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Thalamocortical connectivity in major depressive disorder

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Introduction

Major depressive disorder (MDD) is a common disabling mental disorder characterised by substantial impairments in emotional and cognitive processing (Gotlib and Joormann, 2010). Empirical findings from a large body of neuroimaging literature implicate widespread disruptions in functional and structural connectivity across multiple brain regions in MDD (Price and Drevets, 2010). Growing evidence suggests that mapping thalamic connectivity would allow the characterization of large scale distributed circuit abnormalities in major mental disorders (Anticevic et al., 2014). Two main circuits that have been implicated in depression involve limbic, striatal, pallidal, thalamic and cortical

structures (Drevets et al., 1992; Price and Drevets, 2010; Shepherd, 2013; Swerdlow and Koob, 1987). The thalamus plays a major role in relaying and modulating sensory information from peripheral sensory organs to sensory cortices (first order relay) as well as information from one cortical region to other cortical regions (higher order relay) (Sherman and Guillery, 1996). Among the higher order thalamic relay nuclei, mediodorsal thalamus is critical for cognitive and emotional processes through its modulatory interactions within prefrontal-temporal (cortico-cortical), prefrontal-amygdala (cortico-limbic) and prefrontal-basal ganglia (cortico-striatal) networks (Sherman and Guillery, 1996). Activity within these networks demonstrates both top-down and bottom up modulation of emotion, motivation, drive and attention (Vertes et al., 2015; Wolff et al., 2015), which can all be impacted in MDD (Hamani et al., 2011; Price and Drevets, 2010). Importantly, lesion studies have documented the association between specific thalamic damage and cognitive / emotional deficits (Liebermann et al., 2013).

Previous literature has consistently shown abnormalities in thalamic structure and function in MDD. Studies have reported reduced grey matter volumes (Bora et al., 2012; Nugent et al., 2013; Soriano-Mas et al., 2011), associations between thalamic volume and severity of symptoms (Webb et al., 2014), reduction in white matter tracts in the thalamo-frontal circuits (Jia et al., 2014) and increased metabolism and blood flow in mediodorsal thalamus in MDD (Drevets et al., 2002). One group looking at volumetric changes in untreated first-episode MDD patients interestingly found increased grey matter volumes in the superior frontal gyrus and thalamus, which are key regions in cortico-striato-

pallido-thalamic loops (Qiu et al., 2014). A couple of studies have identified abnormal thalamic functional connectivity in MDD, showing conflicting results, with one demonstrating an increase in thalamic and subgenual cingulate connectivity in MDD (Greicius et al., 2007), and another demonstrating a decrease in thalamic connectivity with cortical areas regulating mood in treatment-resistant patients (Lui et al., 2011). Furthermore, some studies have also documented associations between thalamic activity and treatment outcomes. For example, patients with treatment resistant depression (TRD) had greater spontaneous thalamic activity compared to non-TRD patients (Yamamura et al., 2016). In this same study, a lower clinical improvement in response to antidepressants correlated with higher thalamic activity. One study has also demonstrated an association between thalamic connectivity and treatment response in MDD following repetitive transcranial magnetic stimulation (rTMS) to dorsolateral prefrontal cortex (Salomons et al., 2014). It is important to note here that several of these aforementioned studies found abnormalities in connectivity between frontal regions and the thalamus. Deep brain stimulation of the inferior thalamic peduncle has also been used as an experimental treatment for MDD, showing high efficacy in reducing core depressive symptoms and improving global functioning (Velasco et al., 2005). Taken together, the above lines of evidence suggest that abnormalities in thalamic connectivity may be a potential marker of MDD psychopathology and treatment outcome.

As already mentioned, some previous functional connectivity studies in MDD have provided clues about possible abnormalities in thalamic connectivity in MDD. However, as none of these studies have focused specifically on thalamocortical connectivity, it is

not possible to make strong inferences about impairments in this network. To date, no study has directly investigated disturbances in the thalamocortical system in MDD, although there have been several studies finding specific patterns of thalamocortical connectivity in other severe mental disorders including schizophrenia, bipolar disorder, a ketamine model of psychosis and in autism (Anticevic et al., 2014; Höflich et al., 2015a; Nair et al., 2013). In light of this, there is a need to characterize thalamocortical circuit dysfunction in MDD to understand shared and specific patterns of thalamocortical dysconnectivity in relation to other disorders.

