ONLINE FIRST

Guilt-Selective Functional Disconnection of Anterior Temporal and Subgenual Cortices in Major Depressive Disorder

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Context: Proneness to overgeneralization of self-blame is a core part of cognitive vulnerability to major depressive disorder (MDD) and remains dormant after remission of symptoms. Current neuroanatomical models of MDD, however, assume general increases of negative emotions and are unable to explain biases toward emotions entailing self-blame (eg, guilt) relative to those associated with blaming others (eg, indignation). Recent functional magnetic resonance imaging (fMRI) studies in healthy participants have shown that moral feelings such as guilt activate representations of social meaning within the right superior anterior temporal lobe (ATL). Furthermore, this area was selectively coupled with the subgenual cingulate cortex and adjacent septal region (SCSR) during the experience of guilt compared with indignation. Despite its psychopathological importance, the functional neuroanatomy of guilt in MDD is unknown.

Objective: To use fMRI to test the hypothesis that, in comparison with control individuals, participants with remitted MDD exhibit guilt-selective SCSR-ATL decoupling as a marker of deficient functional integration.

Design: Case-control study from May 1, 2008, to June 1, 2010.

Setting: Clinical research facility.

Participants: Twenty-five patients with remitted MDD (no medication in 16 patients) with no current comorbid Axis I disorders and 22 controls with no personal or family history of MDD.

Main Outcome Measures: Between-group difference of ATL coupling with a priori SCSR region of interest for guilt vs indignation.

Results: We corroborated the prediction of a guilt-selective reduction in ATL-SCSR coupling in MDD vs controls (familywise error–corrected $P = .001$ over the region of interest) and revealed additional medial frontopolar, right hippocampal, and lateral hypothalamic areas of decoupling while controlling for medication status and intensity of negative emotions. Lower levels of ATL-SCSR coupling were associated with higher scores on a validated measure of overgeneralized self-blame (67-item Interpersonal Guilt Questionnaire).

Conclusions: Vulnerability to MDD is associated with temporofrontolimbic decoupling that is selective for self-blaming feelings. This provides the first neural mechanism of MDD vulnerability that accounts for self-blaming biases.

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FREUD OBSERVED THAT DEPRESsion is distinguished from normal sadness by excessive feelings of guilt and self-blame.[1] Subsequently, cognitive psychotherapy of depression tackled selective overgeneralization of self-blame–related information[2] (eg, "If I fail at sports matches, it means I am a total failure."). An influential cognitive model suggested a causal link between self-blaming biases and vulnerability to major depressive disorder (MDD).[3] Indeed, self-blaming biases remain dormant after remission of depressive symptoms,[4] supporting their contribution to MDD vulnerability. New insights into the neural underpinning of vulnerability to MDD can be gained from functional neuroimaging. A comprehensive pathogenetic understanding, however, requires an account of how consistent and distinctive symptoms and cognitive distortions of MDD can be explained at the neural systems level. One key prerequisite for understanding the pathogenesis of MDD is therefore to unveil trait abnormalities in the functional neuroanatomy of self-blaming feelings.

Rather than investigating self-blaming feelings, previous functional neuroimaging studies of MDD have focused on the neural correlates of general increases in

negative emotions and their regulation (reviewed in Elliott et al[5]). However, overall increases in negative emotions cannot explain biases toward self-blaming feelings demonstrated in MDD. Patients with MDD typically feel inadequate and worthless compared with others[6] and often feel inappropriate guilt or self-blame[7,8] but do not typically devalue other people in the same way. This is reflected in the diagnostic criteria for MDD; the criteria do not include irritability or anger directed toward others, which are part of the core diagnostic criteria for its polar opposite, manic episodes in bipolar disorder.[9]

One of the key brain regions involved in the pathophysiology of MDD is the subgenual cingulate cortex.[10] It shows abnormal resting-state metabolism in major depressive (MD) episodes,[11] and its metabolism normalizes with remission of symptoms after treatment.[12] Interestingly, this remission can be induced by subgenual cingulate stimulation with deep-brain electrodes.[13] This region is part of a corticolimbic network that exhibits abnormalities in functional connectivity in people with MD episodes as shown by both resting-state functional magnetic resonance imaging (fMRI)[14,15] and positron emission tomography.[16] The activation of the subgenual cingulate cortex and adjacent septal region (SCSR) has been found to reflect feelings of guilt in healthy participants with low MDD risk,[17,18] and this effect was selective relative to equally unpleasant feelings associated with blaming others (indignation/anger). Furthermore, this selective involvement of the SCSR in guilt relative to anger has been corroborated in patients with septal neurodegeneration.[19]

