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Imbalance of default mode and regulatory networks during externally focused processing in depression

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Attentional control difficulties likely underlie rumination, a core cognitive vulnerability in major depressive disorder (MDD). Abnormalities in the default mode, executive and salience networks are implicated in both rumination and attentional control difficulties in MDD. In the current study, individuals with MDD ($n = 16$) and healthy controls ($n = 16$) completed tasks designed to elicit self-focused (ruminative) and externally-focused thinking during fMRI scanning. The MDD group showed greater default mode network connectivity and less executive and salience network connectivity during the external-focus condition. Contrary to our predictions, there were no differences in connectivity between the groups during the self-focus condition. Thus, it appears that when directed to engage in self-referential thinking, both depressed and non-depressed individuals similarly recruit networks supporting this process. In contrast, when instructed to engage in non-self-focused thought, non-depressed individuals show a pattern of network connectivity indicative of minimized self-referential processing, whereas depressed individuals fail to reallocate neural resources in a manner consistent with effective down regulation of self-focused thought. This is consistent with difficulties in regulating self-focused thinking in order to engage in more goal-directed behavior that is seen in individuals with MDD.

Keywords: depression; rumination; default mode network; executive network; salience network

A core cognitive feature of major depressive disorder (MDD) is the tendency to ruminate—the persistent and passive focus on one's negative mood and the adverse consequences of being in a negative mood (Nolen-Hoeksema, 1991). Rumination is related to a host of unfavorable outcomes including more severe and prolonged depressive symptoms (Nolen-Hoeksema and Morrow, 1991; Nolen-Hoeksema *et al.*, 1993; Just and Alloy, 1997), a poorer response to treatment (Jones *et al.*, 2008) and an increased risk for relapse after remission of a depressive episode (Michalak *et al.*, 2011). Additionally, there is evidence showing that rumination serves as a risk factor for the development of MDD (Just and Alloy, 1997; Nolen-Hoeksema, 2000). Attentional control difficulties, another central trait in MDD (e.g. Gohier *et al.*, 2009; De Lissnyder *et al.*, 2012), may underlay ruminative thinking by undermining the ability to disengage from negative self-relevant material (Koster *et al.*, 2011). A recent study demonstrated that rumination partially mediated the relationship between attentional control difficulties and future depressive symptoms among MDD patients (Demeyer *et al.*, 2012).

The neural underpinnings of both rumination and attentional dyscontrol in MDD are thought to implicate three neural networks (see Hamilton *et al.*, 2013): the default mode network (Raichle *et al.*, 2001), the executive network (Seeley *et al.*, 2007) and the salience network (Seeley *et al.*, 2007). The default mode network is composed of a number of midline regions including the medial prefrontal cortex, the anterior cingulate cortex, the precuneus, the posterior cingulate cortex, the retrosplenial cortex, lateralized areas of the parietal cortex (Raichle and Snyder, 2007), as well as the medial temporal cortex and hippocampal formation (Buckner *et al.*, 2008). The default mode network is thought to subserve a number of internally focused attentional processes (Vanhaudenhuyse *et al.*, 2010) including self-referential information processing in both those with MDD and healthy controls (Nejad *et al.*, 2013). Individuals with MDD exhibit stronger functional connections between the subgenual anterior cingulate cortex (subACC) and other areas within the default mode network (Greicius *et al.*, 2007; Berman *et al.*, 2011). Moreover, greater resting state functional connectivity between the subACC and posterior cingulate cortex has been tied to greater trait rumination in individuals with MDD and healthy controls (Berman *et al.*, 2011). However, when directly comparing depressed and non-depressed individuals during a task that engages self-focus, depressed individuals showed greater activation in a number of default mode network structures compared with non-depressed individuals (Cooney *et al.*, 2010).

On the other hand, when a task is cognitively demanding or requires focus on the external environment, the default mode network normally deactivates (Vanhaudenhuyse *et al.*, 2010). An inability to deactivate the default mode network during such tasks has been positively associated with greater attentional control difficulties among healthy volunteers (Weissman *et al.*, 2006; Mason *et al.*, 2007; Christoff *et al.*, 2009). One study demonstrated that compared with healthy controls, depressed individuals were unable to deactivate the default mode network when instructed to disengage from negative stimuli (Sheline *et al.*, 2009). MDD participants have also shown difficulties deactivating an inferior portion of the anterior medial prefrontal cortex, a central hub of the default mode network, during a task designed to evoke external focus. This impaired deactivation was also associated with self-reported rumination in the MDD group (Johnson *et al.*, 2009).

