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Intensity of repetitive negative thinking in depression is associated with greater functional connectivity between semantic processing and emotion regulation areas

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Abstract

Background. Repetitive negative thinking (RNT), a cognitive process that encompasses past (rumination) and future (worry) directed thoughts focusing on negative experiences and the self, is a transdiagnostic construct that is especially relevant for major depressive disorder (MDD). Severe RNT often occurs in individuals with severe levels of MDD, which makes it challenging to disambiguate the neural circuitry underlying RNT from depression severity.

Methods. We used a propensity score, i.e., a conditional probability of having high RNT given observed covariates to match high and low RNT individuals who are similar in the severity of depression, anxiety, and demographic characteristics. Of 148 MDD individuals, we matched high and low RNT groups ($n = 50$/group) and used a data-driven whole-brain voxel-to-voxel connectivity pattern analysis to investigate the resting-state functional connectivity differences between the groups.

Results. There was an association between RNT and connectivity in the bilateral superior temporal sulcus (STS), an important region for speech processing including inner speech. High relative to low RNT individuals showed greater connectivity between right STS and bilateral anterior insular cortex (AI), and between bilateral STS and left dorsolateral prefrontal cortex (DLPFC). Greater connectivity in those regions was specifically related to RNT but not to depression severity.

Conclusions. RNT intensity is directly related to connectivity between STS and AI/DLPFC. This might be a mechanism underlying the role of RNT in perceptive, cognitive, speech, and emotional processing. Future investigations will need to determine whether modifying these connectivities could be a treatment target to reduce RNT.

Introduction

Repetitive negative thinking (RNT), a cognitive process that encompasses past (rumination) and future (worry) directed thoughts focusing on negative experiences and the self (Harvey, Watkins, Mansell, & Shafran, 2004), is a common feature of major depressive disorder (MDD) and anxiety disorders. RNT is characterized by its focus on negatively valenced thoughts, especially on possible causes and consequences of one's negative emotions and experiences (current, past, and future) (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). RNT is consistently linked to a higher frequency, duration, and severity of depression and anxiety, and it also predicts suicidality (Krajniak, Miranda, & Wheeler, 2013; Surrence, Miranda, Marroquin, & Chan, 2009; Watkins & Roberts, 2020). Higher RNT is also associated with a slower response and poorer outcome to both antidepressant medication and cognitive-behavioral therapy (CBT) (Jones, Siegle, & Thase, 2008; Schmaling, Dimidjian, Katon, & Sullivan, 2002). Although effective treatments for MDD have been established, nearly two-thirds of patients do not respond adequately (Cain, 2007), and treatment of MDD with currently available modalities still leaves some residual symptoms, including RNT (Nierenberg et al., 2010).

RNT could serve as a common risk factor for depression and anxiety, and it may contribute to explaining why MDD and anxiety are highly comorbid. Longitudinal studies found that RNT predicts the level of both anxiety and depression symptoms (McLaughlin & Nolen-Hoeksema, 2011; Nolen-Hoeksema, 2000). Thus, the transdiagnostic nature of RNT probably makes it a promising target for the prevention and treatment for MDD, where anxiety is often comorbid.

However, relatively little is known about the underlying neural circuitry of RNT. For example, some studies reported that RNT may result in increased connectivity within the default mode network (DMN) (Cooney, Joormann, Eugene, Dennis, & Gotlib, 2010; Misaki, Tsuchiyagaito, Al Zoubi, Paulus, & Bodurka, 2020), a set of functionally connected brain nodes linked to self-referential processing, as well as increased connectivity of the DMN with the subgenual anterior cingulate cortex (sgACC) (Berman et al., 2014; Hamilton, Farmer, Fogelman, & Gotlib, 2015). Increased recruitment of the DMN and so-called 'self-related' regions, such as the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and precuneus, is often linked to the frequent occurrence of RNT in depressive patients (Hamilton et al., 2015; Misaki et al., 2020). A meta-analysis also reported that RNT is correlated with increased connectivity between the MPFC and PCC (Zhou et al., 2020).

Nonetheless, recent meta-analyses reported slightly reduced DMN in MDD, with RNT not predicting hyperconnectivity within the DMN components (Tozzi et al., 2021; Yan et al., 2019). Those meta-analyses were in line with other studies that found decreased connectivity in the DMN with MDD individuals with small effect sizes (Chen, Wang, Zhu, Tan, & Zhong, 2015; Zhu, Zhu, Shen, Liao, & Yuan, 2017). Moreover, recent studies have reported that the DMN is not as homogenous as previously assumed and suggested that it can be further subdivided into smaller subsystems (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). Those subsystems of the DMN include a midline core composed of hub of the DMN, i.e., anterior medial prefrontal cortex (aMPFC) and PCC; the dorsal medial prefrontal cortex (dMPFC) subsystem involved in self-referential processing; and the medial temporal lobe (MTL) subsystem involved in episodic memory (see Andrews-Hanna et al. (2010) and online Supplemental material for more detailed explanations). Interaction within and between the DMN subsystems may explain contradictory findings linking DMN to MDD in general, and RNT in particular.