Aims of the study:

In order to investigate thalamocortical functional connectivity in MDD we employed a well-replicated approach similar to that of Zhang et al. (Zhang et al., 2010, 2008) using resting state fMRI in a group of medication-free MDD patients and a group of healthy controls. Given the evidence from a systematic review of neuroimaging studies that prefrontal cortex and medial temporal structures are involved in emotional regulation and are central to MDD psychopathology (Rive et al., 2013), we predicted that the MDD group would show aberrations in thalamocortical connectivity in specific regions, including prefrontal and temporal areas. Furthermore, we predicted that thalamocortical connectivity would be related to the severity of depression.

Method

Participants

Fifty-four people with major depressive disorder (MDD) were recruited through advertisements. The diagnosis of all patients was determined by a trained psychiatrist (RR) using the Structured Clinical Interview for DSM-IV Axis-1 Disorders (SCID for DSM-IV (First et al., 2002)). All were given the 17-item Hamilton Rating Scale for Depression (HAM-D; (Hamilton, 1967)) to assess the severity of depressive symptoms. Patients were only included in the study if they had previously experienced an acute episode of MDD, unipolar subtype, and received a score of 18 or above on the HAM-D. All patients were free of antidepressants and other psychotropic medications, including antipsychotics, lithium, anticonvulsants, benzodiazepines or sedatives, which could potentially influence brain activity and connectivity for a minimum of 3 weeks at the time of scanning in order to avoid possible confounding acute effects of medication. All MDD patients, with the exception of three, had previously been exposed to antidepressant medications. Patients were excluded if they had presence of other Axis I disorders (e.g. bipolar disorder, psychosis), history of substance abuse within 6 months of recruitment, a neurological disorder, severe suicidal thoughts or treatment resistance to three trials of antidepressant medications.

Forty healthy control participants were also recruited through public advertisement and screened for previous or current Axis I psychiatric disorders using the SCID for DSM-IV. Participants with any family history of Axis-I disorders were excluded, as well as those with neurological disorders or substance abuse within the last 6 months. The

investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The local ethics committee approved the study and all participants gave written informed consent before taking part and after all procedures had been fully explained. Clinical and demographic data for all participants are shown in table 1.

MRI data acquisition

Resting-state BOLD images from 45 of the MDD and 18 of the HC participants were collected with a 3T General Electric MR scanner (Signa VHi; General Electric Healthcare, Waukesha, WI, USA) using an eight-channel, phased-array head coil. Images of 9 of the MDD and 22 of the HC participants were collected with a 3T General Electric MR scanner (Discovery MR 750) also using an eight-channel, phased-array head coil. A total of 5 minutes of resting data were acquired using a single- shot gradient-recalled echo, echo planar imaging (EPI) sequence (150 volumes, TR/TE = 2000/30 ms, 24 cm × 24 cm field of view, flip angle = 65°, 30 slices of 4 mm thickness). A T1-weighted structural MRI (TR = 9.2 ms, TE = Minimum, flip angle = 20°, 180 slices at a resolution of 1 mm) was also acquired for anatomical registration of the fMRI data. Of the 9 MDD and 22 HC participants that were collected using the 3T General Electric MR scanner (Discovery MR 750), MDD patients had the same scanning parameters and protocol as that from the other scanner. All of these HC participants were scanned with an EPI sequence (119 volumes, TR/TE = 2500/30 ms, 24 cm × 24 cm field of view, flip angle = 77°, 40 slices of 3 mm thickness). A T1-weighted structural MRI (TR = 8.2 ms, TE =

Minimum, flip angle = 18°, at a resolution of 1.3 mm) was also acquired for anatomical registration.

In all scans, participants were asked to remain as still as possible in the MRI scanner with their eyes open and focused on a fixation cross at the center of a projection screen. The participants were asked to relax, not think about anything in particular, and to stay awake.

Image preprocessing

All image processing was performed with the FMRIB Software Library (FSL; (Smith et al., 2004)). Preprocessing, first-level analysis and higher-level group analysis were all performed using the FEAT tool, which is part of the FSL software suite, and is based on general linear modelling (GLM). For the group-level analysis, FEAT uses FMRIBs Local Analysis of Mixed Effects (FLAME).

