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Altered Functional Magnetic Resonance Imaging Markers of Affective Processing During Treatment of Late-Life Depression

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Abstract

Objective—This study investigated neural substrate changes in affective processing among late-life depression (LLD) patients undergoing antidepressant treatment and determined if these changes correlated with remission status.

Methods—Thirty-three LLD patients were enrolled in a 12-week venlafaxine treatment course. During treatment functional magnetic resonance imaging (fMRI) scans, paired with an affective task that assessed emotional reactivity and regulation, were performed on days 1, 2, 3, and 7 and at week 12. Following treatment patients were classified as remitters or non-remitters. A voxel-wise two-way repeated-measures ANOVA was performed to assess the fMRI data at a significance level of $\alpha = 0.05$, corrected.

Results—The emotional reactivity contrast demonstrated a significant interaction between remission status and scan time in the right middle temporal gyrus (MTG) ($F = 24.1$, $df = 1, 112$, $k = 102$). Further analysis showed increased emotional reactivity-induced activity among non-remitters, and decreased activity among remitters, which significantly differed from baseline at day 7 (95% CI: 0.027, 0.540; Cohen's $d = -1.35$) and week 12 (95% CI: -0.171 , -0.052 ; Cohen's $d = 0.68$), respectively. No significant interaction was observed with the emotional regulation contrast, but multiple regions had significant main effects of scan time, including the cuneus, occipital lobe, insula, lingual gyrus, posterior cingulate cortex, and MTG.

Conclusions—During treatment of LLD patients, affective processing-induced activity in the right MTG shows changes based on remission status. This alteration becomes evident early during the course of treatment, suggesting that antidepressant pharmacotherapy may acutely affect the neural basis of emotional reactivity in a differential manner that is relevant to illness remission.

Keywords

depression; geriatric; neuroimaging; emotions

Late-life depression (LLD) has been estimated to affect 1.8% to 9.8% of community-dwelling older adults.¹ Its disease burden is considerable, with effects on mortality,

functional status, and healthcare utilization.¹ LLD is also a significant risk factor in the development of dementia.² As a disease that affects so many areas of an elderly patient's life, it is unfortunate that it is often underdiagnosed.³ Furthermore, when it is recognized, its treatment poses unique challenges. Although selective serotonin reuptake inhibitors are still considered first-line agents in the treatment of LLD, their efficacy is decreased as compared with response rates seen in younger patients.⁴ Full response to treatment can also be delayed, with many elderly patients requiring 8–12 weeks before experiencing symptom remission, instead of the usual 4–6 weeks.⁵

Treatment response variability in older depressed adults suggests that distinct pathophysiological processes are involved in LLD. This is supported by numerous studies that illustrate LLD as a heterogeneous disorder resulting from a complex interaction between inflammatory, endocrine, immune, and ischemic-related changes influenced by patients' hereditary, psychological, and social vulnerabilities.⁶ LLD and major depressive disorder (MDD) at other ages appear to share similar alterations in distinct neural circuits as measured by functional magnetic resonance imaging (fMRI).⁷ These changes are primarily localized to frontostriatal pathways and are thought to result in impairments in emotional reactivity and regulation. Specifically, decreased activity has been observed in dorsal cognitive structures such as the dorsolateral prefrontal cortex and dorsal anterior cingulate cortex, and increased activity is seen in limbic and rostral cingulate structures.⁸ Furthermore, changes in these networks among mid-life MDD patients have been associated with treatment outcomes. Most previous investigations have demonstrated a relationship between pretreatment fMRI activity in the aforementioned structures and treatment response, with a few able to show normalization of these findings upon remission.^{9–13}

Non-imaging emotion processing research has established key differences between healthy elderly and younger patients. Old age is associated with increases in emotional stability and general emotional well-being.^{14–16} A positive bias is also evident in the elderly, which manifests as increased attention to and recall of positive stimuli compared with negative stimuli.^{17,18} With such distinctions between the emotional states of elderly and young patients, it seems likely that the affective neural circuits underlying them are also altered.