Concurrently, results regarding resting-state functional connectivity in MDD beyond the DMN have also offered nonuniform results. For example, some studies found increased functional connectivity within executive control and affective salience networks (Avery et al., 2014; Connolly et al., 2013; Sheline, Price, Yan, & Mintun, 2010), while other studies found opposite results in the same areas (Alexopoulos et al., 2012; Veer et al., 2010). These contradictory findings might be due to various reasons, including the use of different approaches such as focusing on a predefined regions-of-interest approach or a whole-brain approach, as well as the heterogeneity of MDD populations. For these reasons, we used a whole-brain exploration approach to understand the connectivity patterns underlying RNT in MDD.

Finally and most importantly, the severity of RNT and depressive symptoms in general, could be closely associated; in this scenario, it might be difficult to disentangle the underlying brain mechanisms of either symptom dimension, and thus attribution of DMN abnormalities to RNT severity independently from overall depressive symptom severity is difficult to ascertain. As stated above, findings related to the role of DMN on RNT are not uniform. However, depression in general appears to be associated with increased functional connectivity within the DMN. For example, a higher baseline resting-state connectivity of the pregenual anterior cingulate cortex (pgACC) and ventromedial prefrontal cortex (vMPFC) predicted clinical response to antidepressant treatments, including repetitive transcranial magnetic stimulation (rTMS) treatment, pharmacotherapy, and psychotherapy (Long et al., 2020). Correspondingly, symptom reduction after rTMS was associated with reduced connectivity between DMN, sgACC and insula (Hamilton et al., 2015; Liston et al., 2014; Philip et al., 2018). Pharmacotherapy and psychotherapy have been shown to normalize connectivity within the DMN (Evans et al., 2018; Jacobs et al., 2016; Li et al., 2013; Posner et al., 2013; Straub et al., 2017). Possibly, variable findings related to the role of DMN on RNT may be due to the fact that increased connectivity of the DMN reflect depression in general rather than RNT intensity. One way to reduce potential biases in studying RNT-related brain mechanisms is to use propensity scoring to match the severity of depression, anxiety, and demographic characteristics. The propensity score is defined as the conditional probability of assignment to a particular group given a vector of observed covariates (Rosenbaum & Rubin, 1983). In the randomized experiment, treatment or control is randomly assigned, and the propensity score equals 0.5 for all subjects; however, in an observational study, subjects with certain characteristics can be more likely to receive treatment (or control), and thus the propensity score to receive treatment (or control) varies among subjects based on these pre-treatment characteristics (Rosenbaum, 2015). In our study, the certain treatment or exposure is having high RNT, and the propensity score for having high RNT could vary among subjects based on characteristics such as depression, anxiety and other demographic variables. By applying propensity score matching, we can control for these biases in a quasi-experimental manner.

The aim of the present study was to identify resting-state functional connectivity patterns that are specifically related to RNT in depression, by employing functional magnetic resonance imaging (fMRI) in a propensity-matched sample of patients with MDD and varying RNT severity. On the basis of previous observations related to the DMN findings (Tozzi et al., 2021; Yan et al., 2019) and other resting-state fMRI studies described above, we expected that clinically important connectivity patterns related to RNT may exist outside of the DMN, and conducted a data-driven, whole-brain voxel-to-voxel connectivity pattern analysis to examine functional connectivity alterations specifically related to RNT in MDD. Following prior studies (Andrews-Hanna et al., 2010; Tozzi et al., 2021; Zhou et al., 2020; Zhu et al., 2017), we also conducted ROI-to-ROI connectivity analysis within the DMN subsystems to examine whether RNT as well as depression in general are related to altered connectivity within the DMN (online Supplementary Methods and Results).

Methods

Participants

We studied 158 subjects with MDD (with or without comorbid anxiety including generalized anxiety disorder, social phobia, panic disorder, or post-traumatic stress disorder) [128 females, mean age = 30.93 (S.D. = 10.63) years] from the Neuroscience-Based Mental Health Assessment and Prediction (NeuroMAP, P20GM121312) – Center of Biomedical Research Excellence (CoBRE) at the Laureate Institute for Brain Research (LIBR) (Kuplicki et al., 2021). The diagnosis was based on an abbreviated version of the Mini International Neuropsychiatric Interview (MINI V.6.0 or 7.0) (Sheehan et al., 1998), followed by a clinical case conference by a board-certified clinical psychiatrist (SSK or SMG). A research protocol of CoBRE NeuroMAP was approved by the Western Institutional Review Board (IRB). All participants provided written

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informed consent and received financial compensation for their time participating in this study.

Clinical measures

RNT was evaluated with the Ruminative Responses Scale (RRS) (Nolen-Hoeksema & Morrow, 1991). The RRS consists of 22 items with three subscales (i.e. brooding, reflective pondering and depression-related) (Nolen-Hoeksema & Morrow, 1991). The five-item reflective pondering (e.g. *Go away by yourself and think about why you feel this way.*) is considered an adaptive aspect of RNT, reflecting the degree to which individuals engage in cognitive problem-solving to alleviate the depressive mood. The 5-item brooding dimension of RNT (e.g. *Think 'Why can't I handle things better?'*) is considered a maladaptive aspect of RNT, and it reflects the degree to which individuals passively focus on negative valence and experiences and their meaning. The other 12-item depression subscale captures content related to depressive symptoms (e.g. *'Think about how sad you feel.'*), and could be confounded with depressive symptoms. Among those three subscales, the brooding subscale usually implies a self-critical evaluative viewpoint (Treynor, Gonzalez, & Nolen-Hoeksema, 2003), and studies have consistently demonstrated that MDD is specifically characterized by high levels of brooding (Armey et al., 2009; Burwell & Shirk, 2007; Treynor et al., 2003; Watkins, 2009). Thus, in the present study, we used the brooding subscale of RRS to measure RNT. We also used the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), the Patient Health Questionnaire-9 (PHQ) (Kroenke, Spitzer, & Williams, 2001), and Overall Anxiety Severity and Impairment Scale (OASIS) (Norman, Cissell, Means-Christensen, & Stein, 2006) to measure the severity of depression and anxiety symptoms.