In addition to the default mode network, altered coordinated activity within the executive network, which encompasses areas in the lateral prefrontal cortex and the posterior parietal cortex (Seeley *et al.*, 2007; Dosenbach *et al.*, 2008), has been implicated in MDD (Zhou *et al.*, 2010; Wei *et al.*, 2013). Activation in this network is anticorrelated with the default mode network (Fox *et al.*, 2005) and is essential for paying attention to external environmental demands (Vanhaudenhuyse *et al.*, 2010) as well as engaging in goal-directed or cognitively demanding activities (Dosenbach *et al.*, 2008). Deficient activations within executive network regions have been linked with greater trait rumination amongst healthy individuals (Kuhn *et al.*, 2012), as well as poor attentional control in MDD

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(Fales *et al.*, 2008; Wang *et al.*, 2008) and dysphoric participants (Beevers *et al.*, 2010). Recently, it was shown that MDD individuals recruited executive network regions to a lesser extent when instructed to inhibit both ruminative and emotionally neutral thoughts (Carew *et al.*, 2013). However, some studies have found elevated activity in areas within the executive network when instructed to engage in self-focused thinking (e.g. Lemogne *et al.*, 2009; Cooney *et al.*, 2010), which may potentially be a compensatory mechanism for counteracting cognitive vulnerabilities in MDD (e.g. Harvey *et al.*, 2005).

Another network that is associated with aberrant coordinated activity in individuals with MDD compared with healthy controls is the salience network (Wei *et al.*, 2013; Manoliu *et al.*, 2014), which is composed of the anterior insula/frontal operculum, dorsal anterior cingulate cortex/paracingulate cortex and the superior temporal pole (Seeley *et al.*, 2007; Dosenbach *et al.*, 2008). Activation in the salience network is thought to be associated with monitoring and drawing attention to stimuli that are subjectively relevant (Seeley *et al.*, 2007). Additionally, the salience network plays a role in switching mental sets, with damage to the anterior insula being associated with poor switching ability (Hodgson *et al.*, 2007). In regards to switching behavior, it has been shown that the right frontal insular cortex (RFIC) and dorsal anterior cingulate cortex (dACC) play a role in neural network switching, initiating deactivation of the default mode and activation in the executive network (Sridharan *et al.*, 2008). Evidence suggests that individuals with MDD have reduced connectivity between the RFIC with other regions in the salience network (Manoliu *et al.*, 2014). Specifically, compared with healthy individuals, MDD participants show deficient recruitment of salience network structures when directed to inhibit ruminative and emotionally neutral thoughts (Carew *et al.*, 2013). Furthermore, individuals with MDD show an abnormal relationship between activation in the RFIC and the onset of increased activation in the executive network versus the default mode network. Individuals with MDD show a rise in RFIC activation at the onset of increased executive network activation, whereas healthy individuals show greater RFIC activation during a rise in default mode network activation (Hamilton *et al.*, 2011). Given this evidence, the salience network likely plays a role in attentional dyscontrol and rumination in MDD.

Thus, existing research has shown a potential link between activity in these three networks with rumination and the attentional difficulties that may underlie rumination in MDD. However, these studies contain limitations. While resting state functional connectivity studies have paved the way for understanding of aberrant intrinsic connectivity in these core networks in MDD, the lack of constraints placed on behavior makes it difficult to clarify what role these networks are playing in the cognitive difficulties in MDD. On the other hand, while task-based designs have allowed examination of aberrant brain activity when individuals with MDD are instructed to engage in self-referential processing (e.g. Cooney *et al.*, 2010), researchers have typically not focused on how brain regions work together to contribute to cognitive problems in MDD. It has been proposed that characterizing functional connections amongst neural regions may be a useful approach for understanding the cognitive, behavioral and emotional difficulties in depression (Hamilton *et al.*, 2013).

The current study aimed to examine functional connections within the default mode, executive and salience networks among individuals with and without MDD during a task in which participants were explicitly instructed to think about topics designed to elicit self-focused and externally-focused thinking. Previous studies have found that compared with the external-focus condition, the self-focus condition used in this paradigm effectively generates rumination in depressed individuals (Lyubomirsky and Nolen-Hoeksema, 1993; Nolen-Hoeksema and Morrow, 1993) and differentiates those with and without MDD on levels of neural activity in some default mode, salience and executive network structures (Cooney *et al.*, 2010). We examined group connectivity differences by separately correlating central nodes of each network shown to be aberrant in MDD with other regions contained within that specific network. While there have been some conflicting findings, based on the weight of the extant evidence, we expected that during the self-focused thought induction, the MDD group would show greater connectivity within the default mode network and decreased connectivity within the executive network compared to those without MDD. Within the salience network, we specifically predicted decreased connectivity between the RFIC and dACC in participants with MDD compared with healthy controls, given the role these structures play in attentional control abilities (Eckert *et al.*, 2009; Shenhav *et al.*, 2013).

METHODS

Participants

Eighteen individuals diagnosed with MDD and 18 healthy controls (HC) were administered the Structured Clinical Interview for the DSM-IV (First *et al.*, 1995). MDD participants had to be free of any history of bipolar disorder, schizophrenia or psychosis and current alcohol or substance abuse. Anxiety disorder comorbidity and the use of psychotropic medication were permitted in the MDD group. The HC group was free of any current Axis I psychopathology or lifetime history of a mood disorder. Two participants from the MDD group and two participants from the HC group were excluded from further analysis due to excessive head motion in the scanner, resulting in a final sample of 16 in the HC group (8 males, mean age = 31.13; s.d. = 10.70) and 16 in the MDD group (5 males, mean age = 33.19, s.d. = 11.49; mean duration of current MDD episode = 21.63 months, s.d. = 49.49).

