,18/L)	−15	−67	6	3.48	853
Fusiform G (37/R)	42	−44	−14	4.51	78,205 [c]
Fusiform G (37/L)	−42	−59	−8	4.96	78,205 [c]
Superior occipital G (19/L)	−28	−71	21	5.12	262,912 [b]
Middle occipital G (37/R)	50	−63	−8	4.73	78,205 [c]
Middle occipital G (18/R)	2	−93	17	4.02	350
Middle occipital G (37/L)	−34	−74	1	4.09	78,205 [c]
Cuneus (18/R)	1	−92	−7	3.85	78,205 [c]
Cuneus (18/L)	0	−88	−10	3.82	78,205 [c]
Insula (13/R)	31	19	0	5.21	262,912 [b]
Insula (13/L)	−25	18	7	4.68	262,912 [b]
Lentiform nucleus (R)	22	−10	7	4.13	262,912 [b]
Lentiform nucleus (L)	−17	−9	1	4.14	262,912 [b]
Caudate (R)	15	−2	18	3.88	262,912 [b]
Caudate (L)	−15	−3	15	4.01	262,912 [b]
Thalamus (R)	17	−15	11	4.42	262,912 [b]
Thalamus (L)	−15	−10	8	4.22	262,912 [b]
Brainstem (R)	8	−28	−21	3.72	486
Brainstem (L)	−14	−21	−15	3.53	262,912 [b]
Red nucleus (R)	9	−18	−7	3.40	262,912 [b]
Red nucleus (L)	−9	−20	−6	3.17	262,912 [b]
Cerebellum (R)	6	−56	−30	4.71	78,205 [c]
Cerebellum (L)	−37	−54	−30	4.75	78,205 [c]

[a] Values represent the stereotaxic location of voxel maxima above corrected threshold ($P<0.05$) and spatial extent of 20 voxels (8 mm^3/voxel).
[b,c] Values represent the stereotaxic location of voxel maxima above corrected threshold ($P<0.05$) and spatial extent of 20 voxels (8 mm^3/voxel).

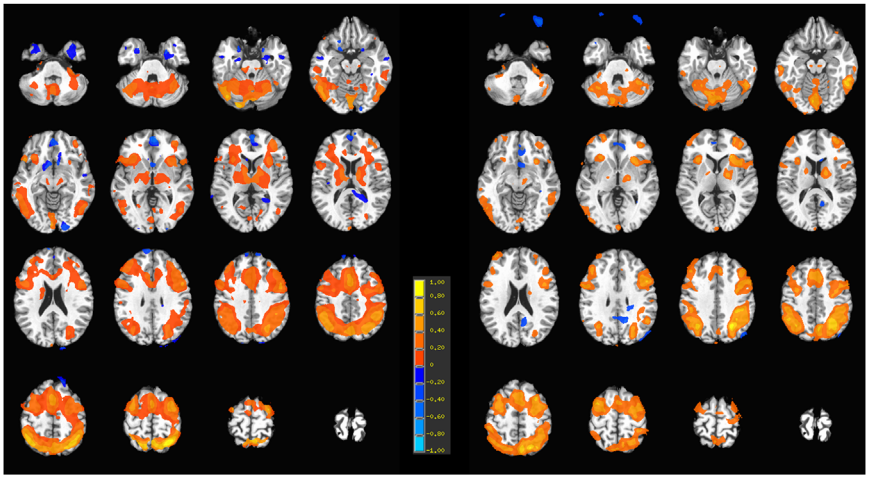

Fig. 2. The results of the Brain activation/deactivation maps in the working memory task for the control (left) and the depressed (right) group. Bold contrasts are superimposed on a T1 structural image in axial sections from $z=71$ mm to $z=-34$ mm, with between slice gap 7 mm. The display orientation is in radiological convention (i.e., left is right). The hot color indicates activation and the blue color indicates deactivation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
The Deactivation map of the one-back working memory task for the non-depressed controls (Rest > Task).