Propensity score matching and experimental group assignment

Figure 1 shows the sampling and data flow in this study. We divided the present MDD sample into participants with high and low RNT ($n = 50$ per group), using a propensity score-matching approach. After excluding 10 subjects due to the excessive head motion during the scan, the dataset of 148 MDD from NeuroMAP (described in detail in 2.1.) was divided into two groups (high RNT and low RNT) based on the median of the brooding subscale of RRS, as described above. The median of RRS brooding subscale was 14 in the dataset, and MDD subjects who scored more than 14 for the RRS brooding were categorized as having high RNT, while MDD subjects who scored less than or equal to 14 for the RRS brooding were categorized as having low RNT. After the median split, 63 MDD subjects were categorized as having high RNT, and 85 MDD subjects were categorized as having low RNT. Of those, 50 subjects were assigned to either high RNT group or low RNT group, while 48 subjects were discarded due to missmatching. The *MatchIt* library (Ho, Imai, King, & Stuart, 2011) in R (https://cran.r-project.org) was used for the matching. Variables used for matching included diagnosis (MDD with or without anxiety comorbidity), PHQ score, OASIS score, age, sex, and body mass index (BMI); both groups resulted in matching also for ethnicity, education level, income, and employment status (Table 1). Using the default 'nearest neighbor' approach, the algorithm used logistic regression to estimate the predicted probability of group membership status (high RNT *v.* low RNT) given this set of matching covariates. Then, 50 MDD subjects with high RNT were randomly selected for high RNT group, and 1-to-1 matching was implemented to select the subject from the low RNT group with the nearest predicted probability (propensity score) for each participant from the high RNT group. Table 1 describes the demographic and clinical characteristics of the resulting groups.

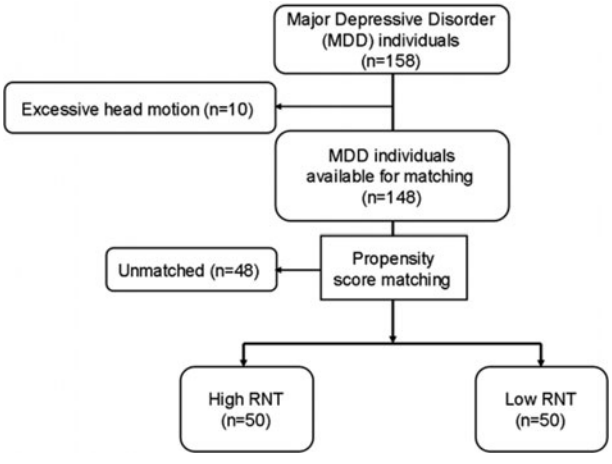

Fig. 1. Flow diagram of participant selection. MDD individuals were divided into two groups resulting from a median split of the total score of Ruminative Response Scale (RRS) as a measure of RNT intensity. Fifty MDD subjects with high RNT and 50 MDD subjects with low RNT were thus selected during propensity score matching, as described in 2.3.

Neuroimaging data acquisition and preprocessing

Resting-state fMRI data were collected on a whole-body 3 Tesla MR750 MRI scanner (GE Healthcare, Milwaukee, WI) with an 8-channel receive-only head array coil. All the participants went through an anatomical scan and then two six-minute resting-state fMRI scans were obtained consecutively (Cho, Korchmaros, Vogelstein, Milham, & Xu, 2021). Details on image acquisition and preprocessing can be found in the online Supplementary material.

Resting-state fMRI whole-brain voxel-to-voxel correlation analysis

A whole-brain voxel-to-voxel correlation analysis was conducted to detect brain areas with different functional connectivity patterns between the high and low RNT groups. We used group multivariate pattern analysis implemented in the CONN-toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). The analysis creates multivariate correlation (MCOR) maps to conduct whole-brain voxel-wise functional connectivity pattern analysis (Anteraper et al., 2019; Anteraper et al., 2020; Byun et al., 2021; Guell et al., 2020; Kazumata et al., 2017; Morris et al., 2021; Muehlhan et al., 2020; Takamiya et al., 2021; Wang et al., 2019; Westfall et al., 2020; Whitfield-Gabrieli et al., 2016). A detailed description of the methodology is provided in online Supplementary material and elsewhere (Anteraper et al., 2019). In essence, pairwise correlations for a single (seed) voxel and all other voxels in the brain (voxel-to-voxel correlation) are calculated, and the dimensionality of the correlation maps across participants is reduced by singular value decomposition (SVD). MCOR is an SVD component score