Additionally, ten MDD participants reported that they were experiencing their first episode or have had one prior episode, three individuals reported experiencing three to six prior episodes, and another three individuals reported experiencing 10 or more prior major depressive episodes. Five MDD participants were currently taking psychotropic medication ($n = 2$ duloxetine hydrochloride/Cymbalta, $n = 1$ bupropion hydrochloride/Wellbutrin XL, $n = 1$ bupropion hydrochloride and fluoxetine hydrochloride/Prozac, $n = 1$ risperidone/Risperdal). Additionally, eleven MDD participants were diagnosed with comorbid anxiety disorders ($n = 2$ social phobia, $n = 2$ social and specific phobias, $n = 2$ generalized anxiety disorder, $n = 1$ generalized anxiety disorder and social phobia, $n = 1$ generalized anxiety disorder and panic disorder, $n = 1$ posttraumatic stress disorder, $n = 1$ specific phobia, $n = 1$ anxiety disorder not otherwise specified). At the scanning session, participants completed the Beck Depression Inventory-II (BDI-II; Beck *et al.*, 1979) and the rumination subscale of the Response Styles Questionnaire (Nolen-Hoeksema, 1991). The study was approved by the University of Wisconsin-Milwaukee Institutional Review Board, and participants provided written informed consent according to the Declaration of Helsinki. Participants were paid for completion of the interview and scanning session.

Self-focused and externally focused thought induction tasks

While in the scanner, participants completed an 8-min self-focus thought induction task and an 8-min external-focus thought induction task (adapted from Lyubomirsky and Nolen-Hoeksema, 1993). The self-focus thought induction statements were designed to generate more abstract, internally focused, open-ended conceptual mental representations. On the other hand, the external-focus statements were meant to evoke more concrete, outwardly-focused, and stereotypical, visually dependent mental representations of external objects or scenes. In each of the thought induction tasks, participants were visually presented with up to 45 statements. The self-focused statements were neither inherently negative nor positive, but open to individual interpretation. An example of a statement from the self-focused thought induction was 'Think about why you react the way you do' and 'Think about sitting down and analyzing your personality.' The externally focused thought induction included more visually dependent statements such as 'Think about and imagine a boat slowly crossing the Atlantic.' For a full list of the thought induction statements, please see the Supplementary Materials. At the beginning of each thought induction task, participants were told to read each statement slowly and silently to themselves. Participants were asked to use their imagination and concentration to focus on each of the ideas being presented. Participants were instructed to proceed with each statement at their own pace. In between each statement, subjects were presented with a one second fixation cross. The order of the two thought induction tasks were counterbalanced within each of the groups.

Imaging parameters

Whole brain imaging was conducted using a 3-T short bore Signa Excite system. Functional images were collected using a T2* weighted gradient-echo, echoplanar pulse sequence (TR = 2 s; TE = 25 ms; FOV = 24 cm, flip angle = 84°; voxel size 3.75 × 3.75 × 4 mm, sagittal orientation). The self-focused and externally-focused thought induction tasks consisted of 232 whole brain scans. High resolution spoiled gradient recalled (SPGR) images (1 mm sagittal slices; TR = 9.6 s; TE = 3.9 ms; field of view = 24 cm; flip angle = 12°; voxel size = 0.9375 × 0.9375 × 1) were collected and served as an anatomical map for the functional images.

Imaging preprocessing

Reconstruction and image processing was conducted in AFNI (Cox, 1996). The first seven images for each scan were excluded to allow for magnetic saturation. The remaining images were despiked, volume registered to correct for motion, spatially normalized to Talairach space, and spatially smoothed by convolution with an isotropic Gaussian kernel (full-width at half-maximum = 6 mm) to decrease high spatial frequency noise. For subsequent analyses, the following nuisance regressors were included: baseline, signal drift, estimates from a rigid-body motion correction that was done in three translational and three rotational directions, and censoring of high motion images (cutoff 0.3 mm). Additionally, a band pass filter was applied to attenuate frequencies above 0.1 Hz and below 0.01 Hz. Subjects who exhibited excessive head motion (greater than an average value of 2.5 mm translation and/or 2.5° rotation) were excluded from further analysis.