Therefore, it is conceivable the affective processing related neural activity in LLD may be unique from that observed in younger patients and healthy controls. Additionally, these changes may be related to treatment outcomes, similar to findings seen in mid-life MDD. In the current study we investigated the dynamic neural basis of emotion processing in LLD by performing repeated fMRI scans paired with an affective task throughout a 12-week treatment trial. The primary hypothesis of this study was that affective processing as measured by fMRI blood-oxygen-level-dependent (BOLD) signal would significantly differ with respect to patients' remission status and across the scan time points during treatment.

METHODS

Study Design

Institutional review board approval was granted for this research. Participants were recruited from two LLD open-label clinical trials. Full protocols for these clinical trials can be found

elsewhere.^{19,20} In brief, both studies enrolled LLD patients from National Institutes of Mental Health–sponsored clinics and treated them with venlafaxine for 12 weeks. Starting dosage was 37.5 mg, and was titrated upwards every 3 days in increments of 37.5 mg to an initial target dosage of 150 mg/day. At week 6, patients whose Montgomery-Asberg Depression Rating Scale (MADRS) score remained greater than 10 had their dosage titrated upwards in 37.5-mg or 75-mg increments up to a target dosage of 300 mg/day.

Inclusion criteria for the current study required age 60 years or greater and presence of current depressive disorder as determined by the Structured Clinical Interview for DSM-IV disorders. Exclusion criteria included medical history significant for mania, psychosis, alcohol/drug abuse, dementia, and neurodegenerative disorders. Patients scoring less than 18 on the Mini-Mental State Examination (MMSE) were excluded to reduce the effect of cognitive impairment on study results. Other factors precluding enrollment were contraindications to MRI including retained paramagnetic materials, claustrophobia, or weight greater than 250 lbs.

Upon enrollment participants underwent structural and functional MRI. Participants were then provided a 1-day placebo lead-in, followed by another fMRI on the morning of day 2. After their scan on day 2 participants began their first dose of venlafaxine. The remaining fMRI scans were performed at day 3, day 7, and week 12 (see Figure 1). The primary depression outcome measure was the MADRS, which was performed on day 1 and at week 12. Remission was defined as a score of 10 or less.

During each fMRI scan participants were asked to perform the affective perception and regulation task.²¹ In this task, participants are presented with emotionally neutral or negative images from the standardized International Affective Picture System (IAPS). Accompanying each image is one of two possible instruction sets. “Look” entails the participant viewing the image and allowing them to respond naturally to its content. “Decrease” tasks the participant with actively altering the emotions provoked by the image through reappraisal. For example, a picture of a person in a hospital bed might prompt the participant to imagine that they are receiving life-saving treatment. Following each image, participants are asked to rate how negative they feel on a scale of 1–5, with higher scores indicating increased negativity. Instruction sets and images were randomized for each scan time point, and these orders were applied uniformly across all participants.

Image Acquisition and Processing

Participant scans were performed using a 3-Tesla Trio TIM MRI (Siemens, Berlin, Germany). The structural MRI scan on day 1 was acquired in the axial orientation with a T1-weighted high-resolution magnetization-prepared rapid gradient-echo sequence. Imaging parameters included slice thickness = 1 mm, number of slices = 176, matrix = 256×224 mm², voxel size = $1 \times 1 \times 1$ mm³, repetition time (TR) = 2,300 msec, echo time (TE) = 3,430 msec, inversion time (TI) = 900 msec, and flip angle = 90°. All fMRI scans were acquired in the axial orientation with an echo planar imaging sequence with the following parameters: slice thickness = 4 mm, number of slices = 28, matrix = 128×128 mm², voxel size = $2 \times 2 \times 4$ mm³, TR = 2,000 msec, TE = 3,400 msec, and flip angle = 90°.