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Table 1. Demographic and symptom profile of propensity score-matched data

	High RNT (n = 50)	Low RNT (n = 50)	Statistics	*p*-value
Age	28.45 (9.57)	30.93 (10.67)	$t(98) = -1.22$	$p = 0.22$
Female (%)	42 (84.00)	36 (72.00)	$\chi^2(1) = 1.46$	$p = 0.23$
Race/Ethnicity: Non-White (%)	19 (38.00)	21 (42.00)	$\chi^2(1) = 0.04$	$p = 0.84$
Asian	1 (2.00)	3 (6.00)		
Black	5 (10.00)	5 (10.00)		
Hispanic	5 (10.00)	7 (14.00)		
Native American	6 (12.00)	5 (10.00)		
Other	2 (4.00)	1 (2.00)		
White	31 (62.00)	29 (58.00)		
Employed (%)	33 (66.00)	31 (62.00)	$\chi^2(1) = 0.04$	$p = 0.84$
Education level (%)			Fisher's exact test	$p = 0.29$
College or higher	23 (46.00)	23 (46.00)		
Some college	17 (34.00)	19 (38.00)		
High school	9 (18.00)	4 (8.00)		
No high school	1 (2.00)	4 (8.00)		
Income	57656.05 (47431.55)	55152.20 (38000.74)	$t(98) = -0.27$	$p = 0.78$
BMI	27.87 (6.38)	27.14 (4.88)	$t(98) = -0.65$	$p = 0.52$
Diagnosis (%)			$\chi^2(1) = 0.09$	$p = 0.76$
Major depressive disorder (MDD) without comorbidity	7 (14.00)	5 (10.00)		
MDD and anxiety	43 (86.00)	45 (90.00)		
Generalized anxiety disorder	34 (68.00)	32 (64.00)		
Social anxiety disorder	27 (54.00)	23 (46.00)		
Panic disorder	5 (10.00)	4 (8.00)		
Post-traumatic stress disorder	11 (22.00)	11 (22.00)		
Medicated (%)	9 (18.00)	10 (17.54)	$\chi^2(1) = 0.09$	$p = 0.76$
Depressive episode (%)			$\chi^2(1) = 0.69$	$p = 0.40$
First episode	16 (32.00)	21 (42.00)		
Recurrent	34 (38.00)	29 (58.00)		
Current psychotherapy (%)	5 (10.00)	3 (6.00)	Fisher's exact test	$p = 0.72$
HAMD	15.28 (4.54)	15.84 (4.14)	$t(98) = -0.64$	$p = 0.52$
PHQ	14.78 (4.11)	14.08 (4.57)	$t(98) = 0.81$	$p = 0.42$
OASIS	10.84 (3.48)	10.76 (3.15)	$t(98) = 0.12$	$p = 0.90$
RRS				
Total	69.54 (8.02)	53.12 (10.12)	$t(98) = 8.99$	$p < 0.001$
Reflection	14.06 (2.89)	11.34 (3.41)	$t(98) = 4.31$	$p < 0.001$
Brooding	17.28 (1.75)	11.52 (2.30)	$t(98) = 14.11$	$p < 0.001$
Depression	38.20 (5.42)	30.26 (6.25)	$t(98) = 6.79$	$p < 0.001$
Head motion (framewise displacement)	0.09 (0.02)	0.09 (0.02)	$t(98) = -0.25$	$p = 0.81$

of each participant for a seed voxel, and the MCOR map is obtained by repeating this analysis voxel-wise in the entire brain.

Following previous studies (Anteraper et al., 2019; Pang et al., 2022; Wang et al., 2019; Westfall et al., 2020), we took the first five components, which explained more than 90% of the variance. Hence, the five participant-specific spatial maps were used as a low-dimensional proxy of the connectivity pattern characterizing each participants' whole-brain voxel-to-voxel connectivity. An

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omnibus F test was performed across five spatial components to evaluate a group difference in this five-dimensional representation of the spatial pattern of this connectivity to all other voxels. Mean head motion was used as a covariate of no interest in all second-level analyses. Clusters surviving threshold of voxel-wise $p < 0.001$ and cluster-level false discovery rate (FDR)-corrected $p < 0.05$ [topological FDR (Chumbley, Worsley, Flandin, & Friston, 2010)] were subjected to post-hoc analyses.

Post-hoc characterization of significant MCOR clusters

Since the MCOR analysis in CONN toolbox is an omnibus test on the component scores (Anteraper et al., 2019), post-hoc analyses with two-sample t tests were conducted to further characterize how connectivity patterns differed between the groups. The significant clusters obtained from the MCOR map analysis were taken as seeds for seed-based whole-brain connectivity analysis. Pearson's correlation coefficients between the time courses of the cluster and all other voxels in the brain were computed and then converted to z scores using Fisher's transformation to carry out general linear model analyses in CONN toolbox. Mean head motion was used as a covariate of no interest in all second-level analyses. Thresholds of voxel-wise $p < 0.001$ and cluster-level FDR-corrected $p < 0.05$ were applied in the group comparison.

Results

Demographic and clinical characteristics

Table 1 shows the demographic and symptom profile of propensity score-matched RNT groups. The high RNT group showed higher scores of RRS and its subscales than the low RNT group. Other demographic variables and symptom profiles were similar in both groups.

