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Resting State Functional Connectivity Correlates of Rumination and Worry in Internalizing Psychopathologies

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Abstract

Background: Rumination and worry are repetitive negative thinking (RNT) tendencies that contribute to the development and maintenance of internalizing psychopathologies. Accruing data suggest rumination and worry represent overlapping and unique transdiagnostic cognitive processes. Yet, prior neuroimaging research has mostly focused on rumination in depression, which points to involvement of resting-state brain activity in default mode, executive, salience, and/or affective networks.

Methods: The current study examined relations between brain activity during rest and RNT in a transdiagnostic sample. Resting-state fMRI data was analyzed in 80 un-medicated patients with internalizing conditions. Regression analysis, controlling for anxiety and depression symptoms, was performed with seed regions implicated in default mode, executive, salience, and affective networks. Rumination and worry were assessed with standard self-report measures.

Results: Whole-brain regression results showed more rumination and worry jointly corresponded with greater positive resting-state functional connectivity (rsFC) between the amygdala and prefrontal regions (i.e., middle frontal gyrus, inferior frontal gyrus). Conversely, more worry (controlling for rumination) corresponded with greater negative rsFC between amygdala and precuneus. No significant results were observed for rumination alone (controlling for worry).

Conclusions: Findings indicate the affective network plays a role in RNT, and distinct patterns of connectivity between amygdala and regions implicated in the executive and default mode networks were observed across patients with internalizing conditions. Results suggest different mechanisms contribute to RNT as a unitary construct and worry as a unique construct.

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Data Availability Statement. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

fMRI; resting-state functional connectivity; rumination; worry; anxiety; depression

Introduction

It has been well documented that individuals with internalizing disorders exhibit elevated levels of rumination and worry (McEvoy et al., 2013; Newman & Llera, 2011; Nolen-Hoeksema et al., 2008). Rumination, which involves dwelling on past negative events and the possible causes and implications of negative mood (Nolen-Hoeksema, 2004), and worry, wherein thoughts are focused on uncertain and future negative events (Borkovec et al., 1983), have been traditionally examined within the context of depression (Nolen-Hoeksema et al., 2008) and anxiety (Newman & Llera, 2011), respectively. However, emerging evidence suggests that these are not fully distinct constructs (Topper et al., 2014) and may be conceptualized as transdiagnostic, dimensional, stable forms of repetitive negative thinking (RNT) (McEvoy et al., 2013; Olatunji et al., 2010; Smith & Alloy, 2009). Indeed, both shared variance between rumination and worry (i.e., RNT) and unique variance attributed to each of these constructs has been observed to correlate with symptoms of depression and anxiety (McEvoy & Brans, 2013; Spinhoven et al., 2015; Topper et al., 2014). Further, evidence that these forms of RNT are not just correlates of internalizing disorders, but also contribute to their development and maintenance (Ehring & Watkins, 2008) indicates they may serve as an important targets for intervention (Mennin & Fresco, 2013). Therefore, the delineation of mechanisms that underlie RNT may provide important insights into novel targets for intervention.

Well-established intrinsic networks support processes that are hypothesized to underlie RNT. The default mode network (DMN), which is anchored in the posterior cingulate cortex (PCC), is involved in self-referential processing (Northoff et al., 2006). The salience network, which is anchored in the dorsal anterior cingulate cortex (DACC), plays a role in the detection of external or internal salient stimuli (Seeley et al., 2007). The executive control network, which is anchored in the dorsolateral prefrontal cortex (DLPFC), supports top-down cognitive control processes (Seeley et al., 2007). Finally, the affective network, which is anchored in the amygdala, plays an important role in emotion processing (Phelps, 2006).

In light of its central role in self-referential processing (Hamilton et al., 2015; Whitfield-Gabrieli & Ford, 2012), the DMN is proposed to play a role in RNT. Other putative neural mechanisms of RNT involve interactions between bottom-up emotional reactivity and top-down inhibitory control (Disner et al., 2011; Hirsch & Mathews, 2012) that may contribute to the negative content and self-focus of RNT. Not surprisingly, seed-based resting-state studies of rumination have largely involved depressed or remitted depressed individuals with a focus on the DMN. Rumination has been shown to positively correlate with resting-state functional connectivity (rsFC) between the PCC and midline cortical regions in healthy and depressed participants (Berman et al., 2011) and negatively correlate with rsFC between these regions in patients with remitted depression (Lois & Wessa, 2016). Furthermore,

Satyshur and colleagues (2018) reported that reflective rumination, thought to be a more adaptive form of rumination than the brooding component of rumination (Treynor et al., 2003), was positively associated with rsFC between the PCC and the medial prefrontal cortex (MPFC) in healthy and depressed participants. Collectively, results provide support for DMN in rumination despite inconsistencies in functional connectivity patterns.