Brain area (Brodmann area/side)	Stereotaxic coordinates [a]			*Z* score	Cluster size
Superior frontal G (8,9/R)	9	59	31	4.08	1074
Superior frontal G (8,9/L)	−16	42	48	4.88	1160
Medial frontal G (10,32/R)	1	44	−4	4.49	4203 [b]
Medial frontal G (9,10,32/L)	−1	51	20	4.19	4203 [b]
Posterior cingulate (32/L)	−20	−46	13	4.53	1795
Superior temporal G (22/R)	64	−41	8	3.31	123
Superior temporal G (38/L)	−50	−6	−8	4.45	906 [c]
Middle temporal G (21/R)	47	−6	−17	4.15	538
Middle temporal G (21/L)	−49	−6	−19	4.10	906 [c]
Inferior temporal G (20/R)	41	3	−30	3.37	4489 [d]
Inferior temporal G (20/L)	−30	−3	−33	4.16	4220 [e]
Parahippocampal G (28/R)	19	−10	−21	4.09	193
Parahippocampal G (28/L)	−35	11	−31	4.42	4220 [e]
Subcallosal G (R)	7	12	−6	4.45	4489 [d]
Subcallosal G (L)	−15	21	−3	3.33	4489 [d]
Uncus (28/R)	25	5	−31	5.05	4489 [d]
Uncus (28/L)	−32	−1	−33	4.26	4220 [e]
Insula (13/R)	36	−20	17	3.34	101
Superior occipital G (19/L)	−37	−85	29	3.77	266
Inferior occipital G (17/L)	−15	−90	−10	3.88	1310
Caudate head (R)	8	19	7	3.31	124
Caudate head (L)	−6	14	11	3.27	101
Amygdala (L)	−25	−6	−21	3.94	4220 [e]

[a] Values represent the stereotaxic location of voxel maxima above corrected threshold ($P<0.05$) and spatial extent of 20 voxels (8 mm^3/voxel).

[b,c,d,e] Values represent the stereotaxic location of voxel maxima above corrected threshold ($P<0.05$) and spatial extent of 20 voxels (8 mm^3/voxel).

differences, we find that for the PMDD group, the right superior and polar temporal regions also lose responsive deactivation in performing the working memory task; see Fig. 4 and Table 5.

4. Discussion

This study used fMRI to measure brain activity in performance of a one-back working memory task to investigate the partial responders of late-onset major depressive disorder, with the recruited non-depressive controls comparable in age, education level, MMSE score, gender distribution and the behavioral performance of one-back task even though the scores of the depressive group are lower in the working memory tasks included in the Trail-making Test and the WCST. The one-back working memory task, in comparison with the resting condition of central fixation, activates widespread cortical and subcortical structures (contrast $W-R$), reflecting the demand of working memory execution and motor response (for review, see Wager and Smith, 2003). The contrast of "resting condition minus working memory condition" (contrast R–W) reveals a pattern similar to the "default-mode" network (Broyd et al., 2009). Although the activation/deactivation brain maps of the PMDD and control groups are alike, the PMDD group activates the left middle frontal and left parietal regions more intensely and mobilizes several extra-brain regions (i.e., outside the brain maps derived from the control group) in carrying out the working memory task, mainly bilateral middle frontal and temporal regions. In addition, the PMDD group demonstrates a trend toward higher activity at the left amygdala in the contrast of $W-R$. It is interesting that during the cognitive challenge, left amygdala and bilateral polar temporal regions reveal an opposite provocation tendency in the two studied groups, with the activity significantly reduced in the control group and the activity not decreased (or slightly increased) in the PMDD group.

The profile of cognitive dysfunction observed in patients with MDD may be partially attributed to a deficit in the capability of working memory. Our results reveals a different pattern of neural responses compared with those discovered in acute depression or remitted depression: It has been reported that patients with acute depression may require more neural activity to achieve a similar level of performance on a working memory task (Harvey et al., 2005; Matsuo et al., 2007) and that the hyperactivation normalizes during the remitted state (Schöning et al., 2009). An fMRI study by Rose et al. collected 10 patients with a diagnosis of MDD and 10 matched healthy controls undertaking a working memory task, revealing that performance of a working memory task is associated with a dysfunctional activation of the fronto-limbic region in MDD (Rose et al., 2006). Conjoint with previous findings, our results suggest that the neural responses to working memory challenge are only partly normalized for the PMDD after at least half a year of treatment, with sustained hyperactivity at left middle frontal and left parietal regions and loss of deactivation at amygdala. Further, the PMDD patients mobilize several brain regions which are not included in the neural nodes of the working

Table 4
Differences in the working memory network between depressed and control groups.

