ORIGINAL ARTICLE

Reduced Medial Prefrontal Responses to Social Interaction Images in Remitted Depression

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Context: Major depressive disorder is associated with impairments in processing emotional stimuli, and residual impairments are observed during remission, possibly indicating trait vulnerability. Stimuli with social context represent a distinct class of emotional stimuli, which in healthy volunteers are associated with specific neural substrates but have not previously been studied relative to vulnerability to depression.

Objective: To explore whether individuals with remitted major depressive disorder had altered neuronal processing of social emotional stimuli.

Design: Cross-sectional design using functional magnetic resonance imaging, combined with a cognitive activation task.

Setting: General community of greater Manchester, England.

Participants: Twenty-five unmedicated participants fully remitted from major depressive disorder and 29 age-matched control subjects.

Main Outcome Measures: Neuronal responses to positive and negative social interaction images vs valence-matched images with less overt social context.

Results: Participants with remitted depression showed attenuated frontopolar response relative to controls for positive and negative images depicting social interactions. For negative social images, participants with remitted depression also showed reduced latero-orbitofrontal response relative to controls.

Conclusions: In the absence of current symptoms, individuals with remitted major depressive disorder showed reduced frontopolar processing of stimuli showing social interactions, a reduction not seen for stimuli showing individual successes and failures and, therefore, not simply an effect of emotional valence. These results suggest a specific trait abnormality in social emotional processing associated with vulnerability to depression, which may have implications for understanding social cognition mechanisms and for developing effective psychological therapies.

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A RANGE OF DEFICITS IN EMOtional processing, both behavioral and neuronal, have been reported in major depressive disorder (MDD). Patients with depression show impaired processing of face emotion stimuli,[1-4] as well as biases in memory for[1,5,6] and attention to[3,7,8] emotionally valenced stimuli. In general, these studies report a bias toward negative information or a bias away from positive information compared with responses of healthy control subjects. Evidence for continuing emotional processing biases following remission of symptoms is more mixed,[9] although the balance of evidence suggests ongoing biases.[3,4,10,11]

Neuroimaging has identified neuronal substrates for a range of emotional processing abnormalities in MDD. For example, Wagner et al[12] reported enhanced hippocampal response to positive images and enhanced amygdala and prefrontal responses to negative images in patients with MDD. By contrast, Lee et al[13] reported reduced activity in right hippocampus and right insula in response to negative images and reduced activity in anterior cingulate cortex and left insula in response to positive images. A different pattern of responses again was reported by Anand et al,[14] showing increased activation of anterior cingulate cortex, insula, and parahippocampal areas for negative images. One explanation of the discrepancy is differences in task demands. Phillips et al[15] argued that limbic overactivity during initial evaluation of emotional stimuli, combined with failure of cortical control, causes a bias toward processing of negative information in MDD. Under this account, the exact neu-

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Table. Demographic Data and Valence Ratings

Variable	Control Group (n=29)	rMDD Group (n=25)
Age, mean (SE), y	32.4 (9.7)	33.8 (10.1)
IQ, mean (SE)	102.3 (11.6)	99.7 (10.9)
Sex		
Male	10	9
Female	19	16
No. of past depressed episodes, mean (SE)	. . .	3.5 (2.4)
Mean (SE) score		
Montgomery-Asberg Depression Rating Scale	0.9 (1.6)	2.3 (2.7)[a]
Clinical Anxiety Scale	0.3 (0.7)	0.8 (1.0)[a]
Neuroticism	46.9 (13.8)	57.6 (11.1)[a]
Extraversion	51.9 (13.2)	42.9 (8.8)[a]
Valence rating, mean (SE)[b]		
Individual positive	7.3 (1.2)	7.1 (1.4)
Individual negative	2.9 (1.1)	3.1 (1.3)
Group positive	7.5 (1.4)	7.2 (1.1)
Group negative	2.5 (1.0)	2.7 (1.3)
Group neutral	4.7 (1.6)	4.9 (1.4)
Individual neutral	5.3 (1.5)	5.1 (1.2)

Abbreviations: Ellipsis, not applicable; rMDD, remitted major depressive disorder.
[a] Significantly different at $P<.05$.
[b] On a scale of 0 (neutral) to 10 (extremely).

ral correlates of any task will depend on the relative emotional evaluative and cognitive demands.

