Guilt-selective functional disconnection of anterior temporal and subgenual cortices in major depressive disorder

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Abstract

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 towards emotions entailing self-blame (e.g. guilt) relative to those associated with blaming others (e.g. indignation). Recent 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 the 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: Use fMRI to test the hypothesis that in comparison with controls, participants with remitted MDD exhibit guilt-selective SCSR-ATL decoupling as a marker of deficient functional integration.

Design: Case-control study from 2008 to 2009.

Setting: Clinical Research Facility.

Participants: 25 patients with remitted MDD (no medication in 16) with no current co-morbid axis-I disorders, and 22 control participants with no personal or family history of MDD.

Main outcome measures: Between-group difference of ATL-coupling with a priori SCSR region of interest (ROI) for guilt vs. indignation.

Results: We corroborated the prediction of a guilt-selective reduction in ATL-SCSR coupling in MDD vs. controls (Family-Wise-Error-corrected p=.001 over ROI) 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 (Interpersonal Guilt Questionnaire).

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

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], e.g. "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 even 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 primarily focussed on the neural correlates of general increases in negative emotions and their regulation (reviewed in [5]). However, overall increases in negative emotions cannot explain biases towards self-blaming feelings demonstrated in MDD. Patients with MDD typically feel inadequate and worthless compared to 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 which do not include irritability or anger directed towards others which are instead part of the core diagnostic criteria for its polar opposite, namely 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 MD episodes [11] and its metabolism normalizes with remission of symptoms on treatment [12]. Interestingly, this remission can be induced by subgenual cingulate stimulation with deep-brain electrodes [13]. This region is part of a cortico-limbic network that exhibits abnormalities in functional connectivity in people with MD episodes as shown by both resting-state fMRI [14, 15] and positron emission tomography (PET, [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). Further, this selective involvement of SCSR regions 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 has also been consistently implicated in moral feelings such as guilt[20]. However, in contrast to the SCSR, the right superior anterior temporal lobe (ATL) was activated irrespective of the type of moral feeling whether it is guilt or indignation [17]. Further, this ATL region showed selective functional coupling with the SCSR for guilt relative to indignation in healthy participants with low risk of MDD [19]. Evidence from fMRI [21] and patient lesion [22] studies suggests that the right superior ATL is important for the representation of social concepts allowing for differentiation between specific qualities (e.g. "faultfinding", "critical") of social behaviours (e.g. "I pointed to a typing error in one of my colleagues e-mails") and thereby allowing us to make differentiated appraisals of behaviour to protect us against overgeneralization of self-blame[17, 21, 22] (e.g. This means: "I am ***critical***" rather than "I am ***unlikable***"). Social concepts (e.g. "stingy", "clumsy", or "unintellectual") are thus a crucial ingredient for tackling patients' self-blaming overgeneralizations in therapy ([2], e.g. "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, we have previously hypothesized that ATL-SCSR functional coupling is the neural correlate of the experience of differentiated forms of guilt[19] that allow individuals with low MDD risk to blame themselves in a specific fashion (i.e. to feel guilt in an adaptive way) without damaging their self-worth as a person or hating themselves (an overgeneralized form of guilt [7]). This is based on a more general model of the ATLs as representing context-independent and modality-independent information allowing for rapid and automatic conceptual differentiation even when accessed nonverbally [23, 24].

Here, we used fMRI to investigate functional integration of temporo-fronto-subcortical networks during emotional judgements of guilt-evoking (e.g. "Tom [participant] acts greedily towards Sam [best friend]") and indignation-evoking (e.g. "Sam acts greedily towards Tom") sentences in individuals with fully remitted MDD to uncover the neural substrates of self-blaming biases. We carefully controlled for overall rated unpleasantness of feelings during fMRI and medication status. The investigation of participants with remitted MDD reveals "trait" vulnerability factors [25] 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 employed psychophysiological interaction (PPI) analysis, an established measure of functional integration [26], 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 Interpersonal Guilt Questionnaire (IGQ-67[27]). This measure is largely elevated in people with MDD during the symptomatic [7] as well as the remitted phase [28]. We predicted that individuals with a lower degree of ATL-SCSR coupling for guilt vs. indignation display higher scores on the self-hate scale.

Methods

Participants

This study was approved by the South Manchester NHS Research Ethics Committee and all participants gave informed consent (oral for pre-screening and written for subsequent stages). Participants were recruited using online and print advertisements. Initial suitability was assessed with a phone pre-screening interview (see eMethods and Appendix).