Regarding other networks one study found that reflective rumination was negatively associated with rsFC between DACC and PCC in healthy and depressed participants (Satyshur et al., 2018); the same study also found that more brooding was associated with less rsFC between amygdala and temporal pole (Satyshur et al., 2018). Rumination as a unitary construct has been shown to positively relate to increased amygdala-PCC rsFC in healthy and remitted depressed adolescents (Peters et al., 2016). Finally, focusing on the executive network, when evaluating rumination as a unitary construct, a study that used a principal component approach demonstrated more rumination was associated with more rsFC between a cluster encompassing DLPFC and the PCC in depressed patients (Bessette et al., 2018). Another study found that in depressed adolescents, more rumination was associated with less rsFC between ACC and prefrontal regions (i.e., DLPFC, inferior frontal gyrus) (Connolly et al., 2013). Thus, findings provide accumulating evidence that rsFC involving DMN, salience, affective, and executive networks underlie rumination, though its neural signature remains unclear due to inconsistencies that may pertain to methodological differences across studies.

In contrast with rumination, less resting-state research has focused on worry. However, similar to rumination, there is evidence of DMN involvement. Studies that examined rsFC correlates of worry in DMN found more worry was associated with less rsFC between PCC and other DMN regions (i.e., MPFC, precuneus) in undergraduates (Burdwood et al., 2016) and individuals with generalized anxiety disorder (GAD) (Andreescu et al., 2014). Another study examining DMN, salience network, and affective network rsFC correlates of worry in healthy controls and patients with GAD found greater worry was associated with greater rsFC between the insula, a node of the salience network (Seeley et al., 2007), and the precuneus (controlling for rumination and anxiety symptoms) (Andreescu et al., 2015). Altogether, this limited research points to DMN and salience network involvement in worry in individuals with and without general anxiety.

Collectively, preliminary evidence based on disorder-specific studies suggests rsFC in DMN and task-positive networks contribute to rumination and worry. Yet, significant gaps remain when considering rumination and worry as transdiagnostic forms of RNT (McEvoy et al., 2013). Furthermore, given evidence of shared and unique variance between rumination and worry (McEvoy & Brans, 2013; Spinhoven et al., 2015; Topper et al., 2014), these constructs are expected to exhibit both shared RNT underpinnings and distinct rsFC patterns specific to rumination and worry. In support of shared pathways, a recent meta-analysis examining resting-state functional correlates of RNT suggests PCC engagement and frontal engagement correspond with rumination and worry (Makovac et al., 2020). This is consistent with reports that both rumination (Berman et al., 2011; Bessette et al., 2018; Lois & Wessa, 2016; Peters et al., 2016; Satyshur et al., 2018) and worry (Andreescu et al., 2014; Berman et al., 2011) are associated with PCC rsFC. Less is known about resting-state

mechanisms that are specific to rumination and worry as few studies examined these forms of RNT simultaneously. However, evidence of salience network involvement in worry (controlling for rumination and anxiety) (Andreescu et al., 2015) suggests the network may be distinct to worry.

It is also important to note that although both rumination and worry are dimensional constructs, ranging from normative to pathological (Olatunji et al., 2010; Smith & Alloy, 2009), they are core processes that maintain internalizing disorders (Mansell & McEvoy, 2017) and individuals with psychopathology endorse significantly more RNT than healthy participants (Kircanski et al., 2015; Samtani et al., 2018; Wahl et al., 2019). Thus, examining individual differences in rumination and worry as they pertain to rsFC in patients has potential clinical utility. Specifically, rumination and worry are core processes that maintain psychopathology (Mansell & McEvoy, 2017) yet they are not typically assessed in clinical settings per se. Delineating intrinsic networks that underlie RNT may highlight its clinical relevance by providing insights into mechanisms of therapeutic change in the context of evidence-based treatments for internalizing psychopathologies and identify potential targets for novel interventions.