In addition to the importance of the SCSR, the anterior temporal lobe (ATL) has been consistently implicated in moral feelings such as guilt.[20] However, in contrast to the SCSR, the right superior ATL is activated irrespective of the type of moral feeling, whether it is guilt or indignation.[17] Furthermore, this ATL region showed selective functional coupling with the SCSR for guilt relative to indignation in healthy participants with low risk of MDD.[21] Evidence from fMRI[22] and patient lesion[23] studies suggests that the right superior ATL is important for the representation of social concepts, allowing for differentiation between specific qualities (eg, faultfinding and critical) of social behaviors (eg, "I pointed to a typing error in one of my colleagues' e-mails") and thereby allowing us to make differentiated appraisals of behavior to protect us against overgeneralization of self-blame[17,22,23] (eg, This means "I am critical" rather than "I am unlikable"). Social concepts (eg, stingy, clumsy, or unintellectual) are thus crucial ingredients for tackling patients' self-blaming overgeneralizations in therapy[2] (eg, "If I fail at sports matches, it means I am clumsy, but I still have other worthy qualities, such as being smart and caring"). Based on this evidence, it has been hypothesized that ATL-SCSR functional coupling is the neural correlate of the experience of differentiated forms of guilt[21] that allow individuals with low MDD risk to blame themselves in a specific fashion (ie, to feel guilt in an adaptive way) without damaging their self-worth or hating themselves (an overgeneralized form of guilt[7]). This is based on a more general model of the ATL as representing context-independent and modality-independent information, allowing for rapid and automatic conceptual differentiation, even when accessed nonverbally.[24,25]

In the present study, we used fMRI to investigate functional integration of temporofrontosubcortical networks during emotional judgments of guilt-evoking (eg, "Tom [participant] acts greedily toward Sam [best friend]") and indignation-evoking (eg, "Sam acts greedily toward Tom") sentences in individuals with fully remitted MDD to uncover the neural substrates of self-blaming biases. We controlled for overall rated unpleasantness of feelings during fMRI and medication status. The investigation of participants with remitted MDD reveals trait vulnerability factors[26] that are independent of the depressive state. We chose closely matched individuals with no personal or family history of MDD as a comparison group so that group differences could be interpreted as arising from differences in MDD vulnerability. We used psychophysiological interaction (PPI) analysis, an established measure of functional integration,[27] to test the hypothesis that individuals with remitted MDD exhibit decreased functional integration between the right superior ATL and the SCSR for guilt relative to indignation compared with a healthy control group. The finding of a self-blame–selective decrease in ATL-SCSR coupling would provide a neural mechanism for proneness to overgeneralization of self-blaming feelings in MDD. This was further investigated by using a validated independent measure of overgeneralized forms of self-blame, the Self-hate subscale of the 67-item Interpersonal Guilt Questionnaire (IGQ-67).[28] The score of this measure is largely elevated in people with MDD during the symptomatic[7] as well as the remitted[29] phase. We predicted that individuals with a lower degree of ATL-SCSR coupling for guilt vs indignation would display higher scores on the Self-hate subscale.

METHODS

PARTICIPANTS

This study was approved by the South Manchester National Health Service Research Ethics Committee, and all participants gave informed consent (oral for prescreening and written for subsequent stages). Participants were recruited using online and print advertisements. Initial suitability was assessed with a phone prescreening interview (eMethods [http://www.archgenpsychiatry.com] and Appendix [http://www.translational-cognitive-neuroscience.org/start/test-materials]).

Participants in the MDD group fulfilled criteria for a past MD episode according to *DSM- IV-TR*[9] and for a moderate or severe depressive episode according to the *International Classification of Diseases,10th Revision,* with at least 2 months' duration requiring treatment and remission of symptoms for at least 12 months (eMethods). Exclusion criteria were current Axis I disorders and history of alcohol or substance abuse or past comorbid Axis I disorders being the likely primary cause of the depressive syndrome (eTable 1 and eTable 2). The healthy control group had no current or past Axis I disorders and no first-degree family history of MDD, bipolar disorder, or schizophrenia.