Inclusion/exclusion of participants (see eMethods): Participants in the MDD group fulfilled criteria for a past major depressive episode according to Diagnostic and Statistical Manual IV-TR [9], and for a moderate to severe depressive episode according to the International Classification of Diseases-10 with at least 2 months duration requiring treatment and remission of symptoms for at least 12 months. Exclusion criteria were current axis-I disorders and history of alcohol or substance abuse or past co-morbid axis-I disorders being the likely primary cause of the depressive syndrome (see eTab.7 for and eTab.8). The healthy control group had no current or past axis-I disorders and no first degree family history of MDD, bipolar disorder, or schizophrenia.

In total, 22 healthy control participants and 25 individuals with remitted MDD (16 with no current antidepressant medication) were included in the final analysis. All participants had normal or corrected-to-normal vision. The groups were matched on age, education and gender (eTab.9). Volunteers were invited for a clinical interview in which psychiatric, medical and family history were assessed and a neurological exam was carried out by a board-certified psychiatrist (RZ). Further, a Structured Clinical Interview for DSM-IV-TR (SCID-I) Mood Disorders Module A [29] and the International Neuropsychiatric Interview [30] 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 [31], the Montgomery Asberg Depression Rating Scale (MADRS, [32]) and the Global Assessment of Functioning (GAF) scale (Axis V, DSM-IV) were employed. Both groups had MADRS scores that were well below the cut-off for depression (10 points), but the MDD group showed slightly higher scores. Both groups had GAF scores indicating minimal or absent symptoms (>80), although control participants exhibited a higher score (see eTab.9).

fMRI paradigm

Participants were presented with written statements describing actions counter to social and moral values described by social concepts (e.g. '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 are further described in [17, 21] and a full list of stimuli is available on request). Self- and other-agency conditions used the same social concepts (self-agency: e.g. "[participant's name] does act stingily towards [best friend's name]", other-agency: e.g. "[best friend's name] does act stingily towards [participant's name]"). 50% of trials used negative social concepts (e.g. 'does act stingily') and 50% used negated positive social concepts (e.g. '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 make a decision 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. Further they were required to "choose the feeling that (they) would feel most strongly" from a choice of: guilt, contempt/disgust towards self, shame, indignation/anger towards self, indignation/anger towards other, contempt/disgust towards other, none, other feeling. As in our previous studies[17, 19], guilt and indignation trials for the fMRI analysis were defined on the basis of individual ratings and restricted to agency-role-congruent responses (i.e. guilt in the self-agency condition and indignation in the other-agency condition, see also eTab.1). 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, one's best friend has done would be mostly maladaptive and we wanted to restrict our analyses to adaptive "healthy" experiences of guilt in order to allow a direct comparison of control and MDD group without confounding differences in the subjective experience. Participants also rated how many different outcomes of the behavior they estimate, 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 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 describes themselves or their best friends on two separate scales (see eMethods).

Image acquisition

Echo-planar T2*-weighted images (405 volumes in each of the 3 runs with 5 dummy scans for each run of 13min40sec) were acquired on a Philips 3 Tesla Achieva MRI scanner with an 8 channel coil, 3mm slice thickness and ascending continuous acquisition parallel to the anterior to posterior commissural line (between 35 and 40 slices depending on size of the participant's head, Repetition Time (TR)=2000 ms, Echo Time (TE)=20.5 ms, Field of View (FOV)=220x220x120 mm, acquisition matrix=80x80, reconstructed voxel size=2.29x2.29x3 mm, SENSE factor=2). In addition 3-dimensional T1-weighted Magnetization-Prepared Rapid Acquisition Gradient Echo structural images were obtained (reconstructed voxel size=1 mm3, 128 slices, TE=3.9 ms, FOV=256x256x128, acquisition matrix=256x164, slice thickness=1 mm, TR=9.4 ms). Axial T2-weighted structural images were acquired for each participant to rule out vascular and inflammatory abnormalities.

Behavioural data analysis

Analysis of between-group differences were performed using 2-sided two-sample t-tests at p=.05 in SPSS15 (www.spss.com). Self-hate subscale scores from the Interpersonal Guilt Questionnaire[27] were found to be significantly elevated in our remitted MDD group (t=4.8, df=36.7, equal variances not assumed, p<.0001) and were reported elsewhere [28]. Here, we used these scores as between-subject covariates in the imaging analysis (see below).

Image analysis

Functional images were realigned, unwarped and coregistered to the subject'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 FWHM=6 mm was used.