Therefore, the objective of the current study was to expand upon previous research by examining the neural correlates of rumination and worry in patients with internalizing psychopathologies. Consistent with previous research (Andreescu et al., 2014; Peters et al., 2016; Satyshur et al., 2018), we chose to focus on commonly examined nodes in DMN, salience, affective, and executive function networks (i.e., PCC, DACC, amygdala, DLPFC). We hypothesized more rumination and worry would correlate with more PCC engagement based on theory and meta-analytic findings (Makovac et al., 2020), though we did not make specific hypotheses as to rsFC connectivity patterns given inconsistent findings. We also expected worry would uniquely involve the salience network (i.e., when controlling for rumination (Andreescu et al., 2015)). Lastly, we explored possible similar and unique RNT correlates across *a priori* resting-state networks and hypothesized similar and distinct correlates of rsFC would be observed for rumination and worry.

Materials and Methods

Participants included 80 un-medicated treatment-seeking adults between the ages of 18 and 65 recruited as part of a study designed in accordance with the Research Domain Criteria initiative to examine mechanisms and predictors of treatment response in internalizing disorders (ClinicalTrials.gov Identifier: NCT01903447). Participants were recruited from a local mood and anxiety disorder outpatient clinic and the community. In the current study, only pre-treatment resting-state data that met quality control was used. Inclusion criteria included a total score of ≥23 on the Depression, Anxiety, and Stress Scale (DASS-21 [total possible scale range: 0 – 63]; Lovibond and Lovibond, 1995) and at least one common anxiety or depressive disorder; diagnostic comorbidity was permitted (see Table 1 for the prevalence of internalizing disorders). Of note, one patient did not meet the DASS-21 cut-point by 1 point (i.e., total score of 22). However, as the DASS-21 is a dimensional measure of psychopathology, the 1-point difference is not expected to have a substantive impact on findings. Also, the patient was diagnosed with a psychiatric disorder indicating a level of

psychopathology sufficient to warrant treatment. Exclusionary criteria included treatment (psychotropic medication, psychotherapy), major medical and neurological illness, contraindications to magnetic resonance imaging (e.g., pregnancy, ferrous objects), current substance dependence (within 6 months of the study), current active suicidal ideation (within 6 months of the study), history of major psychiatric illness (e.g., bipolar disorder, schizophrenia), and cognitive dysfunction (e.g., traumatic brain injury, pervasive developmental disorder).

The study was approved by the University of Illinois at Chicago Institutional Review Board, and informed consent was obtained from all participants. After obtaining consent, a trained master's-level or doctorate-level clinician administered the Structured Clinical Interview (First, Williams, Karg, & Spitzer, 2015), Hamilton Depression Rating scale (HAMD; Hamilton, 1960), and Hamilton Anxiety Rating scale (HAMA; Hamilton, 1959) to assess for DSM-5 diagnoses and current symptoms. All participants were compensated for their time and all procedures complied with the Helsinki Declaration.

Repetitive Negative Thinking Measures

To measure rumination, participants were administered the Ruminative Response Scale (RRS; Nolen-Hoeksema, 1991), which is a 22-item self-report that has demonstrated good reliability and validity in previous studies (Cronbach's αs: 0.88–0.92; Luminet, 2004). The RRS has a total possible range of 22 – 88 and higher scores denote more rumination.

Worry was assessed with the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990). The PSWQ is a 16-item self-report shown to have good validity and reliability (Cronbach's αs: 0.88–0.95; Meyer et al., 1990; van Rijsoort et al., 1999). The PSWQ has a total possible range of 16 – 80 and higher scores denote more worry.

Resting-State Condition

Participants were instructed to view a crosshair centrally displayed on the blank gray screen, relax, and let their mind wander for the duration of the 8-minute scanning period. Padding with foam cushions was used to reduce head movement.

fMRI Data Acquisition and Preprocessing

Scanning during the resting-state condition was conducted on a 3 Tesla GE Discovery System (General Electric Healthcare; Waukesha, WI) with an 8-channel head coil. Functional data were acquired using gradient-echo echo planar imaging (EPI) sequence with the following parameters: TR=2 s, TE=minFull [~25 ms], flip angle=90°, FOV=22 × 22 cm^2, acquisition matrix 64 × 64, 3-mm slice thickness, 44 axial slices, 180 volumes per run. For anatomical localization, a high-resolution, T1-weighted volumetric anatomical scan was acquired.