Seed-based functional connectivity analyses

The time series was extracted from four seeds, including a seed placed in the subgenual anterior cingulate cortex (subACC; Cullen *et al.*, 2009; 0, −12, −7 Right Anterior Inferior (RAI) orientation; 6 mm radius), right dorsolateral prefrontal cortex (DLPFC; Alexopoulos *et al.*, 2012; −36, −27, 29 RAI orientation; 8 mm radius), left dorsolateral prefrontal cortex (Alexopolous *et al.*, 2012; 36, −27, 29 RAI orientation; 8 mm radius) and the right frontal insular cortex (RFIC; Seeley *et al.*, 2007; −38, −13 −3 RAI orientation; 8 mm radius). The subACC is part of the default mode network (Raichle and Snyder, 2007), and numerous studies have reported aberrant functioning in this region in individuals with MDD (see Drevets *et al.*, 2008 for a review). The bilateral DLPFC is a central hub of the executive network (Seeley *et al.*, 2007) and has been consistently reported to be dysfunctional in MDD (Hamilton *et al.*, 2012). Lastly, the RFIC is a fundamental region in the salience network that has shown to be abnormal in depression and related to attentional control and rumination (see Slitz and Hayley, 2012 for a review). Pearson's r maps were generated by correlating each seed with other regions belonging to each of their respective neural networks. The time series of the subACC seed was correlated with every other voxel within the default mode network and the RFIC seed was correlated with every other voxel in the salience network. Similarly, the right DLPFC time series was correlated with regions within the right executive network and the left DLPFC time series was correlated with regions in the left executive network. The analyses were restricted to each of the respective network regions by applying previous established spatial templates representing each of the three networks (Franco *et al.*, 2009; Laird *et al.*, 2011). The r statistics were then normalized using a Fischer's z transformation and then resampled to 1-mm^3 voxels. This normalized data were used to calculate all group-level statistics.

To determine whether network connectivity differed as a function of group and task, a Group (MDD, HC) × Thought Induction (self-focused, externally-focused) ANOVA was calculated separately for each of the three networks. Participant was included as a random factor in each model. To correct for multiple comparisons, cluster thresholding using Monte Carlo simulations was applied to each of the three separate neural network templates. Using a voxel-based $P < 0.01$ and nearest-neighbor selection criteria, accounting for spatial correlation, clusters greater than 570 mm^3 for the default mode network and the salience network, and 567 mm^3 for the right and left executive network achieved a corrected $P < 0.05$. Because our hypotheses were centered on Group × Thought Induction interaction influences on functional connectivity within the three networks, we focused on these findings in the results section below. For a listing of Group and Thought Induction main effects, see Table 1. Additionally, given that there are gender differences in the tendency to ruminate (Johnson and Whisman, 2013) and that the depressed sample did not have the same gender proportions as the control sample, we also conducted secondary analyses examining whether our Group × Thought Induction interaction results were influenced by gender. We also tested whether medication effects influenced our ANOVA findings, as we had five individuals with MDD on psychotropic medication, including an individual taking an antipsychotic medication (not standard for the treatment of depression). These results are in the Supplementary Material section.

Finally, we also correlated Significant Group × Thought Induction interaction findings with the Beck Depression Inventory-II (BDI-II; Beck *et al.*, 1979) and the rumination subscale of the Response Styles Questionnaire (RSQ-Rumination; Nolen-Hoeksema, 1991). These results are also presented in the Supplementary Figures S1–S3.

RESULTS

Participant characteristics

The two groups did not differ significantly with regard to age ($t = .53$, $df = 30$, $P = 0.60$), sex distribution ($\chi^2 = 1.17$, $df = 1$, 32; $P = 0.28$) and proportion that had obtained a college degree ($\chi^2 = 2.00$, $df = 1$, 31; $P = 0.16$). The groups did significantly differ in depression severity ($t(30) = 13.41$, $P < 0.001$) and trait rumination ($t(30) = 7.32$, $P < 0.001$), with the MDD group (Mean BDI-II Score = 23.13, s.d. = 6.33; Mean RSQ-Rumination Score = 56.19, s.d. = 11.42) scoring greater on the BDI-II and RSQ-Rumination than the HC group (Mean BDI-II Score = 1.19, s.d. = 1.64; Mean RSQ-Rumination Score = 31.38, s.d. = 7.33). There were no significant differences in the percentage of images censored between the MDD group ($M = 3.43\%$, s.d. = (4.99)) and the HC group ($M = 2.10\%$,

Table 1 Significant group (MDD, HC) and thought induction condition (Self-Focus, External-Focus) main effects

Region	Side	BA	x	y	z	mm^3
Group main effects						
MDD < HC L DLPFC-L executive connectivity						
Inferior frontal gyrus	L	9/44	52	−7.5	26.5	1511
MDD < HC RFIC-salience connectivity						
Insula/precentral gyrus	R	13/44	−45	−7.5	1.5	730
MDD > HC RFIC-salience connectivity						
Insula	L	13	39	−3.5	−5.5	1103
Thought induction main effects						
Self > External R DLPFC-R executive connectivity						
Supramarginal gyrus/inferior parietal lobule	R	40	−55	48.5	19.5	3215
Insula/inferior frontal gyrus	R	13	−38	21.5	8.5	787
Self > External L DLPFC-L executive connectivity						
Inferior Parietal Lobule	L	40	42	41.5	40.5	990
Self > External RFIC-salience connectivity						
Insula	L	13	35	−14.5	8.5	861

Note. Contrasts that are not listed showed no main effects for group or thought induction.
MDD, major depressive disorder; HC, healthy control; DLPFC, dorsolateral prefrontal cortex; RFIC, right frontal insular cortex; R, right; L, left.

s.d. = (2.57)), F (1, 30) = 0.903, $P = 0.35$, $\eta^2 P = 0.029$). In addition, there was no significant Group × Thought Induction interaction or Thought Induction main effect in the percentage of images censored (all $P > 0.50$).