We tested our main hypotheses about functional integration using a psychophysiological interaction (PPI) analysis in SPM8 ([26], see eData for methods of standard BOLD effect analysis). PPI 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 psychophysiological interaction (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 (e.g. guilt) relative to another (e.g. 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=.0001) for N=47 participants from both groups (***guilt vs. fixation*** inclusively masked by ***indignation vs. fixation*** thresholded at an uncorrected voxel-level significance of p=.001). This activation survived FWE-correction (p<.05) over an a priori right superior ATL ROI used in our previous independent study (sphere of 6 mm radius centered on: x=57, y=−3, z=−6 [19]). The neural time series of this region was estimated by deconvolving the BOLD response using the standard deconvolution algorithm in SPM8.

At the single subject 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 analysed using a two-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, extent threshold of 4 voxels. Thereby, we ensured that reported PPI effects were due to positive effects in the guilt condition rather than due to negative effects in the subtracted indignation condition. Only areas are reported that survived additional voxel- or cluster-level Family-Wise-Error (FWE)-corrected thresholds of p=.05 across ***a priori*** ROIs (small volume correction) or the whole brain. A grey matter mask based on brains of all participants (N=47) was used as an inclusive mask in all analyses (see eMethods). After carrying out between-group analyses, we extracted the individual subjects' 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 (see eFig.1

and eFig.2). Because, the PPI term extracted from a voxel represents the 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 only reflects a relatively decreased coupling that could occur from a lower positive coupling in one condition compared to the other.

To further examine whether SCSR-ATL PPI between-group differences for guilt vs. indignation were associated with individual differences on the Interpersonal Guilt Questionnaire (IGQ-67)-self-hate scale, we modelled the negative effect of IGQ-67-self-hate-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 eFig.1 for effects extracted from the peak voxel of this analysis).

Region of Interest (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 two tiers, as in [19]. Tier 1 regions were regions that we had no specific hypothesis about but which have been previously associated with moral and social cognition [20] including: posterior superior temporal sulcus/temporo-parietal junction, ventromedial PFC, dorsolateral PFC, dorsomedial PFC, insula, amygdala, basal ganglia, hypothalamus, ventral tegmental area, anterior temporal lobes and additional areas highlighted in cortico-limbic network models of MDD [16]: medial temporal lobes and frontopolar cortex (BA 10, see eMethods for 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 sphere with radius of 6 mm around x=-4, y=23, z=-5) and indignation/anger (lateral orbitofrontal cortex ROI as sphere with radius of 6 mm around x=41, y=33, z=-2) and were taken from previous independent studies (further described in [19] and eMethods). We used anatomical landmarks and the Talairach atlas to determine Brodmann areas in our Tables.

Results

Behavioural results

There were no differences between groups in the percentages of trials rated as guilt- or indignation-evoking and no differences in response times for these trials, as well as no between-group differences for guilt- and indignation-evoking sentences on the ratings of unpleasantness, visual imagery, episodic autobiographical memory retrieval, degree of social behavioural detail, and number of imagined consequences of the described social actions (see eTab.1). There were also no differences on self-reference relative to best friend-reference of concepts between guilt and indignation trials ($t[45]=.48$, $p=.63$) and no differences between the groups on this measure (see eTab.1).

fMRI results

On standard blood-oxygenation-level-dependent (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 the MDD group (see eTab.2). There were no regions activated more strongly in the MDD than the control group for ***guilt vs. indignation*** (see eTab.2 for reverse comparisons of ***indignation vs. guilt*** and eTab.3 for separate group analyses). In summary, there were no between-group differences in average BOLD effects for ***guilt vs. indignation*** in our main regions of interest (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), the right lateral hypothalamus and right hippocampus (Tab.1, Fig.1 & eFig.1, see also eResults 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 of these regions in the MDD subgroup currently not taking antidepressants (N=16) compared with the control group (see eResults). In the MDD group compared with the control group, there were no regions which showed increased coupling with the ATL seed region for ***guilt vs. indignation*** (see eTab.4, eFig.2 for reverse comparison of ***indignation vs. guilt*** and eTab.5 for separate group analyses).