Preprocessing of functional images included brain extraction. Spatial smoothing was done by applying a Gaussian filter full-width-half-maximum (FWHM) of 5mm. Slice timing correction was completed with a Hanning-window sinc interpolation shifting the time series relative to the mid-point of the TR period. A temporal high pass filter of 100s was used. Then functional images were co-registered to individual subject's anatomical images and then to a standard MNI template. Each participant's functional image was segmented into grey matter, white matter (WM) and cerebrospinal fluid (CSF) using manual tracing, of which the time series were later used as temporal covariates in the

general linear model (GLM). We did not regress out global brain signal as a nuisance variable in this analysis due to reports of the thalamus highly correlating with this signal (Zhang et al., 2008).

Cortical ROIs used as seeds

The Harvard-Oxford Cortical Structural Atlas probability maps were used to identify specific anatomical regions that were included in each cortical ROI, which were as follows: The frontal cortex ROI included inferior frontal gyrus, superior frontal gyrus, frontal pole, frontal medial cortex, subcallosal cortex, paracingulate gyrus, anterior cingulate gyrus, orbitofrontal cortex, frontal operculum, part of central opercular cortex and part of the precentral gyrus. The motor cortex ROI completely overlapped with the precentral gyrus in the atlas. The somatosensory cortex ROI completely overlapped with the postcentral gyrus in the atlas. The occipital cortex ROI included lateral occipital cortex (inferior and only part of superior divisions), occipital fusiform cortex, supracalcarine cortex, occipital pole, part of intracalcarine cortex, part of the cuneal cortex, part of the lingual gyrus and part of the temporal occipital fusiform cortex. The parietal cortex ROI included postcentral gyrus, superior parietal lobule, supramarginal gyrus (anterior and posterior divisions), angular gyrus, posterior division of the cingulate gyrus, precuneus cortex, parietal operculum cortex, part of precentral gyrus, part of Heschl's gyrus, part of supracalcarine cortex, part of planum temporale, part of the cuneal cortex, part of the superior division of the lateral occipital cortex and part of the intracalcarine cortex. The temporal cortex ROI included temporal pole, superior, middle

and inferior temporal gyrus, parahippocampal gyrus, amygdala, temporal fusiform cortex, Heschl's gyrus, planum polare, planum temporale, part of temporal occipital fusiform cortex, part of anterior hippocampus, part of inferior lateral occipital cortex and part of central opercular cortex.

Thalamocortical connectivity analysis

In order to investigate the functional connections between cortex and thalamus, we followed a similar approach used by Zhang et al. (Zhang et al., 2010, 2008). After preprocessing, we first defined six cortical regions of interest (ROIs) using the Oxford Thalamic Connectivity Atlas (Behrens et al., 2003). This consisted of 6 cortical regions shown to have specific anatomical connections with thalamic regions. These 6 regions consisted of 1) frontal cortex; 2) motor cortex (including primary and premotor cortices); 3) primary somatosensory cortex; 4) temporal; 5) parietal and 6) occipital cortices. Each cortical ROI is shown in figure 1a and specific areas included in each cortical ROI are listed in the supplementary materials. Average BOLD time-courses were extracted from each of these cortical ROIs, which were used as seeds in a seed-to-voxel connectivity analysis to reveal the connectivity between each cortical ROI and each voxel in the thalamus. A separate GLM was created for each cortical seed ROI in which every other cortical ROI was used as a covariate to identify the unique contribution in functional connectivity of that particular cortical ROI, along with motion parameters, and white matter, and cerebrospinal fluid time-courses. In order to ensure that effects were not accounted for by other factors, including differences in the two scanners used, age or sex,

these variables were also included in the GLM as regressors of no interest. Following this, individual functional connectivity maps were created for each cortical ROI, showing connectivity between each cortical ROI and each voxel in the thalamus. Group mean statistical maps were created with z-scores for the HC and MDD groups separately, and following this, group contrasts were performed. All statistical maps were thresholded at a voxel-wise alpha level of $p<0.005$. Small volume correction was performed to correct for multiple comparisons with the SPM WFU Pickatlas toolbox (Maldjian et al., 2003) using a corrected alpha level of $p<0.001$ FWE (greater than 6 voxels), considering only voxels within the Harvard-Oxford thalamus atlas (Behrens et al., 2003).

To investigate the relationship between thalamocortical connectivity and psychopathology, we performed a Pearson correlation analysis with the mean z-values of clusters in the thalamus derived from the MDD group statistical maps and HAM-D scores.