Bhagwagar and Cowen[16] argued that studying remitted MDD (rMDD) may provide insights into trait abnormalities; however, the extent to which abnormal neuroimaging responses to emotional stimuli persist following remission is unclear.[9,17] Some researchers suggest that increased responses to negative emotional stimuli (typically faces) are observed in remitted patients.[18-20] Others have reported normal responses to emotional faces in rMDD[21-23] or elevated responses to negative stimuli only if transient sad mood is induced.[24-26] There are several potential reasons for these discrepancies; for example, we have suggested that the degree to which abnormality persists in remission depends on personality traits associated with vulnerability to relapse.[23] Traits like intraversion and neuroticism are associated with vulnerability to depression and may be related to increased functional magnetic resonance (fMR) imaging responses to negative emotional stimuli in never-depressed individuals[27] and in patients with rMDD.[23] In an explicit test of the association between abnormal emotional responses and vulnerability to relapse in rMDD, Farb et al[28] recently showed that abnormal prefrontal responses to sad films predict relapse.

Another important issue is whether different contexts of emotional processing influence abnormalities observed in rMDD. Recent theories of emotional processing suggest an important distinction between social and nonsocial emotions.[29,30] Although basic emotions like fear also have social connotations, a range of emotions necessarily depend on determining the self-relevance of other individuals' emotions. Positive social encounters tend to elicit positive social emotions (eg, love and pride), while negative social encounters tend to elicit negative social emotions (eg, jealousy and shame). Social emotional processing may be mediated by distinct neural substrates[30-32] that involve brain regions previously identified as important in social information processing.[33-37] For example, studies[32,38,39] of guilt and shame have consistently shown frontopolar activation. Some of these investigations have involved a social condition requiring mentalizing or empathy compared with a condition without this requirement (eg, studies[37,40] taking perspective of self compared with other). A previous study[30] explicitly comparing social and nonsocial emotional processing using script-driven imagery reported increased frontopolar response to social stimuli, as well as responses in other regions of a putative social cognition network. Meanwhile, a study[41] of social exclusion compared with social inclusion reported a focal increase in right inferior frontal activation. Negative social emotions like social exclusion may be particularly relevant in depression and relate to trait vulnerability and current mood,[42] but to date no imaging studies have been explicitly designed to probe socially related emotional processing in people vulnerable to MDD.

The present study investigated neuronal correlates of emotional processing in a sample of unmedicated individuals with rMDD using stimuli designed to differentially probe social emotions, specifically images of social group interactions compared with single individuals. Unlike some previous investigations, we asked participants to imagine themselves in another's situation in all conditions. Rather than varying the nature of the instruction, we varied the degree of social context of the imagined situation. We hypothesized (1) that in healthy controls increased social emotional processing would be associated with increased neuronal responses in regions that include frontopolar cortex, inferofrontal gyrus (IFG), temporoparietal junction, and temporal poles[30,33,35-37,43,44] and (2) that participants with rMDD would show increased response to negative social emotions within these regions.

METHODS

PARTICIPANTS

Participants were recruited using a Web site, local advertisement, general practice, and word of mouth. Potential suitability was established via a postal or an online screening survey (as part of a much larger study [http://www.medicine.manchester.ac.uk/mentalhealth/]), and positively screened participants were invited for interview. After complete description of the study to the participants, written informed consent was obtained. The study was approved by the Central Manchester Local Research Ethics Committee (reference 06/Q1410/72), Manchester, England. All the participants were right-handed and reported normal vision or vision corrected to normal. Their IQ was estimated using the Quick Test. All the participants completed the 240-item NEO Personality Inventory–Revised. Scores on the neuroticism and extraversion subscales are summarized in the **Table**.

PARTICIPANTS FULLY rMDD

Twenty-five participants (9 males and 16 females; mean [SE] age, 33.8 [10.1] years) with rMDD were included in the study.