Whole-brain voxel-to-voxel correlation pattern analysis

Figure 2 displays the clusters showing intergroup differences in the whole-brain voxel-to-voxel correlation analysis. Cluster 1 was found in the anterior part of the superior temporal sulcus (STS) in the right hemisphere, whereas Cluster 2 was located in the posterior part of the STS in the left hemisphere. Table 2 shows peak coordinates for each cluster.

Post-hoc analysis

Results from the post-hoc seed-based whole-brain functional connectivity analysis are shown in Fig. 3. The peak coordinates and t-statistics are summarized in online Supplementary material, Table S1. Right STS seed displayed significantly greater functional connectivity with the bilateral anterior insular cortex (AI) in high RNT compared to low RNT group (left AI: $d = 1.15$ and right AI: $d = 1.19$, Fig. 3a). Connectivity between this seed and left dorsolateral prefrontal cortex (DLPFC) was also greater in high RNT compared to low RNT group ($d = 1.10$, Fig. 3a). Those connectivity values were not correlated with the severity of depression or anxiety (online Supplementary material, Table S2).

Discussion

This investigation aimed to compare the resting-state connectivity patterns in individuals with MDD and high $v.$ low level of RNT. High $v.$ low RNT MDD individuals differed in functional connectivity of bilateral STS. High RNT individuals showed greater connectivity between STS and AI/DLPFC. This study has demonstrated that those connectivity patterns in high RNT $v.$ low RNT group are not attributed to potential confounders–depression and/or anxiety symptoms.

The role of the STS in RNT

The STS, located on the lateral aspect of the brain in the temporal lobe, is a brain region that is important for multiple perceptual and cognitive functions including speech processing, theory-of-mind (ToM), audiovisual integration, motion and face perception, interoception, and threat processing (Garcia-Cordero et al., 2016; Kret, Pichon, Grezes, & de Gelder, 2011; Lahnakoski et al., 2012; Liebenthal, Desai, Humphries, Sabri, & Desai, 2014; Pichon, de Gelder, & Grezes, 2009). Studies have highlighted the pivotal role of the STS, together with other temporal regions and inferior frontal gyrus, in speech processing (Alderson-Day & Fernyhough, 2015a; Lahnakoski et al., 2012; Liebenthal et al., 2014). One possible interpretation of altered functional connectivity in the STS related to RNT is that this symptom assumes the clinical form of verbal thoughts, or inner speech (Alderson-Day & Fernyhough, 2015a; Moffatt, Mitrenga, Alderson-Day, Moseley, & Fernyhough, 2020; Oliver, Smith, & Leigh, 2015; Perrone-Bertolotti, Rapin, Lachaux, Baciu, & Loevenbruck, 2014). Indeed, the bilateral STS clusters showing intergroup differences in this study are encompassed in the predicted activation map related to the term 'inner speech' by the NeuroQuery (online Supplementary material, Fig. S3). Although inner speech can be considered as a mental simulation of overt speech (Alderson-Day & Fernyhough, 2015a), it is not solely related to speech production and comprehension, but also related to conversational and social features (Alderson-Day et al., 2014; Alderson-Day & Fernyhough, 2015b). Similarly, in addition to 'talking to oneself,' RNT consists of self-focused thoughts and evaluations of one's emotional state. For example, RNT involves more evaluative and dialogic (conversational style) inner speech (e.g. think about the causes, consequences, and meanings of your current feelings) than emotionally neutral thoughts (e.g. thinking about a shopping list). Therefore, it has been proposed that RNT can be characterized as an internal conversation, rather than as a monologue (Jones & Fernyhough, 2009; Moffatt et al., 2020). Burgeoning evidence consistently reports that the generation of dialogic speech is associated with a range of regions beyond the classic left-sided perisylvian language network, for example the right STS (Linden et al., 2011; Shergill et al., 2001; Yao, Belin, & Scheepers, 2011, 2012). Our observation of altered functional connectivity in the right STS as well as the left STS in high RNT individuals provides additional support to this view.

Moreover, it has been proposed that dialogic inner speech could draw on ToM capacities, requiring not just the representation of a voice but also the sense and intention of a plausible and realistic interlocutor; activity in the right STS was evident during both dialogic scenarios and ToM reasoning (Carrington & Bailey, 2009), and this region is a major component of the 'social brain' (Blakemore, 2008; Guinjoan, de Achaval, Villarreal, Abusamra, & Nemeroff, 2015; Kennedy & Adolphs, 2012). Together with other regions in the temporal lobe (e.g. anterior temporal lobe, and middle and superior temporal gyrus) and the precuneus, the STS and its neighboring temporoparietal junction constitute a critical node of the mentalization, or ToM, network (Carrington