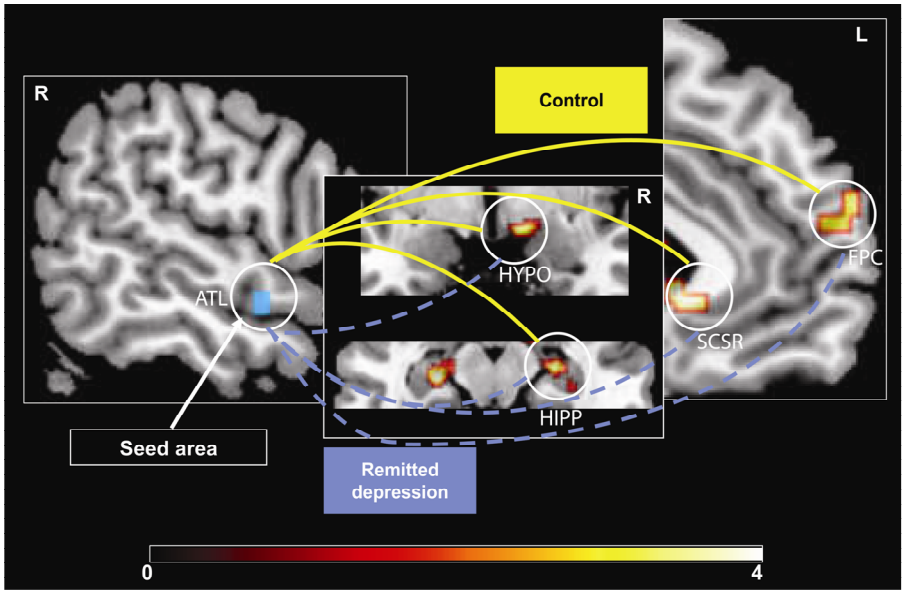

Fig.1

Regions showing decreased coupling with the right superior ATL during the experience of ***guilt vs. indignation*** in individuals with remitted MDD compared with healthy controls including the lateral hypothalamus (HYPO), hippocampus (HIPP), medial frontopolar cortex (FPC) and a subgenual cingulate/septal region (SCSR). Cropped whole brain images were displayed at an uncorrected threshold of p=.005 (extent threshold of 4 voxels). All depicted regions survived FWE-correction over a priori ROIs at p=.05 in separate analyses.

Tab.1 PPI effects for control vs. remitted MDD group: guilt vs. indignation

Hemi-sphere	Region	BA	MNI coordinates			t-value	FWE-corr. p-value
			X	Y	Z		
L	Subgenual cingulate/septal region	25	-6	22	0	4.67	0.001[2]
R	Hippocampus	-	28	-16	-14	4.44	0.03[1]
L	Medial frontopolar cortex~	10	-2	66	20	3.97	0.05[1c]
R	Lateral hypothalamus	-	12	-2	-12	3.67	0.05[1]

Only regions surviving inclusive masking with ***guilt vs. fixation*** are reported. No other regions survived an uncorrected threshold of p=0.005 (extent threshold of 4 voxels) and a voxel- or cluster-corrected (=c) p=.05 over the whole brain or our a priori ROIs. 1=survived FWE-correction over tier 1 ROI, 2=survived FWE-correction over tier 2 ROI. Control: N=22, remitted MDD: N=25. Regions marked ~ = from analysis including N=21 control and N=25 remitted MDD participants.

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 (see Fig.2).