SubACC-default mode network connectivity

When comparing differences in subACC connectivity with other structures within the default mode network, there was a significant Group × Thought Induction interaction, with the MDD group showing greater subACC connectivity with the left medial temporal gyrus (56, 3.5, −8.5; BA 21; 1141 mm^3), left cingulate gyrus (6, 40.5, 33.5; BA 31; 946 mm^3) and the right posterior cingulate/retrosplenial cortex (−14, 45.5, 15.5; BA 29/31; 788 mm^3) during the externally-focused thought induction compared with the HC group (See Figure 1). There were no significant differences between the MDD group and HC group in connectivity between the subgenual ACC and other regions within the default mode network during the self-focused thought induction.

Bilateral DLPFC-executive network connectivity

Connectivity between the right DLPFC and other regions in the right executive network was also characterized by a significant Group × Thought Induction interaction. As with the default mode network findings, the group differences were specific to the externally-focused thought condition; however, the pattern of connectivity was in the opposite direction. During the externally-focused thought induction, the right DLPFC showed decreased connectivity with other right executive network regions among MDD participants compared with controls (See Figure 2). Specifically, the MDD group showed decreased connectivity between the right DLPFC and the right middle frontal gyrus (−35.0, −3.5, 47.5; BA6/8; 3885 mm^3), an area within the right frontopolar prefrontal cortex (−42, −57.5, 1.5; BA10; 1230 mm^3) and the right posterior parietal cortex (−41, 52.5, 26.5; BA 39/40; 696 mm^3) compared with the HC group. The MDD participants did not exhibit any increased right DLPFC-executive network connectivity. There were also no significant differences between the MDD and controls in functional connectivity between the right DLPFC and other regions within the right executive network during the self-focused condition. Additionally, there was no significant Group × Thought Induction interaction between the left DLPFC and other regions within the left executive network.

RFIC-salience network connectivity

Connectivity between the RFIC and other salience network structures was also characterized by a significant Group × Thought Induction interaction. As with the right executive network, during the external-focus condition, the MDD group showed less connectivity between the RFIC and the right dACC (−10, −35.5, 26.5; BA32; 1189 mm^3) compared with the HC group (See Figure 3). The MDD and HC group did not show significant differences in functional connectivity between the RFIC and other salience network structures during the self-focused thought induction task.

DISCUSSION

The aim of the study was twofold: first to identify MDD-related differences in functional connectivity in central nodes of the default mode, executive and salience networks, and second to examine this neural system connectivity in the context of eliciting self-referential thinking and non-self-referential, outwardly focused thinking. Greater activity in the default mode network has been associated with more self-focus, whereas greater activity in the executive and salience network has been linked to more attentional control over these thoughts. Given the different functions of these networks and that excessive self-focus is a cognitive hallmark of MDD, we expected that during the self-focus condition, individuals with MDD would show greater default mode connectivity as well as less executive and salience recruitment to help regulate these thoughts.

However, in contrast to previous work, we found no group differences in connectivity within any of the three networks during the self-focus condition. Our findings may differ from previous studies because research thus far has focused on either trait rumination-related resting state functional connectivity or task-based studies of rumination-related activation in single brain structures. The current study was the first to examine functional connectivity within these networks when participants were instructed to engage in self-focused and externally-focused thinking. This difference in approach likely contributed to dissimilar findings compared with previous studies. With regard to resting state and self-referential task studies, it is thought that resting state and explicitly self-focused tasks may be eliciting different aspects of self-focus (Lemogne *et al.*, 2012). Specifically, it is thought that resting state studies may be tapping into a more spontaneous or automatic self-focus whereas task-based studies using instructed self-referential thought may be tapping into more strategic or controlled self-focus (Lemogne *et al.*, 2012). Both aspects are thought to be important to MDD, but likely have different underlying neural mechanisms (Shestyuk and Deldin, 2010). Shestyuk and Deldin's (2010) results suggest that automatic negative self-focus is associated with a trait-like cognitive vulnerability in MDD that is even present amongst those who have remitted from MDD whereas strategic negative self-focus is more state-related and mood-dependent. Given these results, it is possible that the addition of more explicitly negative mood-congruent self-focused statements may have better captured differences in strategic self-focus in MDD versus healthy participants. Additionally, using other tools with greater temporal resolution such as electroencephalography, which was employed by Shestyuk and Deldin (2010), may better capture differences in automatic versus strategic and elaborative self-focus. Further research is needed to clarify what conditions may best elucidate the neural mechanisms underlying problematic strategic versus automatic self-focus in individuals with MDD.