Results

Thalamocortical connectivity in HC and MDD groups

As shown in figure 1b, the HC and MDD groups both show connectivity between cortical ROIs and distinct regions in the thalamus. There is some degree of overlap between regions of the thalamus when looking at group mean clusters that correlate with cortical

ROIs, particularly with motor and parietal connectivity, although other regions appear mostly distinct and non-overlapping. Common patterns in thalamocortical connectivity appear across both groups. The frontal cortex was most highly connected with an anterior and dorsal part of the mediodorsal / midline nuclei in the thalamus. Motor regions most strongly connected with a posterior and ventral part of the mediodorsal thalamic nuclei. The somatosensory cortical ROI showed little connectivity with parts of the thalamus. Occipital lobe connectivity was mostly localized to lateral and medial geniculate bodies. Parietal cortex was most highly connected to the posterior and dorsal part of the mediodorsal / midline nuclei, including parts of the pulvinar. Notably, the temporal cortex showed the most qualitative difference between groups in terms of connectivity when comparing group means. In MDD, the localization of thalamic areas connected to temporal areas dominate medial / midline areas of the thalamus, whereas medial / midline thalamic connectivity with temporal regions in HCs was much less diffuse.

Differences between HC and MDD in thalamocortical connectivity

When looking at the group contrast in figure 1b, we see clusters representing significant group differences in thalamocortical connectivity between temporal cortex and thalamus, somatosensory cortex and thalamus, and frontal cortex and thalamus. The largest group differences emerge in the thalamocortical connectivity of the temporal region. We see greater connectivity between the temporal ROI and two distinct regions of the thalamus, one being in the medial part of the right mediodorsal and midline thalamic nuclei, and the

other in the right posterior ventral part of the pulvinar. There is also a small cluster showing hypoconnectivity between temporal areas and ventromedial thalamus in MDD. We also see greater connectivity between somatosensory cortex and a dorsal and anterior part of the right mediodorsal and midline thalamic nuclei in MDD compared to HCs. It is also worth noting here that using a marginally lower threshold for small volume correction ($p<0.01$ FWE) reveals group contrasts that show a small but significant clusters of hypoconnectivity in MDD between frontal cortex and right medial thalamus (4 voxels; x=6, y=-20, z=4; z-score=2.65). There is also hypoconnectivity between temporal cortex and left medial thalamus (4 voxels; x=-4, y=-18, z=-8; z-score=2.84) using the same cluster threshold. No other significant clusters emerged from group contrasts. Table 2 displays information on the size and location of significant clusters of group differences in thalamocortical connectivity. It is important to note here that when the voxelwise threshold is reduced to $p<0.001$, no significant group differences remain. Figure 1c shows the significant group mean clusters overlaid on one another, demonstrating spatial distinctions between the connectivity patterns in thalamic regions with cortical seed regions. The pattern of connectivity does generally appear to be coherent with the anatomical distinctions in the thalamus and the separation of different thalamic nuclei. The regions of thalamocortical connectivity also show consistency with previously reported MRI studies looking at both structural and functional thalamocortical connectivity (Behrens et al., 2003; Zhang et al., 2010, 2008).

Relationship between thalamocortical connectivity and depressive symptoms

Correlations were performed between the thalamo-temporal connectivity and symptom scores, as thalamo-temporal connectivity showed the largest group difference. Significant correlations were found between the strength of connectivity between temporal cortex and thalamus, and HAM-D total scores ($r=0.306$, $p=0.026$), whereby patients with more positive thalamo-temporal connectivity also exhibited more severe depressive symptoms (Figure 2). An exploratory analysis of the relationship between somatosensory connectivity and symptom severity did not reveal a significant correlation ($p>0.05$).

Discussion

This is the first study to date examining intrinsic thalamocortical connectivity in patients with MDD using resting state fMRI, with a well-established resting-state functional connectivity method (Zhang et al., 2008). Consistent with our hypothesis, we present evidence for disturbed thalamocortical connectivity across highly specific and localized regions in patients with MDD. Our main findings showed increased thalamo-temporal and thalamo-somatosensory connectivity. Moreover, greater thalamo-temporal connectivity was associated with more severe depressive symptoms, suggesting an association with the core psychopathology of MDD. The locus of hyperconnectivity in thalamus was generally centered on the medial part, which is known to have extensive interactions with prefrontal and limbic structures such as amygdala and hippocampus (Wolff et al., 2015). Additionally, there was modest evidence of small clusters of

decreased connectivity between frontal cortex and medial thalamus. In sum, our main results have shown thalamo-temporal and thalamo-somatosensory hyperconnectivity, possibly reflecting emotional and somatosensory dysregulation in MDD.