Data preprocessing and connectivity analyses were performed using the Functional Connectivity (CONN) toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012), which employs procedures from the Statistical Parametric Mapping software (SPM12; Wellcome Trust

Centre for Neuroimaging, London, UK). Four initial volumes from each resting-state run were discarded to allow for T1 equilibration effects. Images were realigned to correct for motion, corrected for errors in slice timing, subjected to outlier detection, co-registered to the anatomical image, spatially transformed to standard MNI space using transformation calculated to transform the anatomical image to the MNI space, resampled to 2-mm voxels, and smoothed with an 8-mm FWHM Gaussian kernel prior to statistical analysis. For subsequent connectivity analysis, the unsmoothed images were used.

All participants tested negative on a urine toxicology screen prior to imaging and all participants were required to have no movement greater than 2-mm translation or 2 degrees rotation across the run for analysis. Effects of nuisance variables (white matter, CSF signals, and movement parameters) were reduced following the CompCor strategy (Behzadi et al., 2007) and outlier time points were regressed out; data were band-pass filtered to 0.008–0.09 Hz.

Analytic Approach

There were six *a priori* anatomy-based seed regions as follows: PCC, bilateral amygdala, DACC, and bilateral DLPFC to examine default mode, affective, salience, and executive networks, respectively (see Supplemental Figure 1). PCC, bilateral amygdala, and bilateral DLPFC seed regions were obtained from the FSL Harvard-Oxford Atlas, which is the default atlas integrated with the CONN toolbox. As this default atlas does not include DACC, the DACC seed region was derived from the median cingulate gyrus of the Automated Anatomical Labelling atlas. Specifically, DACC was defined as the part anterior to the y = 0 line of the median cingulate gyrus (Klumpp et al., 2017). Temporal correlations of the resting-state BOLD signal time series were examined for each seed and the rest of the brain. Since RNT is a core process that maintains internalizing disorders (Mansell & McEvoy, 2017) we wanted to identify unique variance of RNT not attributable to anxiety and depression symptoms. Accordingly, during second-level processing, a regression model comprised of rumination (RRS) and worry (PSWQ) total scores as covariates of interest and HAMA and HAMD total scores as covariates of no interest. For testing unique rsFC relationships between rumination and worry, RRS was a covariate of interest controlling for PSWQ and vice versa.

Following recent guidelines in response to concerns about false positives resulting from lenient significance thresholds (Eklund et al., 2016; Woo et al., 2014), whole-brain functional connectivity was considered significant if it exceeded adjustment for multiple comparisons across the entire brain (e.g., a whole-brain mask [volume=1,287,920 mm^3]) as determined via simulation using the 3dClustSim utility (10,000 iterations; updated and 'bug-free' on December 2015; [https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html]; Cox, 1996). To adjust for multiple comparisons (i.e., 6 seed regions), Bonferroni correction (0.05/6=0.008) was used to determine thresholds for significance. Therefore, significance at α<0.01 and a voxel threshold of p<0.001 was used, which yielded a minimum cluster size of 390 voxels (volume=3,120 mm^3) for the regression analysis.

To illustrate the magnitude and directionality of significant effects, parameter estimates of functional connectivity (β weights, arbitrary units [a.u.]) were extracted from significant

clusters and submitted to scatterplots in the Statistical Package for the Social Sciences (Chicago, IL; Version 22). Additionally, variance inflation factor (VIF) values for all covariates included in regression models were calculated to ensure that findings did not result from collinearity within the models. VIF values for covariates were as follows: HAMA=1.44, HAMD=1.44, RRS=1.14, PSWQ=1.13. Finally, sex differences have been observed for both rumination and worry (Johnson & Whisman, 2013; Robichaud et al., 2003). To evaluate if sex moderated findings, post-hoc regression analyses were conducted in SPSS. Specifically, significant rsFC extracted clusters were the dependent variable, sex (dummy coded) was entered as an independent variable in the first step of the regression, and HAMA, HAMD, RRS, PSWQ, RRS × Sex, and PSWQ × Sex were entered into the second step of the regression.

Results

Participant Characteristics

See Table 1 for patient principal and comorbid diagnoses, and Table 2 for demographic and clinical characteristics. As seen, 68.75% of patients in the current sample were female, and the average age was 26.93 (*SD*=7.90). Rumination (RRS) and worry (PSWQ) were positively correlated (*r*=.24, *p*=.03). Additionally, rumination was positively correlated with depression symptoms (HAMD) (*r*=.29, *p*=.01) but not anxiety symptoms (HAMA) (*r*=.16, *p*=.15), whereas worry was positive correlated with anxiety symptoms (*r*=.27, *p*=.02), but not depression symptoms (*r*=.13, *p*=.26).