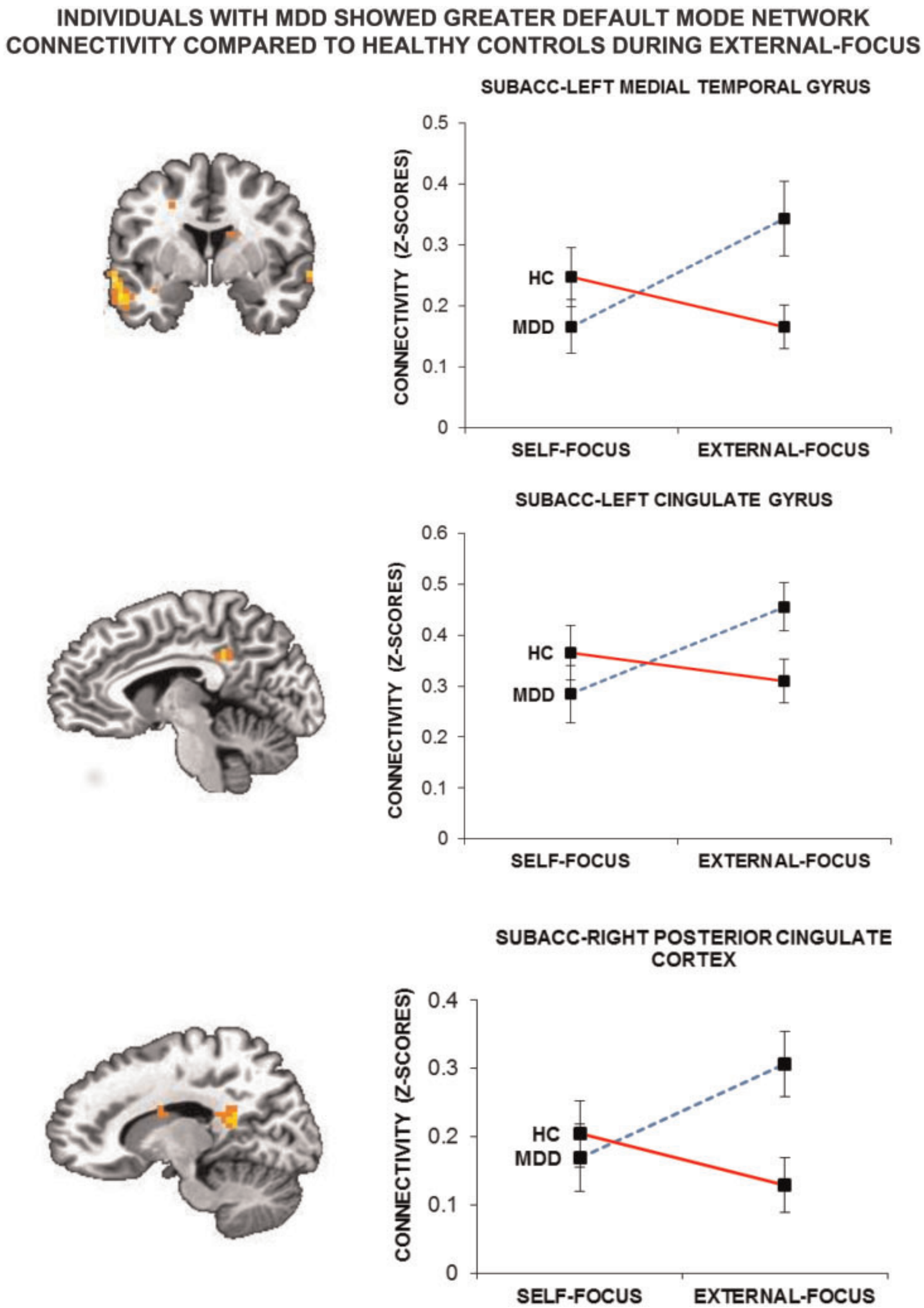

Fig. 1 Significant Group × Thought Induction interactions in the default mode network. Specifically, individuals with MDD compared with HCs showed greater connectivity between the subACC and left medial temporal gyrus (coordinates: 56, 3.5, −8.5), left cingulate gyrus (coordinates: 6, 40.5, 33.5) and right posterior cingulate cortex (coordinates: −14, 45.5, 15.5) during the external-focus condition. There were no significant group differences in the self-focus condition. MDD, major depressive disorder group; HC, healthy control group; SUBACC, subgenual anterior cingulate cortex.

On the other hand, we found robust and consistent differences within all three networks for the external-focus condition. Specifically, the MDD group showed greater default mode and less right executive and salience network connectivity compared with the HC group. This pattern of results suggest that when trying to engage in externally focused thought, individuals with MDD fail to adequately recruit the salience network, which is needed to switch on the executive network in the service of down-regulating self-focused-related default mode network activity. Altogether, previous studies suggest that a pattern of hyperactive connectivity in the default mode network and hypoactive connectivity in the executive and salience networks are indicative of difficulties in disengaging from habitual ruminative thought (e.g. Berman *et al.*, 2011; Carew *et al.*, 2013). Given that during the external thought condition an explicit trigger to engage in self-referential thought was not provided, it may be that this pattern of findings is more representative of the automatic aspects of self-focus that are characteristic of MDD.