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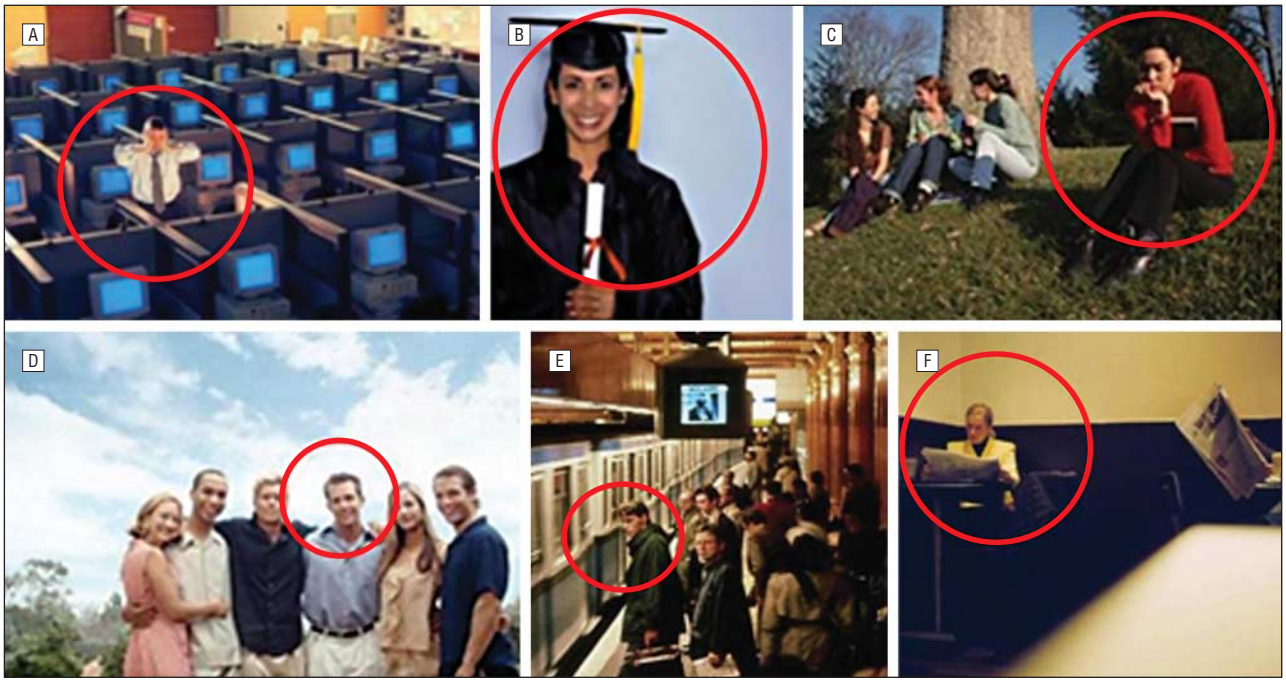

Figure 1. Examples of stimuli in the following tasks: individual negative (A), individual positive (B), group negative (C), group positive (D), group neutral (E), and individual neutral (F).

Participants were required to have had no lifetime history of bipolar disorder, psychosis, obsessive-compulsive disorder, or drug or alcohol misuse, as well as no neurological disorder, unstable medical condition, history of significant head trauma, or contraindication to MR imaging. Thirty-two participants were invited for interview, at which diagnosis was established using the 1994 Structured Clinical Interview for *DSM-IV* by the American Psychiatric Association, administered by a trained researcher (G.J., E.J.T., and D.D.) under supervision of a consultant psychiatrist (I.M.A.). Participants were required to meet *DSM-IV* criteria for at least 1 past major depressive episode but not for a current major depressive episode or any other psychiatric disorder. Participants were required to have a Montgomery-Asberg Depression Rating Scale[45] score of less than 10, which has been proposed as an acceptable definition of clinical remission.[46,47] Two participants were excluded on the basis of Montgomery-Asberg Depression Rating Scale scores above this cutoff point. All the participants with rMDD were required to be unmedicated, and 5 were excluded on the basis of current medication. Of the included participants, 18 of 25 had previously taken antidepressants but had discontinued medication at least 6 months previously, and 24 of 25 had not experienced any depression in the preceding year. The mean (SE) number of past depressed episodes was 3.5 (2.4). Participants with a history of anxiety disorder were not excluded. Depression is frequently comorbid with anxiety,[48] and commonalities of symptoms and treatment response indicate a strong case for considering the disorders together in a neurobiological context.[49] To exclude current anxiety, all participants were required to have a score of less than 8 on the Clinical Anxiety Scale.[50] No one was excluded on this basis, and only 6 of 25 participants had a history of clinical anxiety disorder on clinical interview.

CONTROLS

Twenty-nine controls (10 males and 19 females; mean [SE] age, 32.4 [9.7] years) were included in the study. The same general exclusion criteria applied as for the patients with rMDD. In addition, controls were required to have no reported personal or immediate family history of psychiatric problems on diagnostic interview. Of 32 participants interviewed, 3 were excluded on the basis of current medication.

The rMDD and control groups did not differ in terms of age, IQ, or sex ratio (Table). Participants with rMDD scored within the normal range on the Montgomery-Asberg Depression Rating Scale and Clinical Anxiety Scale but differed significantly from controls. They were also significantly more neurotic and less extraverted than controls.