The predominant finding of this study was thalamo-temporal hyperconnectivity in MDD, which was also related to the severity of depression symptoms. This is in line with some other neuroimaging studies showing a positive relationship between thalamic activity and both symptoms (Milak et al., 2005) and treatment response (Yamamura et al., 2016) in MDD. However, we instead show that connectivity between thalamus and cortex is associated with severity of symptoms, and not just related to activity in thalamus, thus extending the implications of these previous studies into a network context. When looking more closely at the temporal region used in the analysis, the increased thalamo-temporal connectivity we observed in this study does seem coherent with imaging studies in MDD. The temporal cortical region-of-interest used in our analysis encompassed much of the medial temporal regions including amygdala and hippocampus, as well as lateral structures including superior, middle and inferior temporal gyri. Among the medial temporal structures, the amygdala is the centre of affective processing, with numerous neuroimaging studies consistently finding hyperactivation in MDD (Price and Drevets, 2010). Given that the thalamocortical system modulates the amygdala's response to negative emotions, abnormal functional connectivity between amygdala and thalamus may reflect a limbic hyper-responsiveness to negative emotions and a negative bias in MDD. Support for this suggestion comes from previous reports in MDD of increased hippocampal activity accompanied by increased amygdala responses to negative

emotions (Campbell and MacQueen, 2004), thus implying an impairment in the encoding of emotional memories. Additionally, functional activation patterns in lateral regions of the temporal lobe may also provide clues to the implications of the abnormal connectivity between thalamus and temporal lobe seen in our study. For example, numerous PET and fMRI studies have shown that some lateral parts of the temporal cortex play an important role in aspects of affective processing and social cognition (Blair et al., 1999; Eugène et al., 2003; Kimbrell et al., 1999; Phillips et al., 1998). A recent review concluded that the overall function of the anterior temporal lobe may be for semantic processing that is personally, socially or emotionally relevant (Wong and Gallate, 2012). Therefore, the abnormal connectivity we see between temporal areas and thalamus may be a marker for specific psychopathologies / symptoms of MDD, and more specifically, may be related to the aberrations in negative affect and self-related processing commonly seen in MDD.

The observed hyperconnectivity between medial thalamus and somatosensory cortex in MDD is in line with a previous study documenting a positive correlation between severity of depressive symptoms and intrinsic fMRI activity in the somatosensory region and thalamus in an unmedicated MDD population (Tadayonnejad et al., 2015). This abnormality may suggest a thalamocortical network based mechanism for possible somatosensory dysregulation in MDD. Importantly, mediodorsal thalamus is structurally and functionally connected with anterior midcingulate cortex and amygdala, which play a major role in the neurocircuitry of pain processing (Vogt, 2005). The observed hyperconnectivity of the medial part of the thalamus with somatosensory cortex and amygdala, and hypoconnectivity with anterior cingulate cortex may therefore relate to

impairments in pain perception, which is often seen in patients with depression (Dickens et al., 2003). Furthermore, somatosensory processing is modulated through gating of sensory inputs, which occurs via prefrontal cortical inhibition, in which medial thalamus acts as a relay in healthy controls (Bolton and Staines, 2011). Our finding of reduced connectivity of medial thalamus with frontal cortex may imply a decreased modulation from prefrontal regions on somatosensory processing, resulting in somatic symptoms and attentional impairment. However, the thalamo-somatosensory findings should be interpreted with caution, especially as our results found no significant group mean clusters of connectivity between thalamus and somatosensory seed region using the applied statistical threshold. This could be explained by the almost complete overlap in postcentral gyrus with precentral and frontal seeds. In our analysis we covaried out connectivity from other regions, thus removing much of the group mean signal.

We did see some thalamo-frontal hypoconnectivity in MDD, however this finding was weaker relative to other findings as evidenced by a small cluster size, we do believe this to be a potentially important result. In light of the possible thalamo-frontal hypoconnectivity, we suggest that a mechanism that could be driving the thalamo-temporal and thalamo-somatosensory hyperconnectivity, and thalamo-frontal hypoconnectivity may be related to the regulation of the glutamatergic / gamma-aminobutyric acid (GABA) system (Kalueff and Nutt, 2007). It is well known that mediodorsal thalamus receives reciprocal excitatory and inhibitory inputs from prefrontal cortex and medial temporal regions (Mitchell, 2015). An alteration in the glutamate / GABA system likely interferes with modulatory interactions in the thalamocortical

