



Neural signal variability relates to maladaptive rumination in depression

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ABSTRACT

Rumination is a common feature of depression and predicts the onset and maintenance of depressive episodes. Maladaptive and adaptive subtypes of rumination contribute to distinct outcomes, with brooding worsening negative mood and reflection related to fewer depression symptoms in healthy populations. Neuroimaging studies have implicated several cortical midline and lateral prefrontal brain regions in rumination. Recent research indicates that blood oxygen level-dependent (BOLD) signal variability may be a novel predictor of cognitive flexibility. However, no prior studies have investigated whether brooding and reflection are associated with distinct patterns of BOLD signal variability in depression. We collected resting-state fMRI data for 79 women with different depression histories: no history, past history, and current depression. We examined differences in BOLD signal variability (BOLD_{SD}) related to rumination subtypes for the following regions of interest previously implicated in rumination: amygdala, medial prefrontal, anterior cingulate, posterior cingulate, and dorsolateral prefrontal cortices (dlPFC). Rumination subtype was associated with BOLD_{SD} in the dlPFC, with greater levels of brooding associated with lower BOLD_{SD} in the dlPFC, even after controlling for depression severity. Depression history was related to BOLD_{SD} in the dlPFC, with reduced BOLD_{SD} in those with current depression versus no history of depression. These findings provide a novel demonstration of the neural circuitry associated with maladaptive rumination in depression and implicate decreased prefrontal neural signal variability in the pathophysiology of depression.

1. Introduction

Engaging in rumination, consisting of a repetitive and passive focus on symptoms of distress and negative thoughts about oneself, is a common feature of depression associated with the onset and maintenance of depressive episodes (Just and Alloy, 1997; McLaughlin and Nolen-Hoeksema, 2011; Nolen-Hoeksema et al., 2008; Whisman et al., 2020). More frequent rumination also predicts poorer outcomes in psychotherapy and greater risk for relapse in depressive disorders (Blatt et al., 2010; Figueroa et al., 2015, 2019; Michalak et al., 2011). Treatments targeting ruminative thought patterns have shown some promise in reducing depressive symptoms (Watkins, 2015 for review). However, more research is necessary to understand the neural correlates of rumination and identify biomarkers that could help inform new treatment targets for depression.

Behavioral research indicates that rumination can be subdivided into

maladaptive and more adaptive components (Trapnell and Campbell, 1999; Treynor et al., 2003; Watkins, 2008). Specifically, a factor analytic study of the Ruminative Responses Scale (RRS) identified two rumination subtypes, including brooding and reflection (Treynor et al., 2003). Treynor et al. (2003) defined brooding as the passive comparison of one's current situation with an unattained standard, and reflection as the process of consciously turning inward to engage in problem solving about one's mood. Several studies have revealed that brooding is associated with depression severity (Nolen-Hoeksema et al., 2008; Pedersen et al., 2022; Satyshur et al., 2018; Treynor et al., 2003) and other negative consequences in depressed and healthy populations (Duque et al., 2014; Joormann et al., 2006; Kim and Kang, 2022; Miranda and Nolen-Hoeksema, 2007; Owens and Gibb, 2017; Sanchez-Lopez et al., 2019; Surrence et al., 2009). For example, greater levels of brooding have been associated with current depressive symptoms and increased depressive symptoms over time (Treynor et al., 2003). Studies also

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indicate that individuals who engage in brooding have increased attention to negative information and increased suicidal ideation (Duque et al., 2014; Joormann et al., 2006; Miranda and Nolen-Hoeksema, 2007; Owens and Gibb, 2017; Sanchez-Lopez et al., 2019; Surrence et al., 2009). In contrast to brooding, research in healthy populations indicates that reflective rumination may have beneficial effects on cognition, mood, and well-being (Alleva et al., 2014; Bucknell et al., 2022; Joireman et al., 2002; Kross et al., 2005; Mori and Tanno, 2015; Shrimpton et al., 2017; Verhaeghen et al., 2014). A longitudinal study in a community sample also revealed an association between reflection and fewer long-term depressive symptoms (Trenor et al., 2003). Further, other studies have reported relationships between reflection and active coping strategies, whereas brooding was related to passive coping in non-clinical populations (Burwell and Shirk, 2007; Marroquín et al., 2010). However, these findings of the positive aspects of reflection in healthy and community samples may not apply to depressed populations due to the limited range of depressive symptoms. For example, studies suggest that reflection may have negative effects in depressed populations, especially when it contributes to further brooding or global rumination (Joormann et al., 2010; Surrence et al., 2009; Tang et al., 2021). In addition, more recent longitudinal data indicates that reflective rumination relates to later onset of depression symptoms in females (Dawson et al., 2022). Together, prior research has provided some support for distinct relationships between these rumination subtypes and depressive symptoms. However, fewer studies have examined whether these rumination subtypes are associated with different neural mechanisms across depressed and non-depressed populations.