COGNITIVE ACTIVATION TASK

Participants were shown 64 images, each including 1 person highlighted by a red circle. The images were selected on the basis of a pilot study (Appendix, "Methods" section [http://archgenpsychiatry.com]) to differentially probe social emotion. We included images of social group inclusion and exclusion designed to evoke highly social emotions and images of individual success and failure designed to evoke less pronounced social emotions. In the active conditions, each image depicted 1 of the following 4 emotive conditions: individual positive, individual negative, group positive, and group negative (**Figure 1**). We also included 2 control conditions showing nonemotive situations and controlling for the presence of 1 vs several persons in the individual and group conditions (eg, a person sitting reading a newspaper or a person standing in a queue at a supermarket). Red-circled individuals were young adults in all images, with equal numbers of male and female protagonists across the task. In positive images, the individuals had happy expressions; in negative images they had sad or upset expressions, and in neutral conditions they had neutral expressions. None of the negative scenarios showed explicit emotions of fear, anger, or disgust. Participants were instructed to think about how they would feel in a situation similar to that of the person highlighted. Neutral images were divided into 2 groups so that a specific set of control images existed for each emotive condition. For each emotive condition, there were 8 images (divided into 2 blocks of 4), and for each neutral con-

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dition (single person and multiple person), there were 16 images (divided into 4 blocks, 2 with single-person images and 2 with multiple-person images). Emotive conditions were presented in a counterbalanced order, with neutral control blocks interspersed between emotive blocks. The order of presentation was varied among participants. Images were presented at a rate of 1 every 11.25 seconds, with the image on screen for 8.00 seconds, followed by a fixation cross for 3.25 seconds. Therefore, each block lasted 45.00 seconds; there were 8 emotive blocks (2 for each condition) and 8 neutral blocks, rendering a total task time of 12 minutes. No explicit responses were required. After imaging, participants were asked to rate how positive or negative they had found the images seen during imaging using a 10-point Likert-type scale. The groups did not differ in their affective ratings of the images shown (Table). There were also no significant differences for either group in valence ratings between group and individual images (positive, negative, or neutral).

fMR IMAGING PROTOCOL

Participants underwent fMR imaging using a 1.5-T imaging system (Intera; Philips Healthcare, Best, the Netherlands). Three hundred forty volumes were acquired with T2-weighted gradient-echo echoplanar imaging. Repetition time was 2.1 seconds, and echo time was 40 milliseconds. Each volume comprised 40 axial sections, at a section thickness of 4.5 mm with a 0.5-mm section gap and in-plane resolution of 3.5 × 3.5 mm. A T1-weighted structural image was acquired for use in spatial preprocessing and was examined to exclude participants with any structural abnormalities (no abnormalities were observed).

STATISTICAL ANALYSIS

Data were analyzed using statistical parametric mapping (SPM5; Wellcome Trust Centre for Neuroimaging, London, England). Images were realigned to correct for motion using the first image as a reference image. Coregistration of the structural (T1-weighted) and functional (T2-weighted) images was performed. Images were spatially normalized into a standard stereotactic space using a nonlinear transformation and were smoothed using a gaussian kernel filter of full width at half maximum of 3 times the voxel size (ie, 10.5, 10.5, and 13.5 mm). First-level analysis (fixed effects) was performed on each participant to generate a mean image for each of the following contrasts: (1) individual positive vs individual neutral, (2) individual negative vs individual neutral, (3) group positive vs group neutral, and (4) group negative vs group neutral.

At second-level analysis (random effects), we first identified differential responses to individual and group images in healthy controls. A factorial model was then used to determine how differential responses to individual and group images were modulated by diagnosis (rMDD vs controls). We assessed effects within regions of interest (ROIs) predefined using anatomical masks from the automated anatomical labels of the Wake Forest University (Winston Salem, North Carolina) Pick Atlas toolbox.[51,52] Defined ROIs were frontopolar cortex, temporal poles, IFG, and temporoparietal junction, all bilateral. We created a single a priori mask comprising these regions, and within this single composite ROI we report blood oxygenation level–dependent responses surviving statistical thresholds of $P < .05$ (false discovery rate [FDR] corrected), although those that do not also survive at $P < .05$ (familywise error [FWE] corrected) must be viewed with caution. Voxels outside of these regions are reported if they reach statistical significance at $P < .05$ (FWE corrected) for whole brain. Montreal Neurological Institute coordinates are reported.

Correlations with neuroticism and extraversion scores were also evaluated within ROIs. In the rMDD group, correlations with the number of past depressed episodes and residual depressive and anxiety symptoms were also assessed.