One hypothesis is that for MDD participants, the external-focus task did not sufficiently engage working memory resources to effectively compete with the intrusion of ruminative or self-referential thoughts. This is in line with a number of studies suggesting that in order for attentional deployment from negative information to be successful, it must occupy enough working memory capacity so that insufficient resources are available for processing of negative information (e.g. Van Dillen and Koole, 2007; Van Dillen *et al.*, 2009). Additionally, a negative mood has been shown to narrow one's attentional scope

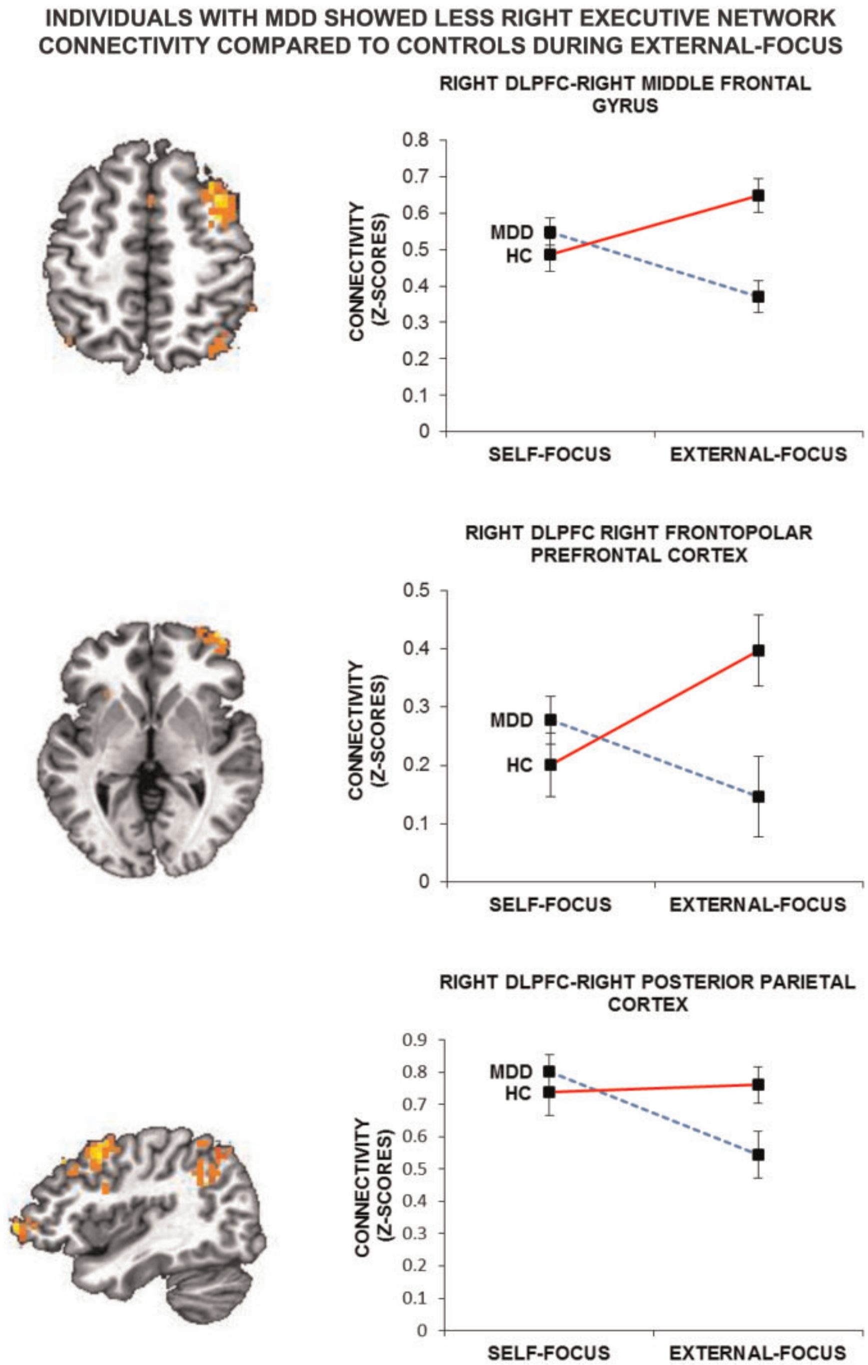

Fig. 2 Significant Group × Thought Induction interactions in the right executive network. Specifically, individuals with MDD compared with HCs showed less connectivity between the right DLPFC and the right middle frontal gyrus (coordinates: −35, −3.5, 47.5), right frontopolar prefrontal cortex (coordinates: −42, −57.5, 1.5) and the right posterior parietal cortex (−41, 52.5, 26.5) during the external-focus condition. There were no significant group differences during the self-focus condition. MDD, major depressive disorder group; HC, healthy control group; DLPFC, dorsolateral prefrontal cortex.

toward mood-congruent thoughts, which may preclude entry of information into working memory that is irrelevant to negative self-focus (see Whitmer and Gotlib, 2013). Because MDD participants are prone to ruminative self-referential thinking, it is possible that during the external-focus task, the MDD participants were more likely to ruminate (despite being task-irrelevant), thus further narrowing attentional scope and interfering with processing of incompatible externally focused information. In summary, our pattern of findings suggest that during the external-focus condition, individuals with MDD were unable to recruit enough regulatory systems (the salience and executive networks) to help attenuate default mode network activity that is associated with the entry of intrusive self-focused thoughts.