Imaging data were then subjected to multiple preprocessing steps using the Statistical Parametric Mapping (SPM) software package (Wellcome Trust Centre for Neuroimaging, London, UK). All fMRI volumes underwent slice time correction to adjust for differences in slice acquisition times. Next, all images were realigned to a mean image of the time-series. The structural volume was then coregistered to the mean fMRI volume. Subsequently, the coregistered structural images were segmented into tissue probability maps, which is necessary for deformation into the Montreal Neurological Institute template space. The deformation fields are saved, and used to normalize the functional images into the template space. A robust weighted least squares technique was used to adjust the imaging data for noise.²² In summary, this method weights each image according to the inverse of an unbiased estimate of its variance, resulting in lower weights of images with increased variance. Finally, all images were smoothed with a Gaussian kernel (full-width at half maximum = 10 mm).

Pre-processed fMRI volumes for each participant were then used to create task-relevant contrast maps, including Look Negative > Look Neutral, and Decrease Negative > Look Negative. The former isolates BOLD signal resulting from emotional reactivity to negative images by subtracting out the signal induced by general visual processing (i.e., emotional reactivity). Likewise, the latter contrast isolates BOLD signal resulting from emotional regulation by subtracting out the signal induced by emotional reactivity to negative images (i.e., emotional regulation). In order to restrict subsequent analysis to gray matter, a gray matter mask was used at this stage of processing.

Statistical Analysis

Participant age, sex, MMSE scores, final venlafaxine dose, and baseline MADRS scores were compared between remitters and non-remitters to assess confounding variables. A χ^2 test was used to assess for a sex imbalance between the groups, and the other variables underwent a two-tailed Student's t test. Statistical significance was set at $\alpha = 0.05$.

To account for the longitudinal nature of this study, we used a two-way repeated-measures analysis of variance (ANOVA) statistical model (i.e., flexible factorial design in SPM).^{23,24} This was a voxel-wise analysis where the ANOVA model consisted of a fixed effect for the factors remission status, scan time, and their interaction, with a random effect for the subject factor to account for repeated observations. This statistical test was administered separately for each of the two contrast maps. Statistical significance was set at $\alpha = 0.001$. A multiple comparison correction was implemented using a Monte Carlo simulation performed by the *3dClusterSim* function, which specified a cluster threshold of k greater than 85 for the given p value.²⁵ If any regions demonstrated a significant interaction between remission status and scan time, no further analysis was performed. If no significant interaction was observed, the main effects of remission status and scan time were assessed. Significant clusters from the ANOVA were anticipated to have their mean parameter estimate differences extracted (i.e., Look Negative > Look Neutral and Decrease Negative > Look Negative), which represent emotional reactivity and emotional regulation, to further assess the directionality and magnitude of fMRI signal changes during treatment. Further analysis would include a correlation coefficient (Pearson or Spearman) between changes in MADRS scores and mean

parameter estimates between day 1 and week 12 to determine the overall association between depressive symptomology and emotional reactivity/regulation. All post-hoc statistical tests had statistical significance set at $\alpha = 0.05$, two-tailed.

Mean participant negativity ratings were calculated for each of the three instructions for each patient for all five fMRI scans. A paired t test compared patients' mean negativity ratings for the Decrease Negative and Look Negative instruction sets to assess the patients' ability to effectively engage in emotional regulation. The same test was performed between patients' mean negativity ratings of Look Negative and Look Neutral to determine if the selected IAPS pictures were appropriately eliciting negative and less negative emotion states, respectively. Statistical significance was set at $\alpha = 0.05$, two-tailed.