RESULTS

In all reported contrasts, the corresponding neutral condition was subtracted from each emotive condition in first-level analysis. This was done to control for any effect of differential responses to images of single and multiple persons. For example, if it was more difficult to process images of several persons, the use of matched–neutral images would control for this.

MAIN EFFECTS IN CONTROL SUBJECTS

Response to Positive vs Neutral Images

For group-positive images compared with group-neutral images, significant response was observed in frontal pole (Montreal Neurological Institute coordinates 4, 49, 35; $z = 4.09$, $\kappa = 22$), surviving correction at $P < .05$ (FWE corrected) in ROI analysis. For individual-positive images compared with individual-neutral images, no significant response was observed in ROI analysis.

Response to Group-Positive vs Individual-Positive Images

Significantly greater response to group-positive compared with individual-positive images was observed in frontal pole (coordinates 4, 49, 35; $z = 4.09$; coordinates 4, 63, 20; $z = 4.07$, $\kappa = 36$), surviving correction at $P < .05$ (FWE corrected) in ROI analysis. There were no regions that showed greater response to individual-positive images than to group-positive images.

Response to Negative vs Neutral Images

For group-negative images compared with group-neutral images, significant response was observed in frontal pole (coordinates 4, 56, 10; $z = 4.54$, $\kappa = 24$), surviving correction at $P < .05$ (FWE corrected) in ROI analysis, and in right IFG (coordinates 38, 45, −10; $z = 3.27$), surviving correction at $P < .05$ (FDR corrected) in ROI analysis. For individual-negative images compared with individual-neutral images, no significant response was observed in ROI analysis.

Response to Group-Negative vs Individual-Negative Images

Significantly greater response to group-negative compared with individual-negative images was observed in frontal pole (coordinates 4, 53, 35; $z = 4.19$, $\kappa = 36$), surviving correction at $P < .05$ (FWE corrected) in ROI analysis, and in right IFG (coordinates 49, 25, −15; $z = 3.62$, $\kappa = 21$), surviving correction at $P < .05$ (FDR corrected) in ROI analysis. There were no regions that showed greater response to individual-negative images than to group-negative images.

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COMPARISONS BETWEEN rMDD AND CONTROL PARTICIPANTS

Response to Positive vs Neutral Images

For group-positive images compared with group-neutral images, controls showed significantly greater response than participants with rMDD in frontal pole (coordinates –14, 60, 20; $z=3.86$, $\kappa=19$), surviving correction at $P<.05$ (FWE corrected) in ROI analysis. There were no regions where responses to group-positive images were greater in participants with rMDD than in controls. For individual-positive images compared with individual-neutral images, participants with rMDD showed greater response than controls in frontal pole (coordinates –4, 60, 10; $z=3.76$, $\kappa=18$), surviving correction at $P<.05$ (FWE corrected) in ROI analysis. There were no regions that showed responses to individual-positive images were greater in controls than in participants with rMDD.

Response to Group-Positive vs Individual-Positive Images

Controls showed significantly greater response than participants with rMDD to group-positive images compared with individual-positive images in frontal pole (coordinates –14, 60, 20; $z=4.09$, $\kappa=12$), surviving correction at $P<.05$ (FWE corrected) in ROI analysis (**Figure 2**). This interaction was driven by enhanced frontopolar signal to group images compared with individual images in controls and by the opposite pattern in participants with rMDD. There were no regions that showed greater responses to individual-positive images in controls than in participants with rMDD.

Response to Negative vs Neutral Images

For group-negative images compared with group-neutral images, controls showed significantly greater response than participants with rMDD in right IFG (coordinates 38, 45, –10; $z=3.27$, $\kappa=14$), surviving correction at $P<.05$ (FDR corrected) in ROI analysis. There were no regions that showed responses to group-negative images were greater in participants with rMDD than in controls. For individual-negative images compared with individual-neutral images, participants with rMDD showed greater response than controls in frontal pole (coordinates 7, 56, 35; $z=3.85$, $\kappa=13$), surviving correction at $P<.05$ (FWE corrected) in ROI analysis. There were no regions that showed greater responses to group-negative images in participants with rMDD than in controls.

Response to Group-Negative vs Individual-Negative Images

Controls showed significantly greater response than participants with rMDD to group-negative images compared with individual-negative images in frontal pole (coordinates 7, 60, 35; $z=3.64$, $\kappa=19$) and in right IFG (coordinates 49, 25, –15; $z=3.57$, $\kappa=15$), surviving correction at $P<.05$ (FDR corrected) in ROI analysis (**Figure 3**). There were no regions that showed greater responses to individual-negative images in controls than in participants with rMDD.