Our study has some notable strengths, particularly that our task design allowed us to examine MDD-related functional connectivity differences within important nodes of the default mode, executive and salience networks during self-referential and externally-focused conditions. That said, there are a number of limitations to consider. We had a small heterogeneous MDD sample with five participants that were on psychotropic medication. While the sample contained variability in terms of number of prior episodes, symptom severity, anxiety comorbidity and psychotropic medication usage, our findings appear to be in line with studies that contained similar heterogeneity within their MDD sample (Greicius *et al.*, 2007; Berman *et al.*, 2011) as well as others that included a more homogenous MDD sample

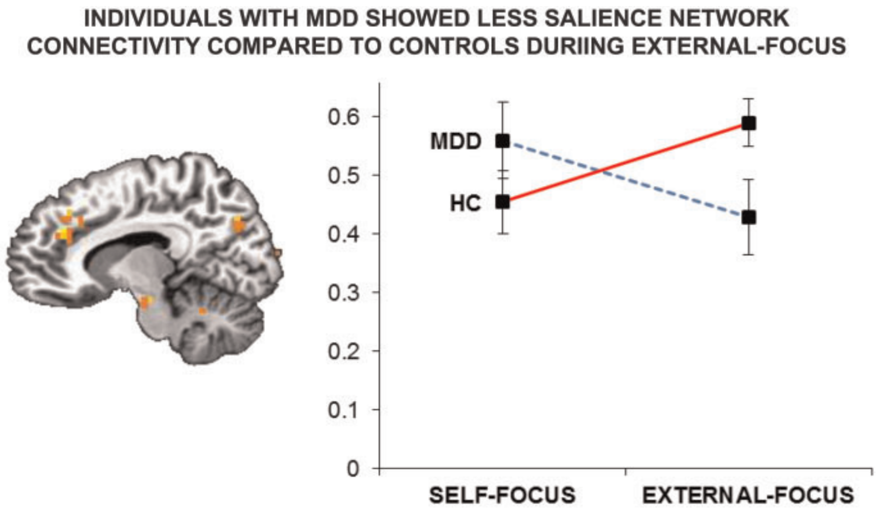

Fig. 3 Significant Group × Thought Induction Interaction in the salience network. Specifically, individuals with MDD compared with HCs showed less connectivity between the RFIC and the right dACC (coordinates: −10, −35.5, 26.5) during the external-focus condition. There were no significant group differences in the self-focus condition. MDD, major depressive disorder group; HC, healthy control group; RFIC, right frontal insular cortex; DACC, dorsal anterior cingulate cortex.

(Hamilton *et al.*, 2011). Additionally, while we cannot rule out medication influences, when removing the five participants on psychotropic medications, the pattern of results remained the same. Furthermore, within the MDD group, there were largely no significant differences between those who were taking psychotropic medications from those who were not (see Supplemental Material). The fact that we still found aberrant functional connectivity within critical regions among each of the three neural networks suggests that the findings are not entirely explained by medication effects.

Additionally, with regards to our task design, the external-focus condition differs from the self-focus condition on a number of other dimensions besides content, including level of abstractness and complexity. While this same paradigm has been used in a number of studies (e.g. Lyubomirsky and Nolen-Hoeksema, 1993; Nolen-Hoeksema and Morrow, 1993), the current study could have benefited from including an 'abstract' control condition to further understand neural substrates specific to self-focus, as was done by Cooney *et al.* (2010). Also, of note with respect to the thought induction task, we did not include a means of verifying that the participants were indeed generating the type of thoughts each condition is designed to elicit. Nor did we assess the number of statements that each participant completed.

In addition to some limitations with the design, we also chose to focus on a small part of within-network functional connectivity in the default, executive and salience networks. In addition to the subgenual anterior cingulate cortex, the central hub that we chose to examine default mode network functional connectivity, the precuneus and dorsomedial prefrontal cortex are also critical to self-focused thought processes including rumination in both individuals with and without MDD (Johnson *et al.*, 2009; Freton *et al.*, 2014; Nejad *et al.*, 2013). We also did not examine differences in connectivity between the three networks. Some studies have found differences in connectivity between these networks in those with and without MDD during a resting state (Sheline *et al.*, 2010), as well as during a self-focus task (Lemogne *et al.*, 2009). Given the complexity of the psychological processes being tapped, future research should incorporate more comprehensive within and cross-network connectivity assessments.

In sum, our study provides novel evidence for dysregulated default mode, executive and salience network connectivity in MDD participants during non-self-referential thought. The results suggest that individuals with MDD are unable to adequately switch off the default mode network and switch on the executive network via the salience network. This pattern of neural network activity is consistent with an inability to disengage from self-focused thought processes, particularly when self-focus is incompatible with engaging in task goals. This attentional control difficulty is thought to contribute to the development of rumination in those with MDD. Future studies would benefit from a more detailed analysis of these core neural networks during tasks that vary in attentional demands and in content to determine what factors are most effective at disrupting rumination.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN*.

Conflict of Interest

None declared.

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