RESULTS

The study enrolled 33 LLD participants undergoing venlafaxine pharmacotherapy. Following treatment, 20 participants were classified as remitters, with the remaining 13 classified as non-remitters. Comparison of participant baseline characteristics using Student's t test (two-tailed) and χ^2 test revealed no significant differences between these groups (Table 1). The paired t test ($\alpha = 0.05$, two-tailed) of patients' mean negativity ratings revealed a significant difference ($t_{(32)} = -4.3$, $p < 0.001$) between the instruction sets Decrease Negative (mean: 2.9, SD: 0.6) and Look Negative (mean: 3.2, SD: 0.5). The analogous assessment between Look Negative (mean: 3.2, SD: 0.5) and Look Neutral (mean: 1.5, SD: 0.3) also revealed a significant difference ($t_{(32)} = 23.6$, $p < 0.001$).

The voxel-wise two-way mixed design ANOVA analysis (i.e., flexible factorial analysis in SPM) was performed for each contrast map using all participant fMRI volumes from each time point. The emotional regulation contrast map (Decrease Negative > Look Negative) did not demonstrate any significant clusters (as defined by the Monte Carlo simulation's threshold $p < 0.001$, $k > 85$) for the interaction term (Remission Status $\times$ Scan Time). Upon examination of main effects for the emotional regulation contrast no significant clusters were observed for Remission Status, but Scan Time yielded multiple significant brain regions. These included clusters in the cuneus, occipital lobe, insula, lingual gyrus, posterior cingulate cortex, and middle temporal gyrus (MTG). Details for these clusters are provided in Table 2, and can be visualized in Figure 2. Extracted emotional regulation values (i.e., contrast parameter estimate differences) from each of these regions were plotted based on scan time, as seen in Figure 3.

For the emotional reactivity contrast map (Look Negative > Look Neutral), a significant cluster for the interaction term (Remission Status $\times$ Scan Time) was observed in the MTG. Figure 4 illustrates this cluster's coordinates, voxel count, and peak F-statistic. Emotional reactivity values (i.e., contrast parameter estimate differences) for this cluster were extracted from each participant at each time point and plotted based on remission status, as displayed in Figure 5. Qualitative assessment demonstrated opposing trajectories during treatment among remitters and non-remitters, with values crossing between day 2 and day 3, which corresponds to the first 24 hours after the initiation of venlafaxine therapy.

Comparison of baseline emotional reactivity (i.e., mean parameter estimates) with each of the other scan time points was performed by calculating mean difference 95% confidence intervals and effect sizes (Cohen's d); see Table 3. The largest effect sizes, and where the confidence intervals do not cross zero, represent significant increases (or decreases) in emotional reactivity. The non-remitters' emotional reactivity significantly increased by day 7, and this increase was maintained through week 12. Among remitters, a significant decrease in emotional reactivity was demonstrated only at week 12.

Finally, the association between change in MADRS scores and emotional reactivity (i.e., mean parameter estimate of MTG) between day 1 and week 12 was investigated by calculating Spearman's rank correlation coefficients ($\alpha = 0.05$, two-tailed). Among all patients the mean change (i.e., week 12 minus day 1 values) in MADRS scores during treatment was -15.00 points (SD: 8.91), and the mean change in parameter estimates was -3.79×10^{-4} (SD: 0.23). A significant correlation was observed between these measures ($r_s = 0.57$, $n = 30$, $p = 0.001$). Upon stratification by remission status, the non-remitters had a MADRS score mean change of -7.65 (SD: 5.7), and a parameter estimate mean change of 0.19 (SD: 0.26). The remitters' MADRS score mean change was -19.26 (SD: 7.58), and parameter estimate mean change of -0.11 (SD: 0.12). No significant correlation was observed between these values in either non-remitters ($r_s = 0.25$, $n = 11$, $p = 0.47$) or remitters ($r_s = 0.23$, $n = 19$, $p = 0.33$).