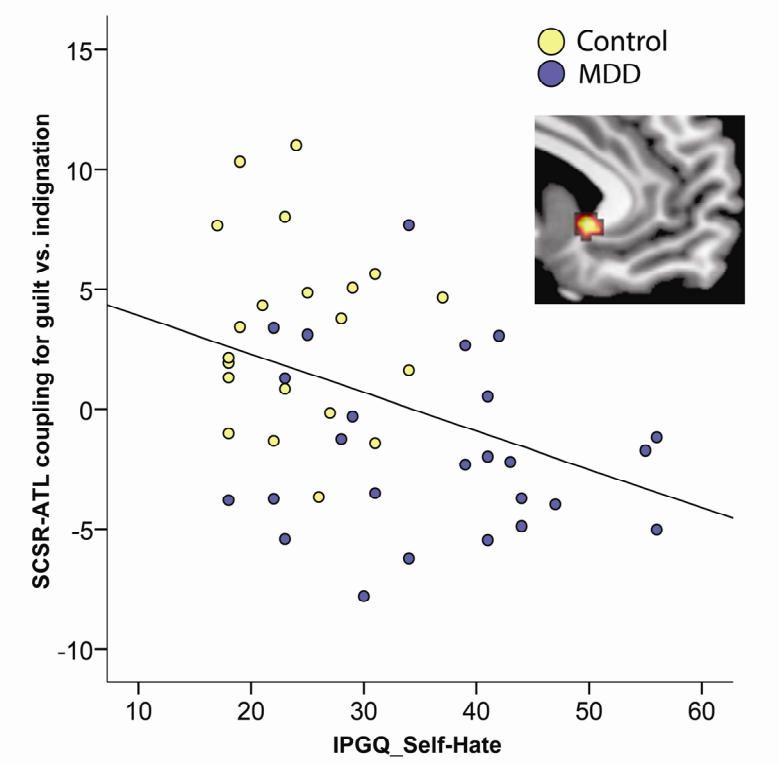

Fig.2

Self-hate subscale scores from the Interpersonal Guilt Questionnaire (IGQ-67) for each participant were plotted against SCSR-ATL coupling regression coefficients for guilt vs. indignation (N=46, r=-.39 (rho=-.38), p=.008 at peak voxel: x=-8, y=22, z=-2, FWE-corrected p=.04 over a priori SCSR ROI inclusively masked with SCSR difference in coupling for control vs. remitted MDD groups at p=.005, see cropped image displaying the ROI analysis at uncorrected p=.05).

The physiological coupling between ATL and SCSR irrespective of psychological condition was positive for both the control and MDD groups and there were no 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***, two-sample t-test: t[45]=-.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 fronto-limbic network with the right superior ATL, a region previously demonstrated to represent differentiated social conceptual knowledge[17, 21]. Despite overall equivalent levels of neural network coupling (i.e. 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 SCSR region, that 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.

Further, 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 Interpersonal Guilt Questionnaire, 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-fronto-limbic decoupling effect in the MDD group was observed despite normal average BOLD signal in this network, highlighting the importance of analyses of neural coupling in order to reveal the functional changes underpinning non-organic psychiatric disorders. Normal physiological coupling (i.e. the coupling among regions irrespective of psychological condition) between right superior ATL, the 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 [33].

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 [34]. Abnormalities of fMRI coupling between subgenual cingulate and other fronto-limbic regions have been demonstrated during the resting state [14, 15] in MDD patients 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 while showing 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. Importantly, functional connectivity was, however, increased in these previous studies of MDD[14, 15] rather than decreased as in our study. In order 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 e.g. "stingily") increases proneness to overgeneralized self-blame (e.g. "I acted badly") [19] 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 [35, 36] is due to implicitly activated social conceptual representations [20, 37]. The right superior ATL was previously associated with making fine-grained differentiations between conceptual qualities of social behaviours as activation of this area rises with increasing conceptual detail describing social behaviour [17, 21]. In addition, neurodegeneration of the right superior ATL was associated with selective loss of social conceptual knowledge [22].

The involvement of the ATLs in social meaning has been recently corroborated in independent investigations [38, 39]. 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 [40] and repetitive transcranial magnetic stimulation studies [40, 41] in healthy individuals. This model of the ATL was derived from numerous investigations of patients with semantic dementia who have progressive atrophy to the anterior temporal lobes, show degradation of conceptual knowledge across modalities (verbal and nonverbal) and make overgeneralization errors across different concepts [23, 24].

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 [42]. Further, degeneration of the septal region has been related to impairments of guilt relative to anger [19]. Thus the role of 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 we were able to

reproduce in this study (see eTab.6). Interestingly, the MDD group did not only show abnormally decreased ATL-SCSR coupling when feeling guilt, but also an abnormal lack of decoupling when feeling indignation (see eResults,eTab.4,eFig.2,eFig.5). Together with above evidence on a guilt-selective role of the SCSR, one may thus 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 cortico-limbic network models of MDD based on PET studies [16]. The hippocampus is involved in encoding and retrieval of autobiographical episodic memories [43] and interestingly, an increased tendency to retrieve overgeneralized rather than specific emotionally relevant autobiographical episodes was described in people with MDD [44]. 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 [33]. This negative finding cannot be attributed to lack of sensitivity, since guilt-selective ATL-amygdala coupling was detected in the control group (see eTab.5). 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 showing normalization of amygdala activation in response to emotional faces when recovering from MD episodes [45-47].

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 [48, 49]. Self-reference relative to best-friend-reference (i.e. the degree to which participants think of e.g. “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, the medial frontopolar region was consistently activated during tasks probing the experience of guilt compared with other moral and non-moral emotions [17, 35, 36] 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 males. The analysis used a random-effects approach to ensure better generalizability of the results by removing between-subject variance in each group [50]. This relative homogeneity of effects within the MDD group was further corroborated by subgroup analyses (see 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. Further, between-group differences cannot be attributed to differences in the number of guilt and indignation trials, response times, or medication status.

Taken together, we demonstrated a guilt-selective decrease in anterior temporal lobe coupling in remitted MDD across a fronto-limbic network of subgenual cingulate/septal region, 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 as 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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