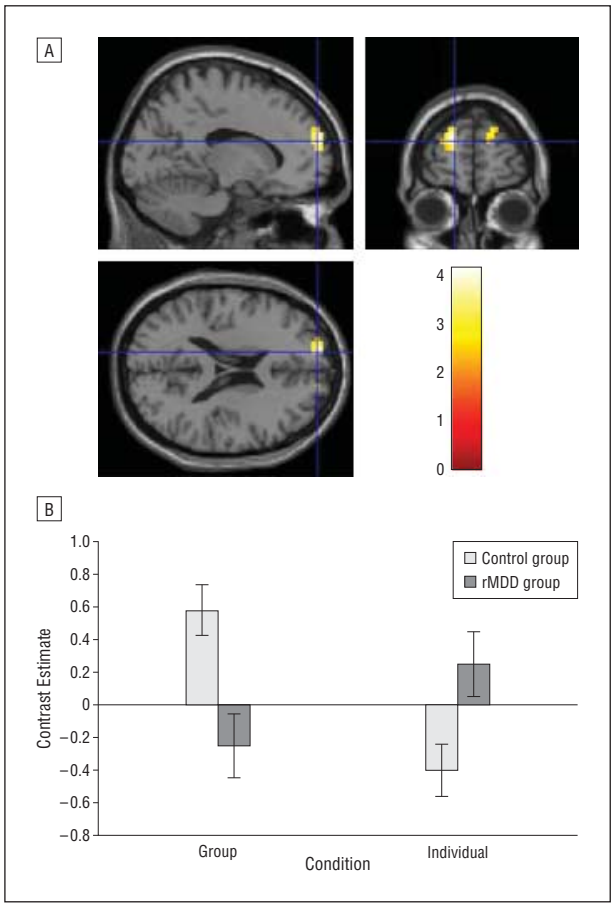

Figure 2. Attenuated frontopolar response to group-positive vs individual-positive images in participants with remitted major depressive disorder (rMDD) compared with control subjects. A, Frontopolar response thresholded at $P<.001$ (uncorrected) and superimposed on a standard structural image. B, Peak voxel signal change associated with group-positive and individual-positive images in control subjects and participants with rMDD.

CORRELATIONS

No significant correlations were noted between the fMR imaging responses reported herein and the number of past depressed episodes, residual depressive symptoms (Montgomery-Asberg Depression Rating Scale score), or anxiety symptoms (Clinical Anxiety Scale score) among participants with rMDD. Furthermore, inclusion of residual depressive and anxiety symptoms as covariates of interest in the between-group analysis did not affect the results reported herein. None of the reported fMR imaging responses correlated significantly with neuroticism or extraversion in controls. For participants with rMDD, there were no significant correlations with fMR imaging signal in the regions reported herein. However, the fMR imaging response to group-negative images compared with group-neutral images was significantly negatively correlated with extraversion in hippocampus (coordinates 25, –25, –10; $z=4.66$, $\kappa=12$), a region that was not seen in any of the main effects or interactions discussed herein. This correlation survived whole-brain correction at $P<.05$ (FWE corrected). Therefore, less extraverted partici-

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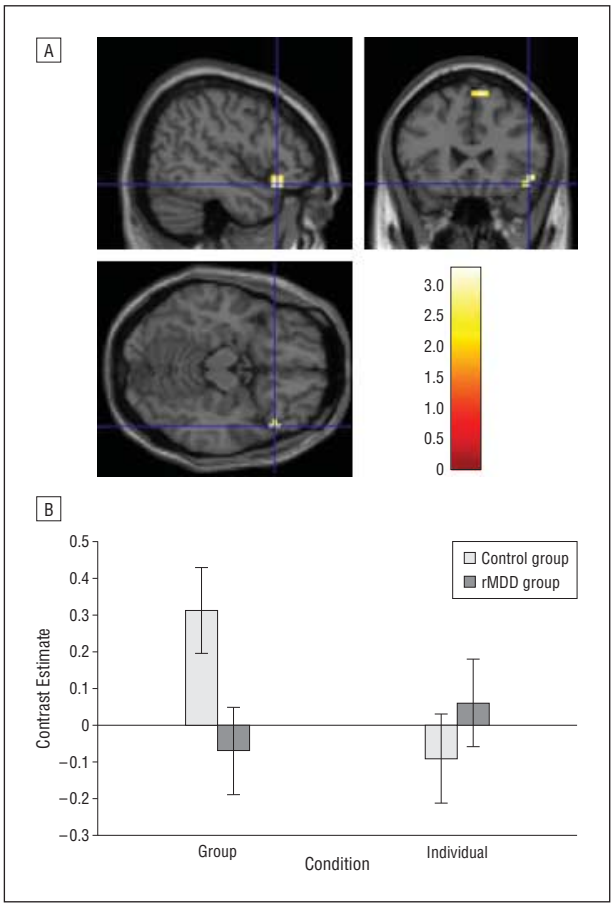