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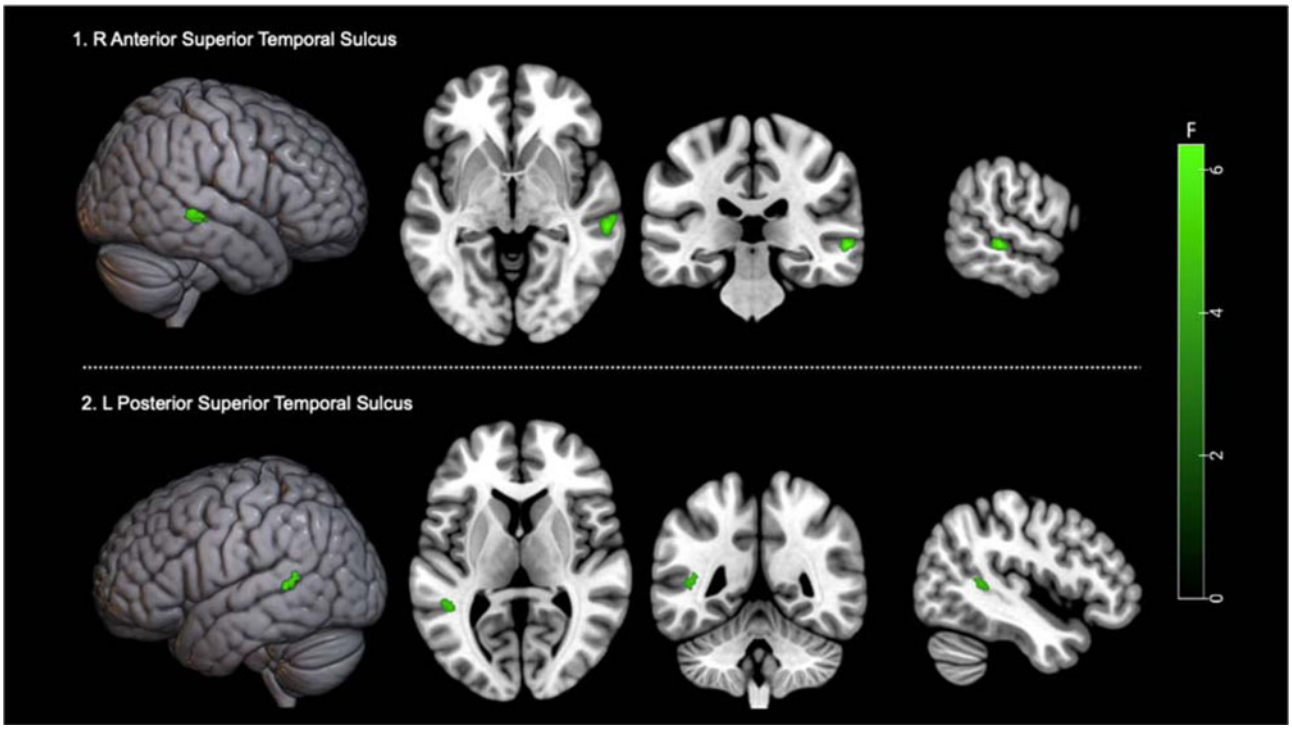

Fig. 2. Regions showing connectivity differences between high RNT *v.* low RNT from the whole-brain voxel-to-voxel correlation pattern analysis. Cluster size (*k*) threshold of $k \geqslant 49$ ($p < 0.05$ FDR corrected) and height threshold of $p < 0.001$ (uncorrected) were used. L, left; R, right; RNT, repetitive negative thinking; FDR, false-discovery rate.

Table 2. Peak coordinates and statistics of the whole-brain voxel-to-voxel correlation pattern analysis (high RNT v. low RNT)

Hemisphere/Location	Brainnetome Atlas Label	Peak MNI coordinates	Cluster size	*F* value
R superior temporal sulcus	aSTS (anterior superior temporal sulcus)	+60, −30, −02	69	6.51
L superior temporal sulcus	cpSTS (caudoposterior superior temporal sulcus)	−42, −50, 12	49	5.89

RNT, repetitive negative thinking; L, left; R, right, MNI, Montreal Neurological Institute; FDR, false-discovery rate.
A voxel-wise threshold of $p < 0.001$(uncorrected) and a cluster size (*k*) threshold of $k \geqslant 49$ ($p < 0.05$, FDR-corrected) were used.

& Bailey, 2009; Gobbini, Koralek, Bryan, Montgomery, & Haxby, 2007; Kennedy & Adolphs, 2012; Watson, Latinus, Charest, Crabbe, & Belin, 2014). The STS plays a key role in social perception and cognition, including the perception of faces and human motion, as well as understanding others' actions, mental states, and language (Deen, Koldewyn, Kanwisher, & Saxe, 2015). Notably, the activation of this mentalizing network to process social information is usually stronger in the right hemisphere (Deen et al., 2015; Dodell-Feder, Koster-Hale, Bedny, & Saxe, 2011; Goldschmidt et al., 2014). In most clinical scenarios, RNT consists of thoughts about relationships with other people, and about how past interpersonal events might have played out differently (Newby & Moulds, 2012). Our observation of different voxel-to-voxel connectivity in the bilateral STS distinguishing high RNT from low RNT suggests that RNT is indeed related to the ToM circuit.