Brain area (Brodmann area/side)	Stereotaxic coordinates [a]			*Z* score	Cluster size
	"Task minus Rest" contrast: Depressed group > Control group (The activation map of control group serves as an *inclusive* mask)				
Superior parietal L (7/L)	−31	−65	48	3.05	82
Inferior parietal L (7,40/L)	−33	−55	44	3.14	192
Middle frontal G (9/L)	−56	10	36	3.49	71
	"Task minus Rest" contrast: Depressed group > Control group (The deactivation map of control group serves as an *inclusive* mask)				
Superior temporal G (22/R)	66	−43	9	3.53	62
Inferior temporal G (38/R)	26	8	−31	3.60	80
Inferior temporal G (38/L)	−29	10	−38	3.87	410
Amygdala (L)	−22	−3	−22	3.77	484
	"Task minus Rest" contrast: Depressed group > Control group (The union of activation and deactivation maps of control group serves as an *exclusive* mask)				
Middle frontal G (10,46/R)	39	55	18	3.44	606
Middle frontal G (10/R)	21	56	−1	4.17	558
Middle frontal G (10/R)	27	62	26	3.39	102
Middle frontal G (46/L)	−47	36	26	3.49	296
Middle temporal G (20/L)	−54	−46	−10	3.42	188
Middle occipital G (18,19/R)	44	−83	4	3.54	749

There is no region of the control group showing greater activity than that of the depressed group regardless of the masks.

[a] Values represent the stereotaxic location of voxel maxima above corrected threshold ($P < 0.05$) and spatial extent of 20 voxels (8 mm^3/voxel).

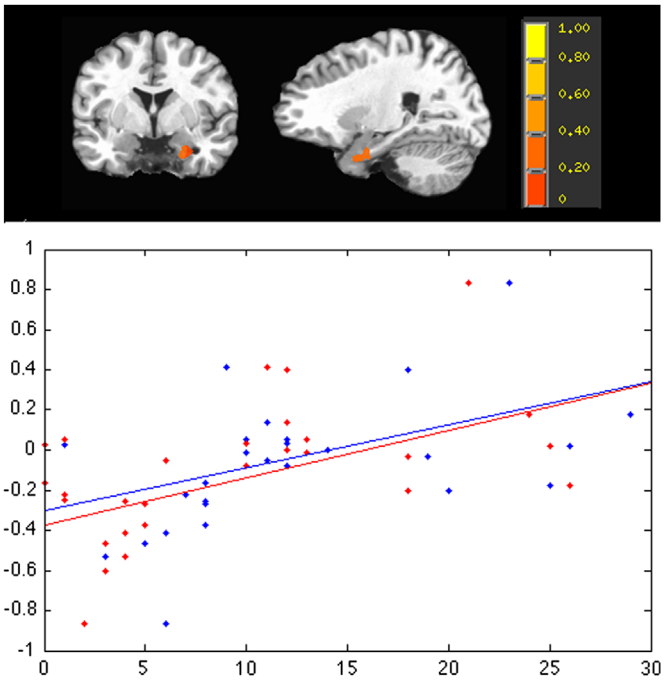

Fig. 3. Upper: The enhanced activities at left amygdala (−22 −3 −22) of the depressive patients in contrast to non-depressive controls during the performance of working memory task. Lower: The scatter plot and regression lines of the scores of HDRS (Red) and HAM-A (Blue) versus the beta coefficients at left amygdala (Ordinate). (For interpretation of the references to color in this figure legend, the reader is reffered to the web version of this article.)

memory task observed in the non-depressive controls, indicating possible neural reorganization of the brain which enables recruiting more resources to carry out executive functioning. The observed partial normalization and reorganization may suggest that the compensatory mechanism to overcome the working memory deficit in MDD alters from simple hyper-activation in the acute phase to a more balanced strategy, namely both hyper-activation and reorganization. The accommodation may partly alleviate the cognitive deficits that accompany PMDD.