Figure 3. Attenuated lateral orbitofrontal response to group-negative vs individual-negative images in participants with remitted major depressive disorder (rMDD) compared with control subjects. A, Latero-orbitofrontal response thresholded at $P<.01$ (uncorrected) and superimposed on a standard structural image. B, Peak voxel signal change associated with group-negative and individual-negative images in control subjects and participants with rMDD.

pants with rMDD showed greater blood oxygenation level–dependent response in posterior hippocampus when viewing group-negative images.

COMMENT

In controls, both positive and negative group images compared with neutral images were associated with responses in frontal pole. Neither positive nor negative individual images compared with neutral images were associated with differential responses in ROIs. When comparing images depicting explicit social group context with images depicting single individuals, differential responses were observed in frontopolar cortices for images of both positive and negative valence. Negative social group compared with individual images were also associated with enhanced right IFG responses. Participants with rMDD showed decreased frontopolar response to positive images and decreased IFG response to negative images compared with neutral images of group interaction and showed increased frontopolar response to both positive and negative images of individuals. When images with different social content were directly contrasted, participants with rMDD showed significantly attenuated frontopolar response to group images compared with individual images. Contrary to our hypothesis, this attenuation was observed for both positive and negative images. Negative social group compared with individual images were also associated with attenuated response in right IFG. Neither frontopolar nor IFG responses correlated with the number of previous depressive episodes, residual depressive symptoms, neuroticism, or extraversion. However, less extraverted participants with rMDD showed significantly enhanced posterior hippocampal response to negative images depicting group exclusion.

In controls, our key finding was enhanced frontopolar response to emotional images of group interactions. Frontopolar responses have been observed in many investigations of self-referential and introspective processing and have been associated with mentalizing and empathy.[33-35,40,43] We explicitly asked participants to imagine themselves in someone else's situation in all conditions (including neutral controls); therefore, all conditions involved mentalizing and empathy. Hence, our results indicate that frontopolar involvement in such processes is enhanced when stimuli have a more overtly social context, consistent with several theoretical accounts that suggest a specific role for frontopolar regions in processing of social interactions.[34,37,53,54]

Our main objective in this study was to evaluate social emotional processing in rMDD, and we demonstrate for the first time to date selective alteration in processing of emotional images depicting overt social interaction. Participants with rMDD showed reduced frontopolar response to both positive and negative images of explicit social interaction compared with images of individuals matched for subjective valence. Previous findings have suggested that rMDD may be associated with ongoing neural abnormalities in processing of positive or negative emotional stimuli, particularly faces.[55] In our study, the positive images (both individual and group) showed happy persons, while the negative images showed sad persons; therefore, responses to happy and sad faces could be a factor in our task. However, opposite effects in frontopolar regions were observed for group and individual images of the same valence. This pattern is incompatible with a hypothesis of general hyperresponse or hyporesponse to stimuli showing emotional faces. Furthermore, postimaging valence judgments did not differ for group compared with individual images or for participants with rMDD compared with controls; therefore, differences in perceived valence of images are unlikely to be a significant factor affecting the results. Reduced responses to positive and negative group images seem to represent a genuine impairment in response specifically to stimuli depicting social interaction.

Schaefer et al[56] showed that patients with MDD were hyporesponsive to images depicting positive social interaction in regions that included frontopolar cortex. However, in their study, this hyporesponse normalized after successful antidepressant therapy, which is somewhat at odds with our finding of hyporesponse in participants with rMDD. This may reflect lack of power in their study (n=9) or the possibility that antidepressants may directly enhance processing of emotional and social information[57] and "mask" underlying hyporesponse. The dis-

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crepancy may also reflect differences between paradigms. The paradigm by Schaefer et al required passive viewing of images. By contrast, we asked participants to imagine themselves in the situations depicted; therefore, our instructions directed participants toward a self-referential mode of processing. Self-referential processing in MDD has been associated with increased medial prefrontal response in studies[58,59] of patients with current depression. Furthermore, this elevation was shown not to normalize in response to effective treatment[60] and has been suggested as a vulnerability marker relating to self-focus in depression.[61]