Whole-Brain Regression

In the regression model where both rumination (RRS) and worry (PSWQ) were covariates of interest (i.e., shared neural processes model), whole-brain results controlling for symptom severity (HAMA, HAMD) indicated that more rumination and worry were associated with greater positive functional connectivity between left amygdala and a large region (peak [−44, 16, 14], k=572 voxels, z=4.25, volume=4,576 mm^3, p< 0.001) primarily composed of left middle frontal gyrus (k=354 voxels) (i.e., DLPFC) extending to the triangular portion of the left inferior frontal gyrus (IGF; k=130 voxels). To illustrate the relationship for worry (*r*=.46) and rumination (*r*=.27) as one construct, see scatterplot (Figure 1). Additionally, post-hoc analyses testing for potential sex differences showed no main effect of sex or interactions between sex and PSWQ or RRS (all *p*s ≥.07).

In the regression model examining unique rsFC correlates of worry (PSWQ), whole brain regression analyses controlling for rumination (RRS) and symptom severity (HAMA, HAMD) revealed more worry (PSWQ) was associated with more negative functional connectivity between right amygdala and a cluster (peak [−12, −62, 26], k=828 voxels, z=4.27, volume=6,624 mm^3, p<0.001) primarily composed of left precuneus (k=249 voxels) extending to right precuneus (k=219 voxels) and left median cingulate and paracingulate gyri (k=111 voxels). For depiction of the association with worry (*r*=−.52), see scatterplot (Figure 2). A similar finding was identified with left amygdala as the seed region, wherein greater PSWQ was associated with greater negative functional connectivity between left amygdala and a cluster (peak [2, −42, 48], k=311 voxels, z=3.92, volume=2,488 mm^3,

p<0.001) primarily composed of bilateral precuneus and left median cingulate and paracingulate gyri; however, the association was at a non-significant trend level (i.e., α<0.03 and voxel level p<0.001) and the number of contiguous voxels was less than the 390 threshold for significance. Post-hoc analyses indicated that patient sex, either by itself or interaction with PSWQ, was not significantly associated right amygdala-precuneus rsFC or left amygdala-precuneus rsFC (all *ps* ≥ .15).

Finally, regression models examining unique rsFC correlates of rumination, controlling for PSWQ and symptoms, did not yield any significant patterns of rsFC for any *a priori* seed region.

Discussion

The current study is the first to our knowledge to examine rsFC correlates of rumination and worry in a transdiagnostic sample of patients with internalizing psychopathologies. Whole brain regression results, controlling for symptom severity, revealed more rumination and worry were associated with more positive rsFC between the amygdala and a cluster comprised of prefrontal regions implicated in the executive control network. Additionally, greater worry, but not rumination, was uniquely associated with more negative rsFC between the amygdala and a DMN cluster encompassing precuneus. Post-hoc analysis indicated sex did not interact with findings. Results provide preliminary evidence of shared and unique patterns of rsFC that may support repetitive negative thinking (RNT) in internalizing psychopathologies.

Evidence of both shared and unique correlates of RNT are consistent with hypotheses though significant findings were limited to when the amygdala was used as a seed region, a structure central to emotion processing, the mediation of fear responses (LeDoux, 2000), and emotional arousal (Phelps & LeDoux, 2005). Specifically, more rumination and worry were associated with greater positive rsFC between the left amygdala a cluster of prefrontal regions implicated in the executive control network, including the DLPFC and IFG. The DLPFC and IFG play important roles in top-down functions such as emotion regulation and executive processes that support regulation and other goal-oriented behavior (Banich, 2009; Disner et al., 2011; Goghari & MacDonald, 2009; Miyake & Friedman, 2012; Swick et al., 2008).

The finding that greater rumination and worry corresponded with increased amygdala-DLPFC/IFG connectivity suggests over-engagement of the executive control network may underlie RNT, regardless of content. Findings are in keeping with cognitive models of rumination and worry that posit impairment in executive and cognitive processes underlie RNT (Beckwé et al., 2014; Disner et al., 2011; Yang et al., 2017). Furthermore, findings are consistent with contemporary models that suggest RNT is an emotion regulation strategy deployed in response to emotional distress to avoid or suppress emotional experiences (Borkovec et al., 2004; Mennin et al., 2002). Thus, increased affective-executive control network functional connectivity may be indicative of increased deployment of cognitive control to engage in RNT and attempts to suppress emotional response. However, it is also possible that the relationship between RNT and affective-executive rsFC is bidirectional

such that increased RNT may also lead to increased regulatory cross-talk between affective and executive networks in the attempt to modulate RNT. While further study is necessary to clarify the mechanism of this relationship, results suggest interaction between affective and executive control networks underlies rumination and worry as a unitary construct.