It is noteworthy that in the execution of working memory tasks, the PMDD group fails to show deactivation at limbic structures (amygdala and superior temporal cortex), whereas the control group shows obvious deactivation. On the one hand, our findings for the amygdala are concordant with previous reports relating enhanced activity in the amygdala to depression relapse and treatment resistance (Drevets, 2000; Ramel et al., 2007). On the other hand, the reduced activity in the amygdala for the control group has been consistently observed during the performance of tasks that demand volitional or effortful engagement of 'higher' cognitive processes or higher attentional load (Hariri et al., 2003; Liberzon et al., 2003; Ochsner and Gross, 2005; Taylor et al., 2003). Recently, Yun et al. reported that reduced suppression of amygdala activity is an index of vulnerability to the loading effect of a working memory task (Yun et al., 2010). Greater impairment of cognitive performance also characterizes geriatric depression and chronicity in disease course (Alexopoulos et al., 2000; Fountoulakis et al., 2003). Together, the amygdala abnormality and the cognitive dysfunction in PMDD might explain the poorer performance in the two-back condition of the PMDD group in our pilot examination. However, we are unable to replicate earlier findings at the subgenual cingulate, which is another key indicator of treatment response (Konarski et al., 2009; Mayberg, 1997). It is possible that the aberrant pre-treatment activity at the ventral anterior cingulate, like other dorsolateral prefrontal regions, is gradually normalized in PMDD. Our findings thus point out the importance of the amygdala in the maintenance of depressive symptoms in partial responders. The significant correlation between amygdala activity and HDRS score strengthens this argument. The heightened activity at left amygdala, manifest as loss of deactivation or slightly increased activity, during cognitive operations may signal dysfunctional fronto-limbic interactions critical to emotional homeostasis, which may result in negative bias in attention deployment and recall, and might further contribute to cognitive distortion, negative interpretations of experiences, and consequently to the formation of dysfunctional attitudes regarding personal adequacy, acceptability, and worth.

As in other research exploring comorbidity of anxiety in elderly depressive disorder, this study also found that the severity of depression is positively correlated with the severity of anxiety (Cairney et al., 2008; King-Kallimanis et al., 2009; Lenze et al., 2001). Greenlee et al. found that more severe psychological symptoms of anxiety after 6 weeks of treatment were associated with

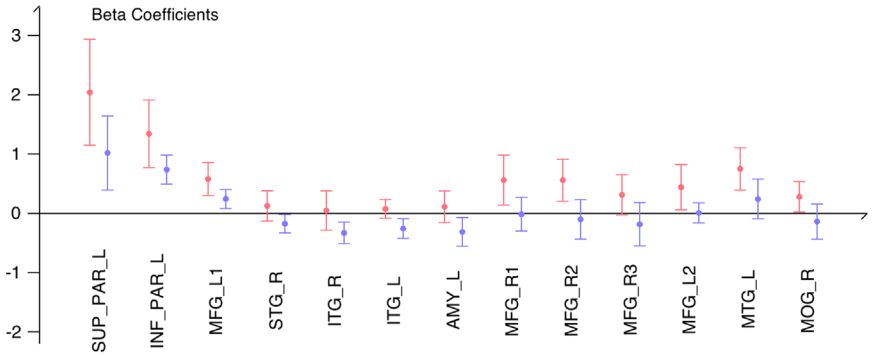

Fig. 4. The beta coefficients, expressed as mean +S.D., of the contrast "Task minus Rest" at the brain regions showing significant between-group differences (please refer to Tables 4 and 5 for the details of statistics and coordinates). Red: patient group. Blue: control group. Abbreviations: MFG, middle frontal gyrus; SUP_PAR, superior parietal lobule; INF_PAR, inferior parietal lobule; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; MOG, middle occipital gyrus; AMY, amygdala; _R, right hemisphere; _L, left hemisphere. MFG_L1 at coordinate (−56 10 36), MFG_L2 at coordinate (−47 36 26), MFG_R1 at coordinate (39 55 18), MFG_R2 at coordinate (21 56 −1), MFG_R3 at coordinate (27 62 26). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 5
The mean beta coefficients of the contrast "Task minus Rest" of the brain regions showing between-group differences.