Findings of abnormalities in rMDD may be associated with a "scarring" effect of prior depressive episodes. However, we observed no correlation between frontopolar abnormalities and the number of previous depressive episodes. Therefore, it is also plausible that reduced frontopolar responses to social images represent a trait vulnerability factor. Notably, Krämer et al[44] reported that frontopolar responses to images of emotionally charged social situations were negatively correlated with participants' tendency to feel distress and anxiety, which has been associated with lack of self-regulation in emotional situations.[62] An association between vulnerability to depression and frontopolar-mediated failure to self-regulate that leads to distress and anxiety in social emotional situations would be a plausible hypothesis.

Another explanation for decreased frontopolar responses in participants with rMDD to images of social interaction may be reduced ability to relate to the social situations depicted. This would be consistent with a history of social anxiety and withdrawal associated with MDD. The extraversion scale of the NEO Personality Inventory–Revised provides a crude measure of tendency to engage in and be motivated by social interaction, and participants with rMDD scored significantly lower on this measure than controls. However, extraversion scores did not correlate with frontopolar responses or other responses within hypothesized ROIs. Notably, among participants with rMDD, there was a significant negative correlation between extraversion and posterior hippocampal response to negative social images. Posterior hippocampal response may reflect greater engagement of autobiographical memory for images evoking feelings of exclusion or rejection. Eisenberger et al[41] showed that in healthy individuals enhanced hippocampal response to social rejection was associated with a stronger link between momentary feelings of rejection and end-of-the-day social disconnection, suggesting that hippocampal responses may reflect a tendency to greater rumination on rejection. It is plausible that this tendency is increased in less extraverted persons vulnerable to depression.

Participants with rMDD also showed no increased right IFG response to negative social group images, although this result must be interpreted with caution because it did not survive stringent statistical thresholding. Enhanced right IFG response to social exclusion in healthy controls supports the finding by Eisenberger et al[41] of social rejection that implicated right Brodmann area 47. Eisenberger et al also reported that functional response in this region correlated negatively with reported emotional distress, suggesting that it may fulfill a regulatory function mitigating the effect of social distress. Our study findings suggest that individuals vulnerable to depression may fail to recruit this regulatory mechanism, compatible with helplessness theories and with recent theories of emotional processing[15] that emphasize a role for lateral prefrontal regions in voluntary suppression of emotions.

There are several limitations to our study. First, although none of the participants with rMDD were showing current clinically significant anxiety, we did not exclude history of anxiety disorder; therefore, it is possible that previous social anxiety symptoms may have contributed to observed effects. However, only 6 of 25 participants had a history of clinical anxiety disorder, and exclusion of these participants did not affect the significance of the results. Further study is required to relate the observed abnormalities to specific traits and to overt social behavior. Second, our design does not allow us to distinguish between potential trait abnormalities and a scarring effect of previous depressive episodes. A future study among never-depressed individuals with risk factors for depression would help address this point. Similarly, an important future direction would be a longitudinal study to determine whether abnormalities in social emotional processing are predictive of relapse in rMDD.

There are also important limitations regarding the task used. We did not require any explicit response during imaging and, therefore, have no overt measure of attention; however, differential effects of different stimuli would argue against a general attention effect. Also, we did not attempt to elicit information about subjective experiences during image viewing and therefore have no measure of the extent to which social emotions were experienced. Results of our pilot study suggest that the images successfully probe different emotions in an independent sample. Our stimuli were selected (described in eMethods) to differentially engage social feelings (inclusion and exclusion) compared with feelings of individual success and failure. Images of single individuals experiencing success and failure can certainly elicit social emotions, but critically we suggest that they do so to a lesser extent than overt images of social group interactions. Future research with more sophisticated paradigms is required to test hypotheses generated by the present study more explicitly.

Despite the limitations, our study reveals potentially important abnormalities in response to social emotion in rMDD. Although affective ratings for the images were not significantly different from those by controls, participants with rMDD showed decreased responses to images of social interaction, which we interpret in terms of a potential trait abnormality in social emotional processing. Previous studies have explored generalized emotional processing correlates, with somewhat equivocal results. In this study of unmedicated participants with rMDD, we suggest that specific social emotional processing abnormalities may represent a trait vulnerability for MDD. Improved understanding of what the neurobiological mechanisms of vulnerability and relapse are and how they relate to psychological models has important implications for developing cognitive and pharmacological approaches to primary and secondary prevention of depression.

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