When examining rumination and worry separately, significant findings were detected for worry such that more worry corresponded to greater negative rsFC between the right amygdala and a cluster of regions implicated in the DMN, including bilateral precuneus. The precuneus plays an important role in integrating internal, self-generated information and externally driven information (for review see Cavanna & Trimble, 2006), and, indeed, is proposed to play a central role in mediating self-referential thought as part of the DMN (Fransson & Marrelec, 2008). In healthy participants the amygdala has been shown to be negatively coupled with precuneus during rest (Roy et al., 2009) indicating down-regulation of internal negative state. Accordingly, evidence that more worry in patients corresponded with greater negative amygdala-precuneus functional connectivity suggests a pattern that represents enhanced modulation of internal state or increased self-related processing.

In contrast to our hypothesis, there was no evidence of rsFC unique to rumination. Although the lack of an affective network finding is consistent with previous rsFC studies of rumination that utilized amygdala as a seed region and reported null effects (Peters et al., 2016; Satyshur et al., 2018), we expected rumination to involve the DMN. Also, it is surprising that significant rsFC findings were limited to amygdala as the seed region, rather than the PCC, whose role in RNT has been implicated in a recent meta-analysis (Makovac et al., 2020). It is possible that our patient sample contributed to limited or null results. Although the study was in accordance with a transdiagnostic design, the majority of patients had an anxiety disorder and comorbid anxiety was prevalent in patients with principal depression, which may relate to the challenge of recruiting un-medicated individuals with depression. Thus, the preponderance of anxiety may have resulted in higher levels of worry than rumination in the current sample, as seen in Table 2, which may have obscured distinct rsFC correlates of rumination. Interestingly, the only other study to-date to examine unique rsFC correlates of RNT in a sample which excluded patients with current depression also failed to detect unique rsFC correlates of rumination (Andreescu et al., 2015). Consequently, findings may not generalize to a depression-only patient sample or samples with higher levels of rumination.

Other limitations include the modest sample size that mostly comprised females, which may have precluded our ability to detect sex effects. Therefore, it will be important to replicate results in a larger sample balanced on sex. Also, we did not obtain any information regarding what participants were thinking about during the resting period. It is possible that individuals who habitually engage in greater rumination and worry automatically engage in other forms of RNT (e.g., idiosyncratic concerns) during rest. A better understanding of what participants think about during an unstructured rest period would aid in the interpretation of current findings. We focused on certain networks, therefore, we cannot rule out the possibility that significant findings may be observed in other networks. Finally, as is conventional, the amygdala was treated as a unitary construct, which may have reduced our ability to detect other rsFC correlates of RNT that are specific to amygdala subdivisions

(Roy et al., 2009). For example, emerging research highlights the role of the bed nucleus of the stria terminalis (BNST), a subdivision of the extended amygdala (Alheid & Heimer, 1988), in anticipating unpredictable threat (Avery et al., 2016), suggesting that this specific subdivision may play a role in RNT. Indeed, as task-based functional connectivity of the BNST has been observed to correlate with both rumination and worry (Naaz et al., 2018), future studies examining rsFC correlates of RNT may benefit from examining the role of this specific structure.