CONCLUSIONS

This study demonstrates a significant divergence in emotional reactivity-induced fMRI BOLD signal between remitters and non-remitters across the 12 weeks of treatment with venlafaxine. This difference is related to the processing of negative visual stimuli and is localized to the right MTG. Further analysis revealed that these results were primarily driven by a within-group increase in signal among the non-remitters and a decrease in signal among the remitters over 12 weeks. It is interesting to note that the signal trajectories for remitters and non-remitters cross immediately after the first dose of venlafaxine, and become statistically reliable on day 7 in non-remitters, and at week 12 in remitters. Together, this suggests venlafaxine has an acute effect on emotional reactivity within the first week of treatment that is potentiated with further medication exposure across the 12 weeks. The significant positive correlation observed between changes in MADRS scores and emotional reactivity (i.e., as a patient's MADRS scores decrease over 12 weeks of treatment, there is an associated decrease in emotional reactivity) among all patients is an intuitive result likely representing the association between the alleviation of depressive symptoms and the decreased ability of negative stimuli to induce neural activity related to negative emotional reactivity. The failure to find significant correlations between these measures upon stratification by remission status may indicate a more complicated relationship between symptomatology and the neural basis of emotional reactivity, however.

Previous research has suggested that antidepressants, including serotonin reuptake inhibitors and norepinephrine reuptake inhibitors, can mediate acute effects on affective-related neural activity as measured by fMRI in as early as 2 hours after dosing.^{27–29} The specific neural structures affected vary based on the antidepressant type, affective task used, and patient

sample, but primarily appear to modulate activity in regions such as the amygdala, hippocampus, and prefrontal cortex. These results are complemented by a non-imaging-based study by Harmer et al. that showed that MDD patients have increased recognition and memory of positive valence stimuli 3 hours after reboxetine administration compared with those who received placebo.³⁰ A meta-analysis performed by Outhred et al. suggests that serotonin reuptake inhibitors and norepinephrine reuptake inhibitors may distinctly alter affective processing after acute administration.²⁹ No similar investigations have specifically examined agents such as venlafaxine, however, which simultaneously affect both of these neurotransmitters at higher doses.

With compelling evidence for acute changes in affective processing after antidepressant administration, it is conceivable that these early neural circuit changes may vary based on remission status. The current study demonstrates that this may indeed be the case, with observed differences in fMRI signal from the MTG diverging continuously throughout treatment. Nevertheless, as this study was only powered to test whether there was a significant interaction between remission status and scan time point during the full 12 weeks of treatment, no firm conclusions can be drawn regarding acute effects between remitters and non-remitters within the first week of treatment. Investigations using repeated-measures fMRI's with multiple scans early in the treatment of LLD are presently very limited, and no studies have utilized such a paradigm to evaluate fMRI changes based on treatment outcomes. Therefore, despite the inability to conclusively assess acute differentiation between remitters and non-remitters, these results provide evidence that such a study design can provide informative data to advance the understanding of the early neural-substrates associated with remission status.

Across the full 12 weeks of treatment, this study's demonstration of divergent affective-induced activity in the right MTG is compatible with previous research. Two meta-analyses that assessed studies using fMRI paired with an affective task in MDD identified the MTG as a region of interest. The first analysis, by Fitzgerald et al., demonstrated decreased activation in the MTG among patients compared with controls when exposed to negative stimuli.³¹ The second meta-analysis, by Delaveau et al., demonstrated an effect of antidepressant treatment on activity in the MTG among MDD patients following a minimum of 6 weeks of treatment.³² Specifically, after antidepressant treatment there was increased activity in response to both positive and negative emotionally valenced stimuli. As that meta-analysis primarily focused on studies comprising treatment responders, the latter finding is seemingly in opposition to the current study's finding of decreased activity among remitters in the MTG throughout treatment. This view is tempered by the heterogeneity of the affective tasks used by the included studies, and by the potential for antidepressants to affect MTG activity differently in LLD as compared with younger-patient MDD.