The STS, together with *salience network* (SN), also plays an important role in interoception and threat processing (Drabant et al., 2011; Garcia-Cordero et al., 2016; Sripada et al., 2012). During an interoceptive attention task (relative to an exteroceptive task), greater activity in regions of the superior temporal gyrus, insula cortex, and precentral gyrus was associated with reduced attentional control and greater distraction and worry (Stern et al., 2017). The role of the STS in interoceptive awareness might have a bearing on the influence of RNT on anxiety. Altered bodily sensation and interoceptive awareness have been implicated in the pathophysiology of anxiety disorders (Clark et al., 1997; Khalsa et al., 2018; Paulus & Stein, 2010; Wells & Papageorgiou, 2001), while the ability to control and regulate attention on bodily sensation is thought to help psychological well-being (Farb et al., 2015). Moreover, the STS is thought to be involved in threat processing. Studies found hyperactivation in the STS for threatening (fear and angry) body expressions (Kret et al., 2011; Pichon et al., 2009), and several brain regions showed responses to threat anticipation including the bilateral insula, ACC, and STS (Drabant et al., 2011). There is increasing evidence to suggest that interoception and threat processing guide our cognitive processes such that fluctuations in bodily arousal and interpretation of threatening stimuli under uncertainty contribute to cognitive processes themselves by feeding back to decision making and RNT [as worry or rumination; (Bechara, Damasio, Tranel, & Damasio, 1997; Bonaz et al., 2021; Garfinkel & Critchley, 2013; Matthews & Wells, 2004; Paulus & Stein, 2010)].

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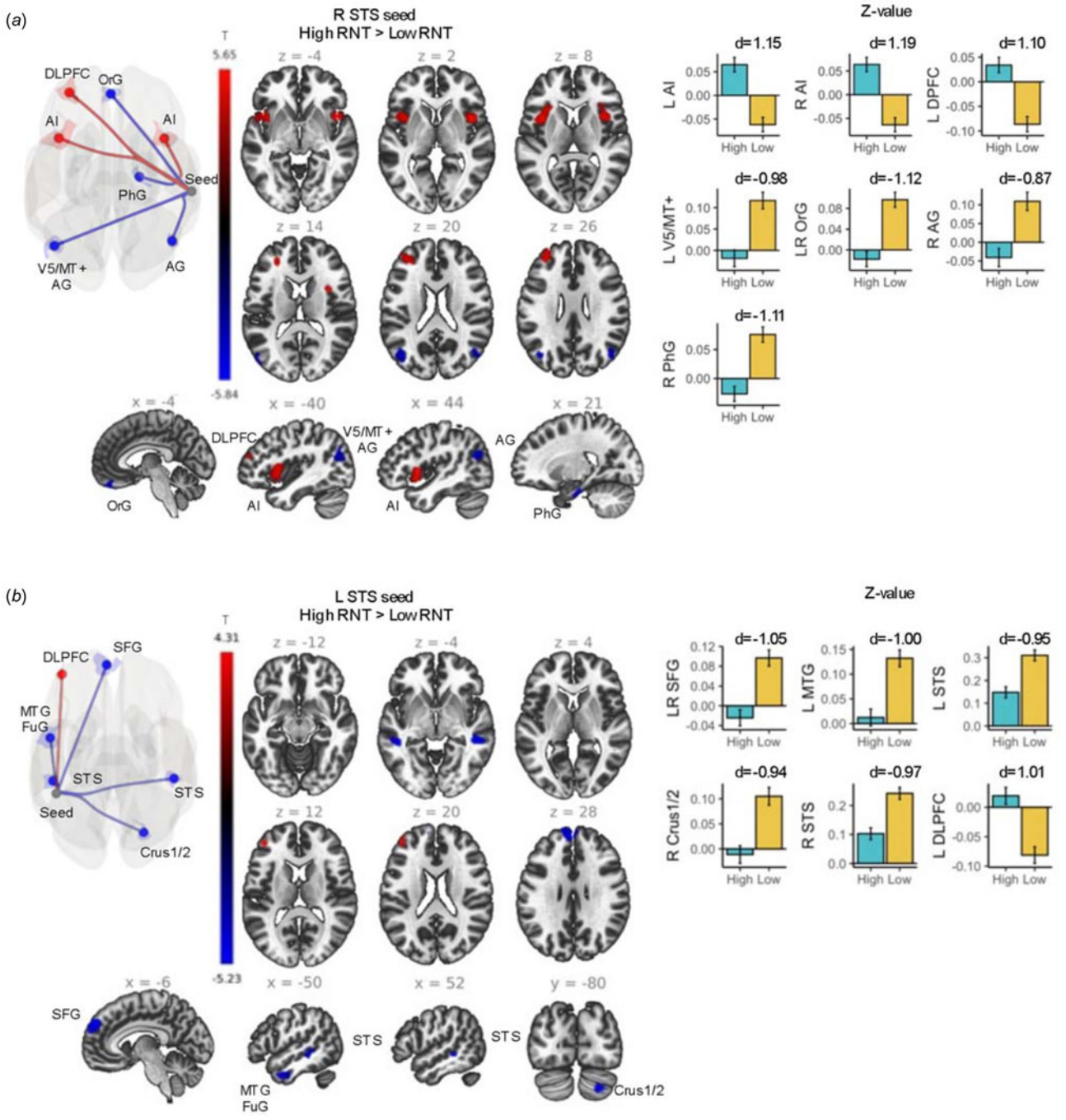