Conclusion

Despite limitations, preliminary results suggest there are both shared and unique patterns of rsFC that correlate with rumination and worry in internalizing disorders. Specifically, increased positive amygdala-executive rsFC may support RNT more broadly, whereas greater negative amygdala-DMN rsFC may be specific to worry. Evidence of shared and distinct neural correlates of rumination and worry dovetails nicely with previous studies that have shown that both the shared variance of RNT as well as the unique variance of rumination and worry relate to depression and anxiety (McEvoy & Brans, 2013; Spinhoven et al., 2015; Topper et al., 2014). Findings build upon the existing body of literature by highlighting rsFC correlates of rumination and worry, which have implications for neuromodulation techniques, particularly those that target prefrontal areas to reduce symptom severity (Salomons et al., 2014). Given the role of rumination and worry in the maintenance of internalizing disorders (Ehring & Watkins, 2008), results suggest successful neuromodulation or rumination-focused interventions (e.g., Watkins et al., 2007) may reduce RNT by modulating rsFC of the affective network, thereby highlighting this intrinsic network as a potential novel target for clinical intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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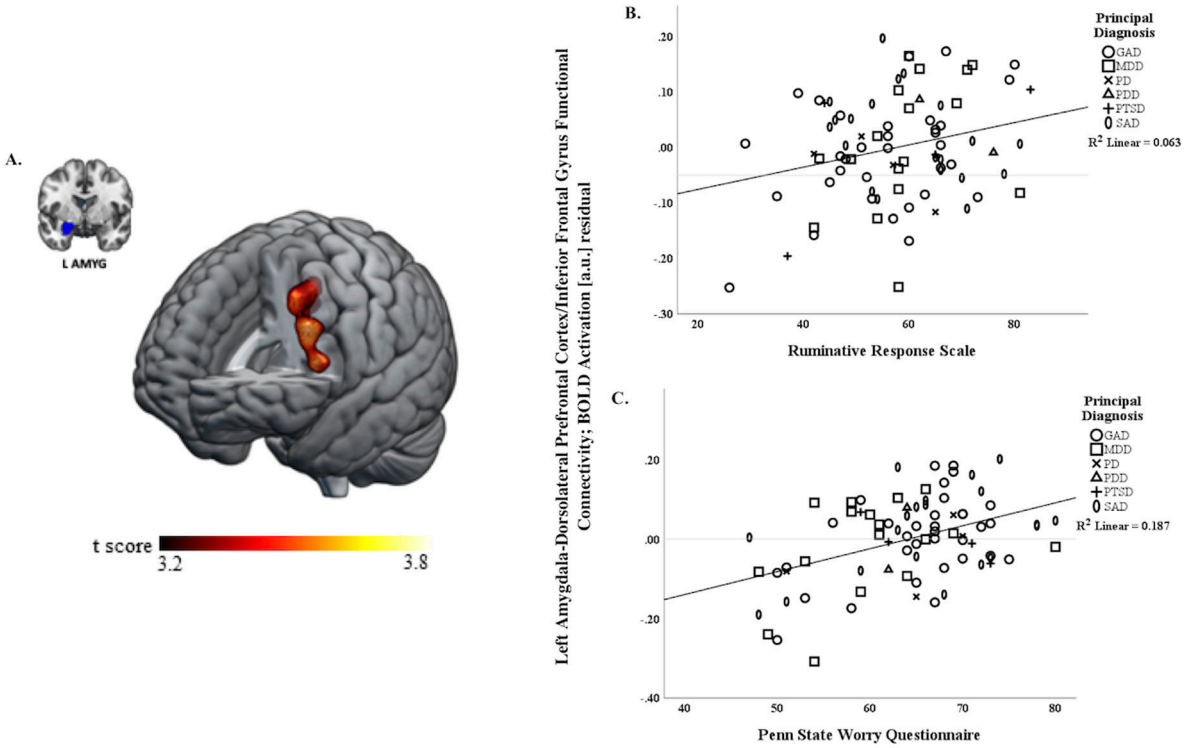

Figure 1.

A) Whole-brain analysis of covariance with rumination assessed with the Ruminative Response Scale (RRS) and worry assessed with the Penn State Worry Questionnaire (PSWQ) as covariates of interest showing left amygdala-left dorsolateral prefrontal cortex extending to left inferior frontal gyrus (DLPFC/IFG) parameter estimates of functional connectivity, controlling for symptom severity with the Hamilton Depression Rating scale (HAMD) and Hamilton Anxiety Rating scale (HAMA) on a statistical t-map at $p<0.001$. B) Scatterplot of regression analyses depicting extracted parameter estimates of left amygdala-DLPFC/IFG and relationship to RRS, controlling for HAMA and HAMD, illustrating greater connectivity is associated with more rumination (higher RRS total scores). C) Scatterplot of regression analyses depicting extracted parameter estimates of left amygdala-DLPFC/IFG and relationship to PSWQ, controlling for HAMA and HAMD, showing greater connectivity is associated with more worry (higher PSWQ total scores).