Twenty-two healthy individuals serving as control participants and 25 individuals with remitted MDD (16 not currently receiving antidepressant medication) were included in the final analysis. All participants had normal or corrected-to-normal vision. The groups were matched on age, educational level, and sex (eTable 3). Volunteers were invited for a clinical

interview in which psychiatric, medical, and family history were assessed and a neurological examination was carried out by a board-certified psychiatrist (R.Z.). Furthermore, a Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders Module A[30] and the Mini International Neuropsychiatric Interview,[31] which was adapted to allow assessment of lifetime Axis I disorders including substance and alcohol abuse, and a shortened version of the Weissman Family History Screen,[32] the Montgomery-Åsberg Depression Rating Scale,[33] and the Global Assessment of Functioning scale (Axis V, *DSM-IV*) were used. Both groups had Montgomery-Åsberg Depression Rating Scale scores that were well below the cutoff for depression (10 points), but the MDD group showed slightly higher scores. Both groups had Global Assessment of Functioning scores indicating minimal or absent symptoms (>80), although the control participants exhibited a higher score (eTable 3).

fMRI PARADIGM

Participants were given written statements describing actions counter to social and moral values described by social concepts (eg, stingy, tactless) in which the agent was either the participant (self-agency condition [n=90]) or their best friend (other-agency condition [n=90]). Norms for the stimuli have been further described,[17,22] and a full list of the stimuli is available on request). Self- and other-agency conditions used the same social concepts (self-agency, eg, "[participant's name] does act stingily toward [best friend's name]" and other-agency, eg, "[best friend's name] does act stingily toward [participant's name]"). Fifty percent of the trials used negative social concepts (eg, does act stingily) and 50% used negated positive social concepts (eg, does not act generously). In addition, we used a low-level resting-state baseline condition: fixation of visual pattern with no button press (null event [n=90]). Stimuli were presented in an event-related design for a maximum of 5 seconds within which participants had to decide whether they would feel "extremely unpleasant" or "mildly unpleasant" from their own perspective (see also eMethods).

After the scanning session, participants rated each statement on the degree of unpleasantness (7-step scale) to control for the degree of negative valence and emotional intensity. They also were required to "choose the feeling that" they "would feel most strongly" from choices of guilt, contempt/disgust toward self, shame, indignation/anger toward self, indignation/anger toward other, contempt/disgust toward other, none, and other feeling. As in previous studies,[17,21] guilt and indignation trials for the fMRI analysis were defined on the basis of individual ratings and restricted to agency-role congruent responses (ie, guilt in the self-agency condition and indignation in the other-agency condition; eTable 4). This was because agency-role incongruent responses occurred relatively rarely and may not be directly comparable with agency-role congruent feelings. For example, feeling guilty for something that one's best friend has done would be mostly maladaptive, and we wanted to restrict our analyses to adaptive "healthy" experiences of guilt to allow a direct comparison of the control and MDD groups without confounding differences in the subjective experience. Participants also rated how many different outcomes of the behavior they estimated, in how much detail the sentences described social behavior, how intensely they visualized the behavior, and how intensely they were reminded of a specific episode or scene they had experienced during their life. In addition, they were presented with each of the 90 social concepts contained in the stimulus set and rated how well the concept described themselves or their best friends on 2 separate scales (eMethods).

IMAGE ACQUISITION

Echo-planar T2*-weighted images (405 volumes in each of the 3 runs with 5 dummy scans for each run of 13 minutes, 40 seconds) were acquired on an MRI scanner (3-T Achieva; Philips) with an 8-channel coil, 3-mm section thickness, and ascending continuous acquisition parallel to the anterior to posterior commissural line (between 35 and 40 sections, depending on the size of the participant's head; repetition time, 2000 milliseconds; echo time, 20.5 milliseconds; field of view, 220 × 220 × 120 mm; acquisition matrix, 80 × 80 voxels; reconstructed voxel size, 2.29 × 2.29 × 3 mm; and sensitivity encoding factor, 2). In addition, 3-dimensional, T1-weighted, magnetization-prepared, rapid-acquisition gradient-echo structural images were obtained (reconstructed voxel size, 1 mm^3, 128 sections; echo time, 3.9 milliseconds; field of view, 256 × 256 × 128 mm; acquisition matrix, 256 × 164 voxels; section thickness, 1 mm; and repetition time, 9.4 milliseconds). Axial T2-weighted structural images were acquired for each participant to rule out vascular and inflammatory abnormalities.

BEHAVIORAL DATA ANALYSIS

Analysis of between-group differences was performed using 2-sided 2-sample *t* tests with significance set at $P=.05$ (SPSS 15; http://www.spss.com). Self-hate subscale scores from the IGQ-67[28] were significantly elevated in our group with remitted MDD ($t_{36.7}=4.8$, equal variances not assumed, $P<.001$) and were reported elsewhere.[29] Herein, we used these scores as between-subject covariates in the imaging analysis.

IMAGE ANALYSIS

Functional images were realigned, unwarped, and coregistered to the participant's T1 images. These images were normalized by first normalizing the participant's T1 image to the standard T1 template in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and applying the same transformations to the functional images. A smoothing kernel of full-width half-maximum equal to 6 mm was used.