This plausible difference between LLD and MDD at other ages can be further substantiated by recognizing that regions of the MTG may be involved in registering the emotional content of facial stimuli, and how this process is known to be impaired in the elderly. Numerous studies have demonstrated differences in MTG activity during the processing of negative faces between MDD patients and controls.^{33–37} With approximately 47% of presented images in the current study's Affective Perception and Regulation Task containing

faces ranging from neutral to negative expressions, it is possible the significant interaction between remission status and scan time was being driven by changes in facial processing among patients. Moreover, with the elderly's known latency and accuracy deficits in recognizing emotional facial stimuli, this may suggest that antidepressant treatment is differentially affecting MTG facial processing in LLD remitters and non-remitters in a manner that is unique from that observed in younger MDD patients.^{38–41} Nonetheless, the lack of overlap between the significant region within the MTG in this investigation and the earlier emotional facial processing studies indicates that such an association is merely speculative until research specifically designed to assess MTG function is undertaken.

In addition to this study's primary focus on differentiating remitters and non-remitters, there are likely many changes in neural activity induced by antidepressant treatment that do not diverge based on treatment outcomes. This is substantiated by the fMRI analysis of the emotional regulation contrast, where no significant interaction was observed between remission status and scan time. Instead, numerous structures demonstrated main effects of scan time, indicating that regardless of whether patients remitted or not, they experienced altered activity in these regions. Previous research has implicated many of these structures in emotional processing including the cuneus, insula, posterior cingulate cortex, lingual gyrus, and MTG.^{12,42–44} Furthermore, studies have shown that antidepressant therapy in MDD patients alters emotional processing–related activity in each of these areas.⁴⁵ On a cursory level this seems to confirm that antidepressant-treated LLD patients are undergoing similar alterations to their affective neural circuitry as younger MDD patients, but specific details likely differ substantially and will require further study.

This investigation's findings demonstrate that MTG activity induced by emotional reactivity diverges based on treatment trajectories among LLD patients, and that these alterations first become evident within several days of antidepressant administration. Furthermore, having identified multiple neural structures previously implicated in affective processing that are also functionally altered throughout treatment of LLD provides added insight into the neural substrates of emotion that are affected during LLD antidepressant treatment. This study's ability to detect these changes provides a basis for future repeated-measures fMRI investigations of affective processing in LLD patients with the potential to further inform current understanding of the disease's dynamic neural changes in response to pharmacotherapy. This study's primary limitation was its limited sample size, which may have resulted in a reduced sensitivity to detect other brain regions affected during treatment. Additionally, having enrolled patients from two separate clinical trials with similar but not identical protocols may have impacted results in an unexpected manner.

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FIGURE 1.

Overall study design. fMRI: functional magnetic resonance imaging; LLD: late life depression; MADRS: Montgomery-Asberg Depression Rating Scale.

FIGURE 2.

Statistical parametric map from voxel-wise two-way mixed design ANOVA analysis (i.e., flexible factorial analysis) of emotional regulation contrast (Decrease Negative > Look Negative contrast). Results for main effect of Scan Time with threshold of $p = 0.001$, $k = 85$. Visualized with BrainNet Viewer software.²⁶

FIGURE 3. Change in emotional regulation mean parameter estimate difference (Decrease Negative > Look Negative) throughout treatment for brain regions with significant main effects of Time.

FIGURE 4.

Statistical parametric map from voxel-wise two-way mixed design ANOVA analysis (i.e., flexible factorial analysis) of emotional reactivity contrast (Look Negative > Look Neutral). Results displayed for interaction term (Remission Status $\times$ Scan Time) with threshold of $p = 0.001$, $k = 85$. Significant interaction between Remission Status and Scan Time in cluster in right middle temporal gyrus ($-68, -36, -6$), with peak F-statistic = 24.1, $df = 1,112$, and $k = 102$. Visualized with MRIcron software (Chris Rorden, University of South Carolina).

FIGURE 5.