system, thus possibly resulting in the abnormal thalamocortical connectivity we see in our findings, and thus consequently leading to depressive psychopathologies. This is consistent with growing evidence of glutamatergic dysfunction in depression, and the therapeutic efficacy of ketamine, a NMDA receptor antagonist, in treatment resistant depression (Sanacora et al., 2012). Furthermore, inappropriate glutamate receptor activation is thought to be associated with an imbalance of anti- and pro-inflammatory mediators, in the context of neuroinflammation theories of depression (McNally et al., 2008). Increases in functional connectivity may be representative of a compensatory reallocation of resources (Cabeza et al., 2002), which has been suggested to be associated with a neuroinflammatory effect especially in patients with early stage MDD (drug-naive MDD with shorter duration of illness) (Guo et al., 2015). However, since most of our patients were not drug naïve or at the early stage of MDD, the exact neurophysiological basis of hyperconnectivity remains to be clarified.

In light of studies looking at thalamocortical connectivity in other disorders, it is important to ask the question of how specific our findings may be to MDD. Despite some differences in methodology and analysis, other studies have found some similar findings in other psychiatric disorders. Thalamo-frontal hypoconnectivity combined with thalamo-sensorimotor hyperconnectivity has been consistently observed in schizophrenia, and similar abnormalities were found, but to a lesser degree, in bipolar patients (Anticevic et al., 2014). Hyperconnectivity of the thalamo-temporal circuit has also been documented in one study in schizophrenia (Klingner et al., 2014). In two separate studies, one using the ketamine model of psychosis, and another in autism, hyperconnectivity of both

thalamo-temporal and thalamo-somatosensory circuits were found (Höflich et al., 2015b; Nair et al., 2013). In sum, it is evident from our results that there may be some common areas of thalamocortical disturbances across different disorders, and regional differences may not distinguish between diagnoses, but instead, a graded effect may be present when looking trans-diagnostically.

One main limitation of our study was that most patients were not medication naïve, and thus we cannot make strong inferences about how thalamocortical connectivity might be affected by chronic antidepressant medication use. However, as all had been off medication for at least 3 weeks prior to scanning, we can say that acute medication effects were not driving these effects. Future studies are needed on first episode drug naïve MDD patients to exclude possible medication effects. Furthermore, the use of two different scanners may have introduced additional confounding variance on the results. We did control for these potential confounding effects by including scanner as a variable of no interest in our model, however we cannot completely rule out possible influences this may have had on the results. Another limitation may come from the thalamocortical atlas we used in our analysis, which was a standard atlas was used (Behrens et al., 2003), however there was some overlap between cortical seed regions, which likely resulted in the lack of significant group mean clusters in thalamo-somatosensory connectivity. The lack of group difference at a more stringent voxelwise threshold of $p<0.001$ as suggested by Eklund et al. (Eklund et al., 2016) make these findings preliminary, to be replicated by future studies using larger sample sizes. Future studies may also benefit from defining smaller cortical regions to identify more localized abnormalities in thalamocortical

connectivity in MDD and also using analysis methods that tap into causal inference such as Grainger causality (Liao et al., 2010).

To conclude, here we demonstrate abnormal thalamocortical connectivity in MDD for the first time, specifically showing abnormal thalamo-temporal and thalamo-somatosensory connectivity. Furthermore, thalamo-temporal connectivity was associated with severity of depression. These findings are a first step in further understanding the underlying abnormalities in the thalamocortical circuit that may be responsible for the psychopathology of MDD. These results warrant further investigation of aberrations in large-scale thalamic networks in the brain to help in understanding the central role of thalamocortical systems in cognitive, sensory and emotional information processing and how they are related to symptoms in MDD.

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Figure 1: Statistical maps of thalamocortical connectivity in major depressive disorder (MDD) patients and healthy controls (HC): A) Six cortical ROIs used as seed regions in seed-to-voxel analysis of thalamocortical connectivity B) First two rows showing group mean clusters from HCs and patients with MDD. Third row shows significant clusters from group contrasts. C) Overlaid group mean clusters to demonstrate differences in spatial distribution of thalamocortical connectivity regions in the thalamus. *Note: All statistical maps corrected at a voxel level of $p<0.005$, and for multiple comparisons at the cluster level of (FWE) $p<0.001$*

Figure 2: Scatterplot showing significant correlation between thalamo-temporal connectivity and depression severity on the Hamilton Depression Rating Scale (HAM-D)