We tested our main hypotheses about functional integration using a PPI analysis in statistical parametric mapping (SPM) 8[27] (see eMethods for methods of standard blood oxygenation level–dependent [BOLD] effect analysis). Psychophysiological interaction analysis requires the extraction of the signal from a seed region (in this case, the right superior ATL) and the creation of the interaction term, which is the multiplication of the psychological variables (the main effects of the conditions) with the physiological variable (the ATL signal time course irrespective of condition). A whole-brain search identifies all voxels in which a significant fraction of variance in signal can be explained by the PPI term. *Physiological* coupling refers to the ATL signal time course predicting activity in another brain area throughout the experiment (independent of psychological condition). In contrast, a PPI effect refers to the slope of the regression effect of the ATL on another brain area changing for one condition (eg, guilt) relative to another (eg, indignation). The PPI effect therefore indicates a selective modulation of functional integration by psychological condition.

The seed region was a sphere with a radius of 4 mm around the peak coordinate of the ATL activation in the standard BOLD analysis that was common to both the comparisons of guilt vs fixation and indignation vs fixation ($x=58$, $y=0$, $z=-12$, $t=4.47$, $P<.001$) for 47 participants from both groups (guilt vs fixation inclusively masked by indignation vs fixation with the threshold at an uncorrected voxel-level sig-

Table. PPI Effects for Control vs Remitted MDD Group: Guilt vs Indignation[a]

Hemisphere	Region	BA	MNI Coordinates			*t* Value	FWE-Corrected *P* Value
			x	*y*	*z*		
L	Subgenual cingulate and adjacent septal region	25	−6	22	0	4.67	.001[b]
R	Hippocampus	. . .	28	−16	−14	4.44	.03[c]
L	Medial frontopolar cortex[d]	10	−2	66	20	3.97	.05[c,e]
R	Lateral hypothalamus	. . .	12	−2	−12	3.67	.05[c]

Abbreviations: BA, Brodmann area; ellipses, not applicable; FWE, familywise error; L, left; MDD, major depressive disorder; MNI, Montreal Neurological Institute; PPI, psychophysiological interaction; R, right.

[a] Only regions surviving inclusive masking with guilt vs fixation are reported. No other regions survived an uncorrected threshold of $P = .005$ (extent threshold of 4 voxels) and a voxel- or cluster-corrected $P = .05$ over the whole brain or a priori regions of interest (ROIs). Analysis included 22 control participants and 25 patients with remitted MDD.

[b] Survived FWE correction over tier 2 ROI.

[c] Survived FWE correction over tier 1 ROI.

[d] Analysis included 21 control participants and 25 patients with remitted MDD.

[e] Cluster corrected.

nificance of $P = .001$). This activation survived familywise error (FWE) correction ($P < .05$) over an a priori right superior ATL region of interest (ROI) used in a previous independent study (sphere of 6-mm radius centered on $x = 57$, $y = -3$, $z = -6$).[21] The neural time series of this region was estimated by deconvolving the BOLD response using the standard deconvolution algorithm in SPM8.

At the single-participant level, the physiological variable, the psychological variable, and the PPI terms for guilt vs fixation and indignation vs fixation were entered into a common general linear model. Both PPI and BOLD analyses (for further details, see eMethods) were carried out using the same contrasts, masking procedures, and thresholds. Between-group differences were analyzed using a 2-sample *t* test (allowing for unequal variances in the groups) comparing guilt vs indignation inclusively masked with guilt vs fixation (mask at uncorrected voxel-level threshold, $P = .005$), with an uncorrected voxel-level threshold of $P = .005$ and extent threshold of 4 voxels. Thereby, we ensured that reported PPI effects were due to positive effects in the guilt condition rather than to negative effects in the subtracted indignation condition. The only areas reported are those that survived additional voxel- or cluster-level FWE-corrected thresholds of $P = .05$ across a priori ROIs (small volume correction) or the whole brain. A gray matter mask based on brains of all 47 participants was used as an inclusive mask in all analyses (see eMethods). After carrying out between-group analyses, we extracted each subject's interaction (PPI) and physiological coupling regression coefficients from the peak voxel of the SCSR effect for the contrasts guilt vs indignation and extracted the same regression coefficients from the same voxel for the other contrasts (eFigure 1 and eFigure 2). Because the PPI term extracted from a voxel represents coupling of that voxel with the ATL seed during one contrast relative to another, a negative PPI term does not necessarily reflect a negative coupling between regions but reflects only a relatively decreased coupling that could occur from a lower positive coupling in one condition compared with the other.