Brain area (Coordinate)	Patient (S.D.)	*P*-value	Control (S.D.)	*P*-value
Superior parietal L (−31 −65 48)	2.041 (0.928)	$1.641 \times \exp(-6)$	1.018 (0.649)	$5.462 \times \exp(-5)$ [a]
Inferior parietal L (−33 −55 44)	1.341 (0.593)	$1.209 \times \exp(-6)$	0.736 (0.255)	$7.208 \times \exp(-8)$ [a]
Middle frontal G (−56 10 36)	0.576 (0.288)	$4.609 \times \exp(-6)$	0.242 (0.165)	$1.052 \times \exp(-4)$ [a]
Superior temporal G (66 −43 9)	0.126 (0.264)	0.097	−0.175 (0.160)	$1.263 \times \exp(-3)$ [a]
Inferior temporal G (26 8 −31)	0.047 (0.344)	0.618	−0.330 (0.190)	$2.010 \times \exp(-5)$ [a]
Inferior temporal G (−29 10 −38)	0.075 (0.166)	0.114	−0.257 (0.173)	$9.260 \times \exp(-5)$ [a]
Amygdala (−22 −3 −22)	0.111 (0.276)	0.155	−0.313 (0.252)	$4.609 \times \exp(-4)$ [a]
Middle frontal G (39 55 18)	0.560 (0.436)	$3.477 \times \exp(-4)$	−0.014 (0.294)	0.859
Middle frontal G (21 56 −1)	0.558 (0.367)	$7.387 \times \exp(-5)$	−0.101 (0.348)	0.298
Middle frontal G (27 62 26)	0.311 (0.351)	$5.606 \times \exp(-3)$	−0.184 (0.377)	0.091
Middle frontal G (−47 36 26)	0.440 (0.394)	$1.084 \times \exp(-3)$	0.008 (0.175)	0.867
Middle temporal G (−54 −46 −10)	0.749 (0.370)	$4.032 \times \exp(-6)$	0.241 (0.347)	0.022
Middle occipital G (44 −83 4)	0.280 (0.266)	$1.726 \times \exp(-3)$	−0.140 (0.308)	0.115

The order and arrangement of anatomical regions are the same as those in Table 4, organized into three blocks.
The statistical test was based on a one-sample *t*-test with test value 0 (d.f.=13).

[a] indicates the regions within the activation/deactivation maps of the non-depressive control group.

lower remission rates in later life depression (Greenlee et al., 2010). Steffens et al. reported that symptoms of generalized anxiety disorder were associated with longer time-to-remission (Steffens and McQuoid, 2005). The observed co-linearity of neural response at the amygdala, depression severity and anxiety severity in PMDD is not only compatible with the extant literature but also implicates the central role of the amygdala in mediating comorbidity of anxiety symptoms and resistance to antidepressant treatment in geriatric depression. Our left-hemispheric amygdala finding is in line with the double dissociation observed in patients with unilateral temporal lobectomy where the right medial temporal structure relates to emotion processing per se, and the left medial temporal structure modulates emotional responses via cognitive representation (Funayama et al., 2001). An interesting study by Siegle et al. found that higher activity in the amygdala during cognitive appraisal predicts better treatment response to cognitive-behavior treatment (Siegle et al., 2006). Since our PMDD patients mainly received antidepressant treatment, it is possible that the PMDD patients will benefit from psychotherapy or anxiety reduction techniques in addition to pharmacological intervention. The pattern of opposite activation (PMDD) and deactivation (control) at right superior temporal and bilateral polar temporal regions was not expected, which might be related to abnormal cognition–emotion interaction and aberrant emotional self-regulation mediated by the temporal lobe in depression (Beauregard et al., 2006; Canli et al., 2004; Levesque et al., 2003). It is noticed that our deactivation map includes several regions outside the conventional default-mode network, such as the amygdala and the head of the caudate. Our finding is a reminder that the default-mode network is not to be equated with an exhaustive account of the deactivation brain map, which might include a task-specific component.