Table 1: Demographic and clinical variables

	MDD Patients (N=54)	**Healthy Controls (N=40)**
Age (years)	36.9 ±10.8	31.3 ±9.7
Sex	19 male, 35 female	18 male, 22 female
HAM-D TOTAL	21.7 ±3.8	-
Age of onset	24.9 ±10.7	-
Number of episodes	2.8 ±4.0	-
Duration of illness (months)	52.4 ±65.1	-

Note: MDD = Major depressive disorder; HAM-D = Hamilton Rating Scale for Depression

Table 2: Cluster table of significant clusters from group contrasts

Region	R=right L=left	Cluster size	MNI coordinate (local maxima)			z-score
			x	y	z	
HC > MDD						
Frontal	-	-	-	-	-	-
Somatosensory	-	-	-	-	-	-
Motor	-	-	-	-	-	-
Temporal	-	-	-	-	-	-
Parietal	-	-	-	-	-	-
Occipital	-	-	-	-	-	-
MDD > HC						
Frontal	-	-	-	-	-	-
Somatosensory	R	10	6	-2	16	3.05
Motor	-	-	-	-	-	-
Temporal	R	29	18	-32	-8	3.63
Temporal	R	25	6	-16	8	2.96
Parietal	-	-	-	-	-	-
Occipital	-	-	-	-	-	-

Note: Note: All corrected at a voxel level of p<0.005, and small volume correction (FWE) p<0.001, considering only voxels within the Harvard-Oxford thalamus atlas.

Highlights

- We demonstrate abnormal thalamocortical connectivity in major depressive disorder.
- Abnormalities were in thalamo-temporal, and thalamo-somatosensory connectivity.
- Thalamocortical connectivity may serve as a marker of depressive psychopathology.