To further examine whether SCSR-ATL PPI between-group differences for guilt vs indignation were associated with individual differences on the IGQ-67 Self-hate subscale, we modeled the negative effect of IGQ-67 Self-hate subscale scores as a between-subject covariate and looked at its effect on ATL-SCSR PPI for guilt vs indignation across both groups. We inclusively masked the result by the between-group differences in ATL-PPI effects for guilt vs indignation and by our a priori SCSR ROI (see eFigure 1 for effects extracted from the peak voxel of this analysis).

ROI DEFINITION

All regions surviving our uncorrected voxel-level threshold (minimum cluster size of 4 voxels) that did not survive a whole-brain FWE-corrected threshold of $P = .05$ were further examined using FWE correction over bilateral a priori ROIs in 2 tiers.[21] We had no specific hypothesis about tier 1 regions, but these have been associated with moral and social cognition,[20] including posterior superior temporal sulcus/temporoparietal junction, ventromedial prefrontal cortex (PFC), dorsolateral PFC, dorsomedial PFC, insula, amygdala, basal ganglia, hypothalamus, ventral tegmental area, ATLs, and additional areas highlighted in corticolimbic network models of MDD[16] (ie, medial temporal lobes and frontopolar cortex [Brodmann area, 10]). eMethods includes further details on ROI construction.

Activations that did not survive FWE correction over these ROIs were then subjected to FWE correction over tier 2 ROIs. Tier 2 ROIs were constructed around center coordinates that have been consistently identified for guilt (SCSR ROI as a sphere with a radius of 6 mm around $x = -4$, $y = 23$, and $z = -5$) and indignation/anger (lateral orbitofrontal cortex ROI as a sphere with a radius of 6 mm around $x = 41$, $y = 33$, and $z = -2$) and were taken from previous independent studies (further described by Green et al[21] and in eMethods). We used anatomical landmarks (eFigure 3) and the Talairach atlas to determine Brodmann areas in our **Table**.

RESULTS

BEHAVIORAL RESULTS

There were no significant differences between groups in the percentages of trials rated as guilt or indignation evoking and no significant differences in response times for these trials, as well as no significant between-group differences for guilt- and indignation-evoking sentences on the ratings of unpleasantness, visual imagery, episodic autobiographical memory retrieval, degree of social behavioral detail, and number of imagined consequences of the described social actions (eTable 4). There were also no significant differences on self-reference relative to best friend–reference of concepts between guilt and indignation trials ($t_{45} = 0.48$, $P = .63$) and no significant differences between the groups on this measure (eTable 4).