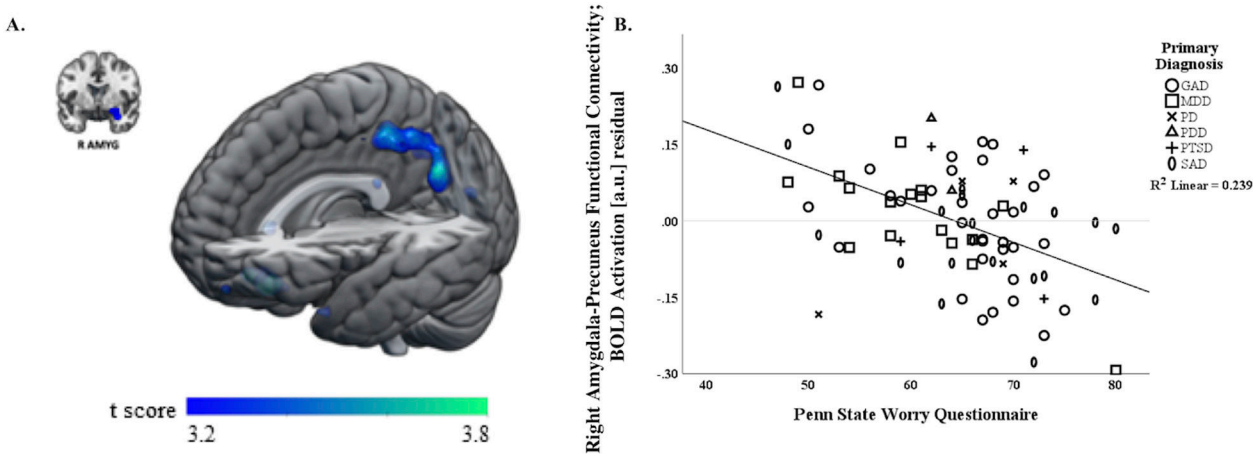

Figure 2.

A) Whole-brain analysis of covariance with worry assessed with the Penn State Worry Questionnaire (PSWQ) as the covariate of interest controlling for rumination indexed with the Ruminative Response scale (RRS) and symptom severity assessed with the Hamilton Anxiety Rating Scale (HAMA) and Hamilton Depression Rating scale (HAMD), showing right amygdala-precuneus parameter estimates of functional connectivity on a statistical t-map at $p<0.001$. B) Scatter plot of the regression analyses depicting extracted parameter estimates of right amygdala-precuneus functional connectivity, controlling for rumination (RRS) and symptom severity (HAMA, HAMD), illustrating more negative connectivity is associated with more worry (higher PSWQ total scores).

Note: circles = principal generalized anxiety disorder, squares = principal major depressive disorder, x's = principal panic disorder, triangles = principal persistent depressive disorder, crosses = posttraumatic stress disorder, ellipses = principal social anxiety disorder.

Table 1.

Principal and comorbid diagnoses.

	Count	Percentage
PRINCIPAL DIAGNOSIS		
General anxiety disorder	33	41.25
Social anxiety disorder	20	25.00
Major depressive disorder	17	21.25
Panic disorder	4	5.00
Posttraumatic stress disorder	4	5.00
Persistent depressive disorder	2	2.50
COMORBID DIAGNOSES		
Social anxiety disorder	29	36.30
Major depressive disorder	27	33.80
General anxiety disorder	25	31.30
Panic disorder	16	20.00
Specific phobia	12	15.00
Persistent depressive disorder	11	13.80
Posttraumatic stress disorder	7	8.80
Agoraphobia	5	6.30
Alcohol abuse	2	2.50
Obsessive compulsive disorder	2	2.50
Two or more concurrent diagnoses	65	81.25

Table 2.

Demographics and clinical characteristics.

Total Participants (*n*=80)			
	Mean	**Standard Deviation**	**Range**
DEMOGRAPHIC MEASURES			
Age (years)	26.93	7.90	18 – 50
Education (years)	16.26	2.94	12 – 26
CLINICAL MEASURES			
DASS-21	31.90	7.25	22 – 55
HAMA	17.13	6.64	6 – 41
HAMD	12.15	4.30	4 – 23
PSWQ	64.30	7.89	47 – 80
RRS	57.76	12.19	26 – 83
	Count	**Percentage**	
SEX			
Male	25	31.25	
Female	55	68.75	
HISPANIC ORIGIN			
Hispanic or Latino	15	18.75	
Not Hispanic or Latino	65	81.25	
RACE/ETHNICITY			
White	45	56.25	
Black	15	18.75	
Asian	12	15.00	
American Indian or Alaskan Native	3	3.75	
More than one race	1	1.25	
Other	4	5.00	

Note: DASS-21 = Depression, Anxiety, and Stress Scale; HAMA = Hamilton Anxiety Rating Scale; HAMD = Hamilton Depression Rating Scale; PSWQ = Penn State Worry Questionnaire; RRS = Ruminative Response Scale.