Fig. 1

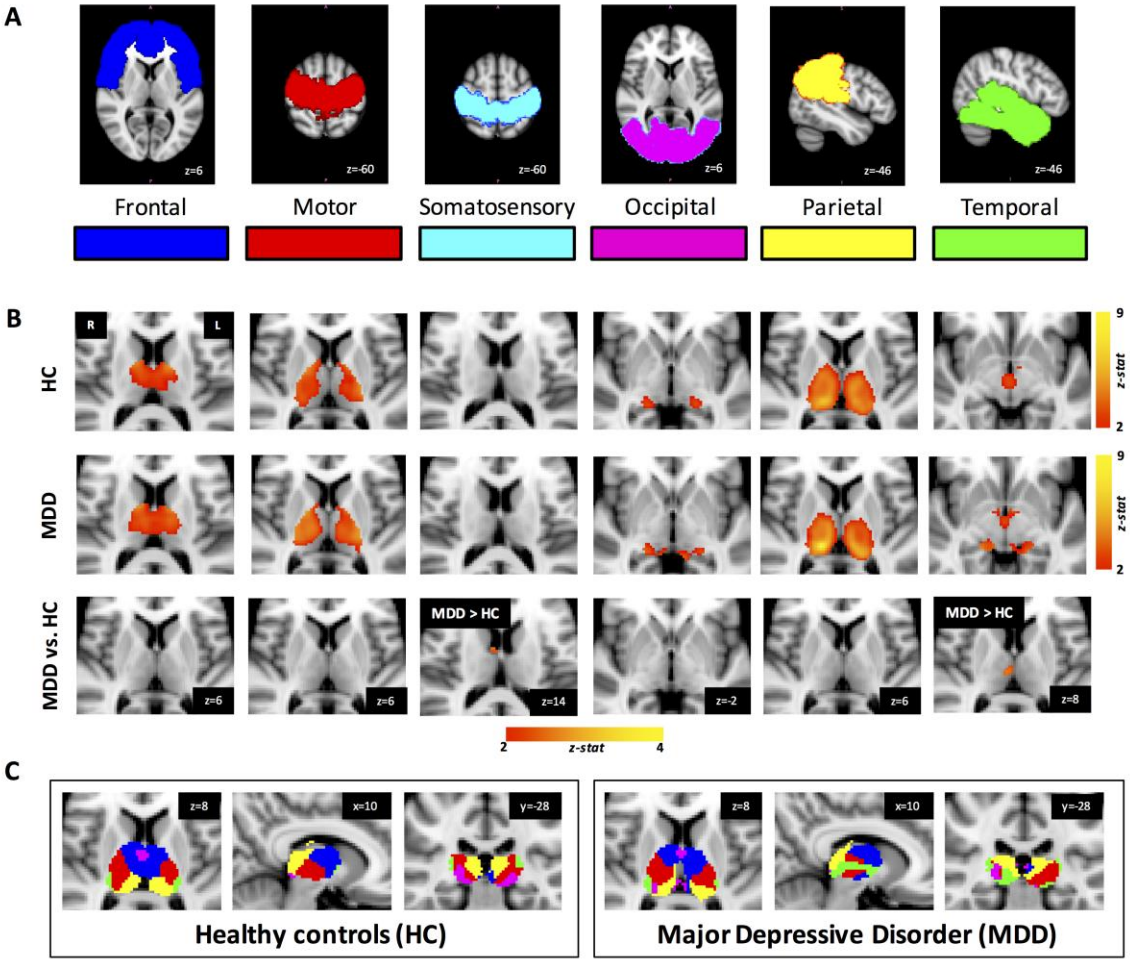
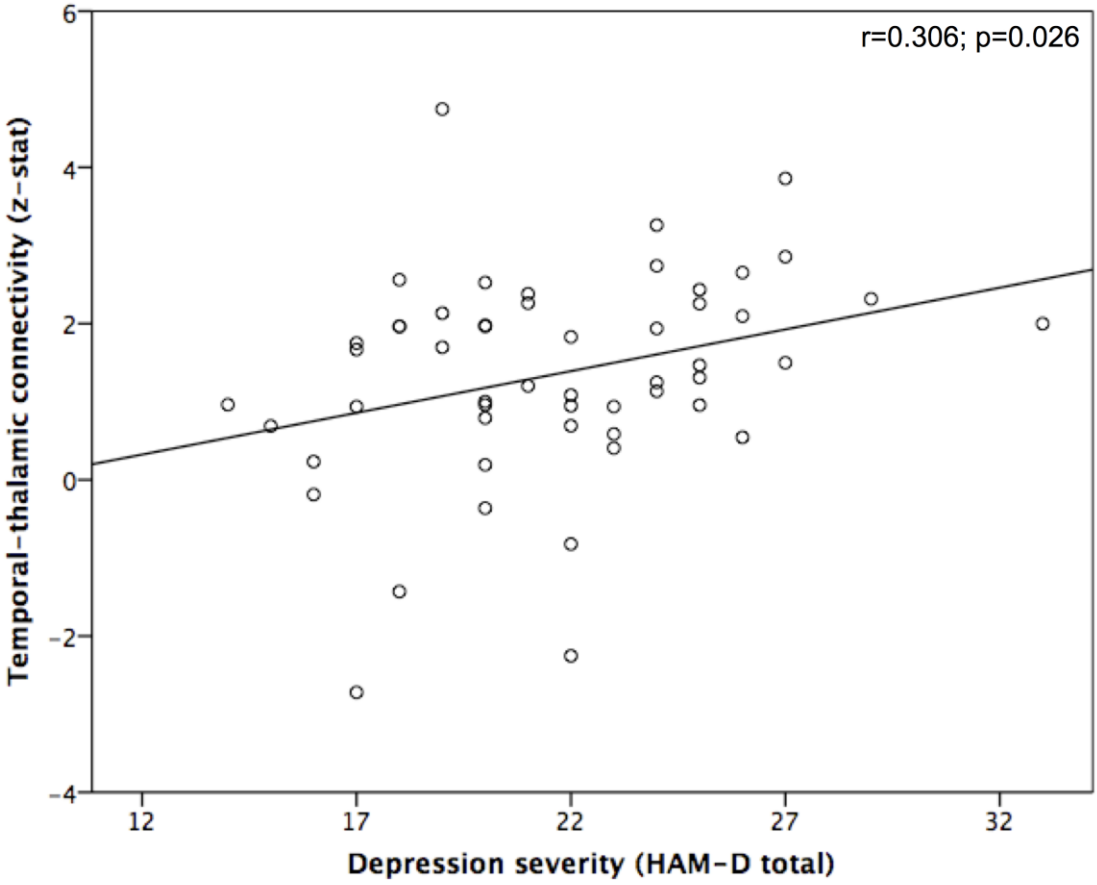


Fig. 2


r=0.306; p=0.026
Temporal-thalamic connectivity (z-stat)
6
4
2
0
-2
-4
12
17
22
27
32
Depression severity (HAM-D total)