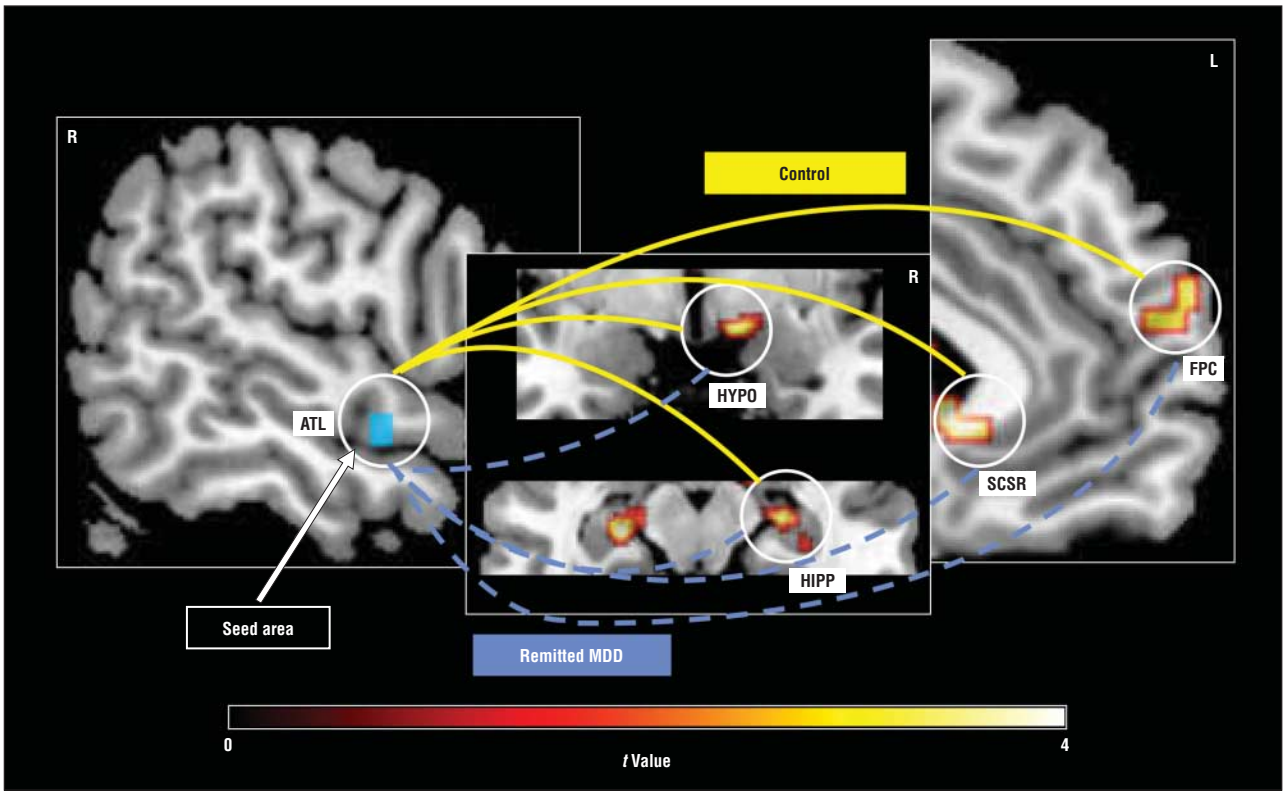

Figure 1. Regions showing decreased coupling with the right superior anterior temporal lobe (ATL) during the experience of guilt vs indignation in individuals with remitted major depressive disorder (MDD) compared with healthy control participants including the lateral hypothalamus (HYPO), hippocampus (HIPP), medial frontopolar cortex (FPC), and a subgenual cingulate and adjacent septal region (SCSR). Cropped whole-brain images are displayed at an uncorrected threshold of $P=.005$ (extent threshold of 4 voxels). All depicted regions survived familywise error correction over a priori regions of interest at $P=.05$ in separate analyses. L indicates left; R, right.

fMRI RESULTS

On standard BOLD effect analyses for guilt vs indignation, the control group showed greater activation within the right posterior insula/superior temporal and the left parieto-occipital junction than did the MDD group (eTable 5). There were no regions activated more strongly in the MDD than the control group for guilt vs indignation (see eTable 5 for reverse comparisons of indignation vs guilt and eTable 6 for separate group analyses). In summary, there were no significant between-group differences in average BOLD effects for guilt vs indignation in our main ROIs (SCSR, ATL).

The PPI analysis for guilt vs indignation revealed that, compared with the control group, participants with remitted MDD showed decreased coupling between the right superior ATL seed region and left SCSR, the bilateral medial frontopolar cortex (with a left hemisphere peak), and the right lateral hypothalamus and right hippocampus (Table, **Figure 1**, and eFigure 1; see also eResults and eFigure 4 for a supporting analysis to rule out influences of rated unpleasantness on these group differences). A secondary data analysis also demonstrated significantly lower coupling for guilt vs indignation in all these regions in the MDD subgroup currently not taking antidepressants (n=16) compared with the control group (eResults). In the MDD group compared with the control group, no regions showed increased coupling with the ATL seed region for guilt vs indignation (see eTable 7 and eFigure 2 for reverse comparison of indignation vs guilt and eTable 8 for separate group analyses).

A secondary data analysis across both groups showed that individuals with higher Self-hate subscale scores on the IGQ-67 showed lower degrees of ATL-SCSR coupling for guilt vs indignation (**Figure 2**).

The physiological coupling between ATL and SCSR irrespective of psychological condition was positive for both the control and MDD groups, and there were no significant between-group differences in physiological ATL-SCSR coupling (physiological coupling coefficients were extracted from the peak SCSR coordinate from the contrast of guilt vs indignation, 2-sample t test: $t_{45}=-0.67$, $P=.51$, 2-tailed).

COMMENT

We were able to confirm the prediction that, compared with the control group, people with remitted MDD show decoupling of a frontolimbic network with the right superior ATL, a region previously demonstrated to represent differentiated social conceptual knowledge.[17,22] Despite overall equivalent levels of neural network coupling (ie, irrespective of the psychological content), decoupling was selectively observed for guilt relative to indignation or relative to a resting-state (visual fixation) condition. More specifically, self-blame selective decoupling with the right superior ATL was found in the predicted