Fig. 3. Seed-to-voxel whole brain analysis comparing high RNT and low RNT using clusters obtained from voxel-to-voxel correlation analysis as seeds. a. Cluster 1 in the right superior temporal sulcus (STS) (MNI: + 60, −30, −02) as a seed. b. Cluster 2 in the left STS (MNI: −42, −50, 12) as a seed. The spheres illustrate the locations of the peak voxel. Positive connectivity from the seed is presented as red spheres and red lines, and negative connectivity from the seed are presented as blue spheres and blue lines. The red colored and blue colored areas indicate cluster extensions for either positive or negative connectivity from each seed respectively. A height threshold of $p < 0.001$(uncorrected) and FDR-corrected cluster threshold of $p < 0.05$ were used. The bar graphs show the z values between each significant cluster and seeds (mean ± S.E.). RNT, repetitive negative thinking; L, left; R, right; AG, angular gyrus; AI, anterior insular; DLPFC, dorsolateral prefrontal cortex; FuG; fusiform gyrus; MTG, middle temporal gyrus; OrG, orbital gyrus; PhG, parahippocampal gyrus; SFG, superior frontal gyrus.

DMN, RNT, and depression

In our study, we did not find any DMN connectivity pattern differences between the groups (online Supplementary material, Figs S1 and S2). Our results are in line with recent meta-analyses reporting that RNT did not predict hyperconnectivity within the DMN components (Tozzi et al., 2021; Yan et al., 2019). To the best of our knowledge, this is the first study investigating the functional connectivity linked to the intensity of RNT taking into account the severity of both depression and anxiety. Our MDD subjects were mostly (81%) unmedicated. This characteristic of our sample needs to be considered for the interpretation of our results in light of prior studies.

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Altered functional connectivity of the STS in MDD individuals with high RNT

In summary, altered STS functional connectivity in the high RNT group may potentially relate to dysfunction in several areas, including perceptive, cognitive, and speech processing. Several studies indicated that the functional subdivisions of the STS, e.g., left, right, anterior, and posterior part of the STS, have distinct functions (Hein & Knight, 2008; Lahnakoski et al., 2012; Liebenthal et al., 2014). On the other hand, the fact that lesions in equivalent STS regions can cause diverse functional deficits could argue against a clear-cut functional subdivision (Akiyama et al., 2006a, 2006b; Hein & Knight, 2008; Samson, Apperly, Chiavarino, & Humphreys, 2004). Possibly, the role of the STS may vary depending on its functional connectivity with other regions, rather than on the functional subdivision of the STS itself (Hein & Knight, 2008). In our study, individuals with high RNT showed hyperconnectivity between right STS and AI, and between bilateral STS and left DLPFC. Hyperconnectivity between the STS and AI may support a role for the STS in interoceptive and threat processing because the AI serves as a strategic neural node in body integrity, peripheral autonomic output, and appraisal of emotional responses (Craig, 2009; Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Paulus & Stein, 2010). Similarly, hyperconnectivity between STS and DLPFC may underlie the role of the STS in speech processing related to emotion regulation (e.g. reappraisal), since those cognitive-behavioral strategies engage prefrontal cortices including the DLPFC (Gilmartin, Balderston, & Helmstetter, 2014; Goldin, McRae, Ramel, & Gross, 2008). We provide additional discussion on the potential implications of altered STS connectivity in MDD and high RNT in the online Supplementary material. The question remains regarding the directionality of connectivity between the STS and other regions since our approach can only inform about coactivated regions. This is a topic that deserves further consideration given the paucity of reports addressing it (Hamilton et al., 2011; Kumar, Stephan, Warren, Friston, & Griffiths, 2007; Noppeney, Josephs, Hocking, Price, & Friston, 2008).

Limitations and future directions

This study has several limitations. First, a majority of participants in our sample were female (78%), resulting in a female:male ratio of 3.5:1, while most epidemiological data reported female:male prevalence ratios in MDD are approximately 2:1 (Salk, Hyde, & Abramson, 2017). This overrepresentation of the female sex in our sample could reduce the generalizability of our findings. Second, we used a propensity score matching approach to minimize the effect of potential confounders. Our approach has some advantages, including the statistical efficiency of using a propensity score instead of using multiple covariates, no assumptions of linearity between covariates and outcomes, and a quasi-randomized design without model selections which could be biased by the researcher (Benedetto, Head, Angelini, & Blackstone, 2018). However, the propensity score matching yielded smaller samples than initially obtained in the data collection process, which could lead to a loss of information that would have been held in the original data. We used PHQ as a covariate measuring the severity of depression to match the sample instead of HAMD, and the use of a different set of covariates would lead to a different matching set, although both MDD groups were matched for HAMD score as well. Also, the use of a regression approach might have yielded different results. Third, we relied on a self-report scale to measure the participants' level of RNT. As we stated, the important aspect of RNT is its perseverative nature, or the stickiness of the recurrent negative thoughts. Although the RRS can capture the trait aspect of RNT, it relies on the person's retrospective observation, and may not be enough to measure how RNT instantly varies in face of negative events. Fourth, our cross-sectional findings of altered functional connectivity do not inform directional influence between those brain regions as we stated in 4.3.

An important avenue for future work will be comparing altered functional connectivity prior, during, and after the antidepressant treatments, with the potential to use the current neural findings for the therapeutic monitoring factor as RNT symptoms change over time. From a therapeutic perspective, direct modulation of altered functional connectivity patterns described herein may also be of interest, exploring them as targets of diverse established and emerging neuromodulation techniques.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291722002677

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