Successful execution of working memory relies on the synergy of a set of mental capabilities. Baddeley proposed central executive, phonological loop, visuo-spatial sketchpad and episodic buffer as a four-compartment mode to support working memory (Baddeley, 2000; Baddeley and Della Sala, 1996). Other researchers address the roles of attention in the operation of working memory tasks, attention can be expanded under different levels of working memory load (McElree, 2001; Oberauer, 2002, 2006). The operation of working memory is not an isolated mental process. It may be the orchestration of central executive function, lower and higher perceptual processing, perceptual buffering, focal attention, general attention level, expansibility of mental capabilities, efficiency in information transfer and their interaction, and so on, that determines the performance of working memory. Our analytic contrast of one-back minus resting, in opposition to two-back minus one-back, may carry a drawback that the lower level perceptual processing is not well controlled in single group analysis; however, it provides a holistic neural pattern that supports the execution of working memory. In addition, the between-group comparison should eradicate the primitive neural responses to delivered visual stimuli given that the experimental material are the same for the two studied groups. Our finding at the lateral occipital region in the between-group comparison thus may be related to impaired lower level

perceptual processing in depressive disorders, which has also been addressed by other researchers (Mannie et al., 2010; Peng et al., 2011; Zhang et al., 2011). It is premature to assign a correspondence between each of our neuroimaging findings and the impaired neuropsychological sub-components associated with working memory; however, our results in inclusive/exclusive masks and outside conjoint mask echo the heterogeneity and complexity of MDD.

We acknowledge that since the recruited patients have received psychotropic treatment for 1.48 years on average, chronic effects of medication, e.g., antidepressant, might explain the differential neural responses. It is difficult to discuss this issue for now given that most previous studies of emotion or affective disorder address the "acute" drug effects on the brain (Anderson et al., 2008). However, the amygdala has been noticed to be modulated pharmacologically in emotional processing as opposed to purely cognitive tasks (Anderson et al., 2008; Del-Ben et al., 2005). Further, the acute and chronic modulatory effect of antidepressants is generally inhibitory, not excitatory, on amygdalar activity (de Almeida et al., 2010; Del-Ben et al., 2005). In parallel with the observation at amygdala, subchronic and chronic administration of antidepressants is associated with hypo-activation in insula during anticipation and with reduced neural responses at amygdala, anterior insula and ventral cingulate during emotional face matching tasks (Simmons et al., 2009; van Marle et al., 2011). In addition, chronic administration of antidepressants would decrease baseline metabolism in a wide range or neuromatrix for depressed patients, covering anterior cingulate, frontal, inferior parietal, parahippocampal, precuneus, insula, caudate, and putamen regions (Smith et al., 2011). We thus hold our findings of enhanced activities at limbic structures, especially left amygdala, heuristic. This report did not incorporate the groups of acute-depressed and fully-remitted MDD, since their neural characteristics have been depicted by abundant neuroimaging experiments in adult depression and whether geriatric depression represents an independent clinical entity is still not widely acknowledged (Laks and Engelhardt, 2010). Nevertheless, to conclude the neural manifestations of different groups of treatment response categories among geriatric MDD, it is worthwhile to design a large-scale prospective imaging study to compare the MDD patients categorized retrospectively by the treatment responses into subgroups of responders, partial responders (can also be described as partially treatment resistant) and refractory cases. In contrast to the abnormal "deactivation" at amygdala in PMDD as demonstrated in this working memory study, it is also encouraged to explore whether there is an abnormal "activation" pattern using an emotional task potent in eliciting amygdalar response.

5. Conclusion

Although PMDD accounts for a substantial portion of MDD (Steffens et al., 2003), very few studies have addressed the neural characteristics of PMDD. This study provides insight into the possible neural normalization and neural reorganization of PMDD. We highlight that in contrast to the commonly observed deactivation of limbic structures during cognitive appraisal, left amygdala and polar temporal regions are not deactivated or even activated in PMDD during a working memory task. The opposite activation/deactivation profiles might contribute to the inferior treatment response. Given the complexity and heterogeneity of MDD, our research sample is restricted to the late-onset population. Comparing late-onset PMDD with younger PMDD and early-onset geriatric PMDD is encouraged to extend our understanding of neural fingerprints of treatment response across different ages. To delineate the temporal courses of neural plasticity of PMDD, prospective longitudinal studies are also warranted.

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