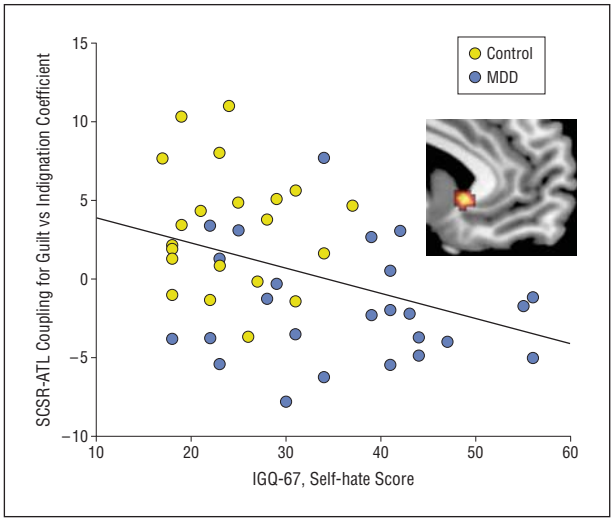

Figure 2. Self-hate subscale scores from the 67-item Interpersonal Guilt Questionnaire (IGQ-67) for each participant were plotted against subgenual cingulate and adjacent septal region (SCSR)–anterior temporal lobe coupling regression coefficients for guilt vs indignation (n=46, $r=-0.39$ [$\rho=-0.38$], $P=.008$ at peak voxel: $x=-8$, $y=22$, $z=-2$, familywise error–corrected $P=.04$ over a priori SCSR region of interest [ROI] inclusively masked with SCSR difference in coupling for control vs remitted major depressive disorder [MDD] groups at $P=.005$ [see cropped image at upper right displaying the ROI analysis at uncorrected $P=.05$]).

SCSR, which had previously been implicated in representing guilt-specific feeling contexts.[17,18] In addition, we found medial frontopolar cortex, right hippocampus, and lateral hypothalamus to show self-blame selective decoupling with the ATL.

Furthermore, we were able to confirm the prediction that individuals with high levels of overgeneralized self-blame, as measured on the Self-hate subscale of the IGQ-67, show lower degrees of ATL-SCSR coupling for guilt vs indignation. This finding directly links ATL-SCSR decoupling with maladaptive forms of self-blame that are a characteristic of MDD.[7]

The robust ATL-frontolimbic decoupling effect in the MDD group was observed despite a normal average BOLD signal in this network, highlighting the importance of analyses of neural coupling to reveal the functional changes underpinning nonorganic psychiatric disorders. Normal physiological coupling (ie, coupling among regions irrespective of psychological condition) between the right superior ATL, hippocampus, subgenual cingulate area, and medial frontopolar cortex in the MDD group indicates their intact structural connectivity. Functional connectivity effects may be mediated by anatomical connections between these regions and the superior ATL.[34]

The results of this study point to a functional disconnection mechanism that is dependent on contents of experience, which is compatible with the known interaction of psychosocial learning and heritable neurobiological factors in the pathogenesis of MDD.[35] Abnormalities of fMRI coupling between subgenual cingulate and other frontolimbic regions have been demonstrated during the resting state[14,15] in patients with MDD in the symptomatic stage. However, to our knowledge, this is the first study showing fMRI coupling abnormalities involving the subgenual cingulate in MDD after remission of symptoms. The fact that partly overlapping brain networks show abnormal coupling in the resting state in the symptomatic stage of MDD and demonstrate self-blame selective decoupling after remission could be explained by the abundance of spontaneous experience of automatic self-blaming thoughts in people with symptomatic MDD[2] when compared with healthy participants. Functional connectivity was, however, increased in these previous studies of MDD[14,15] rather than decreased as in our study. To resolve this discrepancy and interpret its physiological basis, future studies need to directly compare resting-state fMRI and PPI methods.

The finding that guilt-selective right superior ATL decoupling is associated with MDD vulnerability is in keeping with the hypothesis that deficient integration of conceptual social knowledge detail (what it means to act, eg, stingily) increases proneness to overgeneralized self-blame (eg, "I acted badly")[21] described as a central cognitive feature of MDD.[2,3] This is in keeping with the view that the ATL may implicitly enrich moral feelings such as guilt with detailed social meaning, even in the absence of verbalization.[20] According to this view, ATL activation found in response to morally relevant materials[36,37] is the result of implicitly activated social conceptual representations.[20,38] The right superior ATL was previously associated with making fine-grained differentiations between conceptual qualities of social behaviors because activation of this area rises with increasing conceptual detail describing social behavior.[17,22] In addition, neurodegeneration of the right superior ATL was associated with selective loss of social conceptual knowledge.[23]