Change in emotional reactivity/medial temporal gyrus mean parameter estimate difference (Look Negative > Look Neutral) by remission status throughout 12-week treatment course. Data presented as mean values with error bars representing 95% confidence interval of mean parameter estimate.

Table 1

Patient characteristics and depression ratings

	Remitters (N = 20)	Non-remitters (N = 13)	Statistic t/χ^2 (df)	p-value
Age, y	68.1 (6.7)	66.7 (4.0)	0.73 (30.8)	0.47
Sex, M/F	4/16	6/7	2.55 (1.0)	0.11
MMSE	28.6 (1.8)	29.3 (0.9)	-1.33 (31.0)	0.20
Venlafaxine dose in mg at week 12	181.9 (62.4)	274.4 (46.8)	-4.57 (31)	<0.01 *
MADRS baseline, day 1	23.7 (7.6)	26.2 (5.9)	-1.00 (31.0)	0.33
MADRS follow-up, 12 weeks	3.9 (3.0)	18.5 (5.3)	-9.00 (16.9)	<0.01 *

Notes Data are reported in format of mean (standard deviation) unless otherwise indicated. Two-sided Student's t test (age, MMSE, venlafaxine dose, MADRS scores), χ^2 (sex), $\alpha = 0.05$.

MADRS: Montgomery Asberg Depression Rating Scale; MMSE: Mini-Mental State Exam.

* statistically significant.

Table 2

Repeated-measure ANOVA results

	Coordinates (x, y, z)	Voxels (k)	Peak F-statistic (df)
Emotional Regulation Contrast			
Main Effect of Time			
Cuneus	-14, -96, -2	339	31.4 (1,112)
Occipital lobe	-28, -90, 24	462	27.1 (1,112)
Insula	40, -20, 22	100	20.9 (1,112)
Lingual gyrus	-2, -80, -4	89	19.5 (1,112)
Posterior cingulate cortex	-10, -38, 40	155	17.5 (1,112)
Middle temporal gyrus	46, -74, 20	92	14.5 (1,112)
Emotional Reactivity Contrast			
Interaction Term [Remission Status × Time]			
Middle temporal gyrus	-68, -36, -6	102	24.1 (1,112)

Notes: Two-way repeated-measures ANOVA (i.e., flexible factorial design in SPM), $\alpha = 0.001$, $k > 85$.

MADRS: Montgomery Asberg Depression Rating Scale; MMSE: Mini-Mental State Exam; SPM: Statistical Parametric Mapping statistical software.

*Statistically significant.

Table 3

Comparison of mean parameter estimates

	Baseline MRI	Subsequent MRI	Mean Difference (95% CI)	Effect Size (Cohen's d)
Remitters (N = 20)				
Baseline vs. day 2	0.029 (0.168)	0.004 (0.174)	-0.025 (-0.128 to 0.078)	0.15
Baseline vs. day 3	0.029 (0.173)	-0.059 (0.175)	-0.087 (-0.186 to 0.012)	0.51
Baseline vs. day 7	0.029 (0.168)	0.006 (0.164)	-0.023 (-0.126 to 0.081)	0.14
Baseline vs. week 12	0.029 (0.168)	-0.082 (0.157)	-0.111 (-0.171 to -0.052)	0.68
Non-remitters (N = 13)				
Baseline vs. day 2	-0.105 (0.293)	-0.113 (0.144)	-0.008 (-0.217 to 0.201)	0.03
Baseline vs. day 3	-0.105 (0.293)	0.010 (0.250)	0.115 (-0.34 to 0.264)	-0.42
Baseline vs. day 7	-0.159 (0.246)	0.124 (0.166)	0.283 (0.027 to 0.540)	-1.35
Baseline vs. week 12	-0.105 (0.293)	0.086 (0.299)	0.191 (0.020 to 0.363)	-0.65

Notes: Data are reported in format of mean (standard deviation) unless otherwise indicated.