The involvement of the ATLs in social meaning has been recently corroborated in independent investigations.[39,40] This evidence is in agreement with a more general view of ATL function as a hub representing context-independent aspects of concepts, which received support from recent fMRI[41] and repetitive transcranial magnetic stimulation studies[41,42] in healthy individuals. This model of the ATL was derived from numerous investigations of patients with semantic dementia who have progressive atrophy to the ATLs, show degradation of conceptual knowledge across modalities (verbal and nonverbal), and make overgeneralization errors across different concepts.[24,25]

The exact role of the SCSR region in the experience of self-blaming feelings is elusive. However, fMRI studies have revealed activation of the SCSR during the experience of guilt in healthy individuals when compared with indignation/anger[17,18] and during charity donation.[43] Furthermore, degeneration of the septal region has been related to impairments of guilt relative to anger.[19] Thus, the role of the SCSR in those studies cannot be attributed to the presence of negative emotions alone. Neither can its activations be attributed to successful emotion regulation, because SCSR activation increased in individuals with increased guilt proneness,[17,18] a finding that we were able to reproduce in this study (eTable 9). Interestingly, the MDD group not only showed abnormally decreased ATL-SCSR coupling when feeling guilt but also an abnormal lack of decoupling when feeling indignation (eResults, eTable 7, eFigure 2, and eFigure 5). Together with the evidence of a guilt-selective role of the SCSR, one may speculate that the MDD group exhibited a context-inappropriate access to

guilt-related SCSR representations when experiencing indignation. This mechanism may contribute to self-blaming biases in addition to a lack of ATL-SCSR integration when experiencing guilt.

The result of decreased coupling with the hippocampus is in keeping with its importance in corticolimbic network models of MDD based on positron emission tomography studies.[16] The hippocampus is involved in encoding and retrieval of autobiographical episodic memories,[44] and, interestingly, an increased tendency to retrieve overgeneralized rather than specific emotionally relevant autobiographical episodes was described in people with MDD.[45] Decreased ATL-hippocampal integration during the experience of self-blaming feelings in remitted MDD may therefore be a correlate of diminished integration of specific autobiographical episodes that could contribute to overgeneralizations of self-blame.

We found no decoupling effects with the amygdala in the remitted MDD group despite its direct and reciprocal anatomical connections with the ATL.[34] This negative finding cannot be attributed to lack of sensitivity, since guilt-selective ATL-amygdala coupling was detected in the control group (eTable 8). Normal amygdala function in remitted MDD is in keeping with recent evidence on its role as a marker of the depressive state rather than of the vulnerability trait conferring MDD. This was demonstrated in studies[46-48] showing normalization of amygdala activation in response to emotional faces when recovering from MD episodes.

The medial frontopolar region showing decreased coupling is close to a region with abnormal resting-state coupling in symptomatic MDD[15] and is located rostrally from the dorsomedial frontal regions associated with abnormal self-reference of social concepts describing personality traits in symptomatic MDD.[49,50] Self-reference relative to best-friend reference (ie, the degree to which participants think of, eg, stingy, as a characteristic trait of their own personality relative to their best friend's personality) was separately assessed in our study and did not differ between guilt and indignation trials or between groups. In previous studies,[17,36,37] the medial frontopolar region was consistently activated during tasks probing the experience of guilt compared with other moral and nonmoral emotions, and its neurodegeneration was specifically associated with loss of prosocial moral feelings (guilt, pity, and embarrassment), but not with loss of anger and disgust.[19] The frontopolar region has also been implicated in representing consequences of social actions.[20] Decreased integration between the ATL and frontopolar cortex could therefore reflect decreased integration of conceptual details of social actions with contextual information regarding their consequences.

This study investigated predominantly younger people and will therefore need replication in a sample of older participants and ideally with a higher proportion of men. The analysis used a random-effects approach to ensure better generalizability of the results by removing between-subject variance in each group.[51] This relative homogeneity of effects within the MDD group was further corroborated by subgroup analyses (eResults).

Our results were independent of group differences in intensity of negative emotions and therefore cannot be accounted for by a general emotion regulation deficit. Furthermore, between-group differences cannot be attributed to differences in the number of guilt and indignation trials, response times, or medication status.

We demonstrated a guilt-selective decrease in ATL coupling in remitted MDD across a frontolimbic network of the SCSR, medial frontopolar cortex, lateral hypothalamus, and hippocampus. These results shed new light on the pathophysiology of vulnerability to MDD by providing a specific neural mechanism that can account for self-blaming biases long known to be a core and distinctive feature of MDD. Prospective studies will need to establish whether self-blame selective decoupling can predict recurrence of future episodes of depression and thereby support its suspected causal relationship with vulnerability to MDD.

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