Previous neuroimaging research has revealed altered activity and connectivity in cortical midline structures, lateral prefrontal cortex, and subcortical regions during rumination. Task-based neuroimaging studies have shown greater activity and connectivity of the subgenual anterior cingulate cortex (sgACC), medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), dorsolateral prefrontal cortex (dlPFC), and amygdala during rumination in healthy and depressed populations (Burkhouse et al., 2017; Cooney et al., 2010; Kaiser et al., 2016, 2018; Li et al., 2017; Lydon-Staley et al., 2019; Makovac et al., 2020; Zhang et al., 2020; Zhou et al., 2020). For example, a recent neuroimaging meta-analysis of rumination and self-related thought paradigms in healthy participants revealed increased activity in brain regions within the default mode network (DMN), including the mPFC and PCC (Zhou et al., 2020). These findings for rumination align with previous research implicating the DMN more generally in self-related thought (Buckner et al., 2008; Gusnard et al., 2001; Qin and Northoff, 2011; Whitfield-Gabrieli et al., 2011). In another study, adults with depression exhibited elevated activity in sgACC, mPFC, PCC, and dlPFC during a rumination condition when compared with healthy controls (Cooney et al., 2010). In terms of functional connectivity, a separate study found that during a sad mood induction participants with greater connectivity between DMN and frontoparietal network regions (including dlPFC) were more likely to experience high levels of repetitive negative thought in daily life (Lydon-Staley et al., 2019). Considering the role of the dlPFC in the top-down regulation of emotion and cognitive control (Buhle et al., 2014; Cole et al., 2014; Dosenbach et al., 2007; Frank et al., 2014; Kohn et al., 2014; Ochsner and Gross, 2008; Vincent et al., 2008), such aberrant connectivity with DMN regions may impair the regulation of negative emotions and the ability to shift away from ruminative thought patterns in depression (Holtzheimer and Mayberg, 2011; Koster et al., 2011). In addition, resting-state neuroimaging studies have also reported correlations between functional connectivity within the DMN and rumination in individuals with depression, for both brooding and reflection rumination (Berman et al., 2011; Hamilton et al., 2011b; Kaiser et al., 2018; Satyshur et al., 2018). In sum, these studies identified associations between rumination and alterations in specific brain regions using primarily average blood oxygen level-dependent (BOLD) activation and functional connectivity measures in healthy and depressed populations. However, no studies to our knowledge have

investigated whether brooding and reflection rumination are associated with distinct patterns of BOLD signal variability in these same DMN, lateral prefrontal, and subcortical brain regions in depression.

Recent research indicates that BOLD signal variability may contribute to cognitive flexibility and adaptive behavior, with variability generally decreasing with age (Beck et al., 2008; Easson and McIntosh, 2019; Garrett et al., 2011, 2013b; Nomi et al., 2017; Waschke et al., 2021). Other theories suggest that an optimal amount of neural variability, including variation in the BOLD signal, is crucial for network integration and shifting between brain networks or mental states (Beck et al., 2008; Garrett et al., 2018). Common measures of BOLD signal variability include the standard deviation of the BOLD signal (BOLD_{SD}) and amplitude low frequency fluctuations (ALFF), and are thought to contribute to more efficient neuronal functioning and may reflect coherent communication between brain regions (Garrett et al., 2013b). Using task-based and resting-state fMRI in depressed populations, patterns of reduced BOLD signal variability have been reported in the same brain regions and networks implicated in rumination. For example, one study found that individuals with melancholic depression exhibited lower BOLD_{SD} in the mPFC while freely viewing a negative emotional film clip (Guo et al., 2015). Other resting-state fMRI studies have reported reduced ALFF in the mPFC, PCC, and dlPFC in individuals with major depressive disorder as compared with non-depressed controls (Song et al., 2017; Wang et al., 2012; Zhang et al., 2019; Zheng et al., 2020). Conversely, several studies demonstrate that greater BOLD signal variability is related to enhanced cognitive flexibility and adaptive cognition (Fujino et al., 2017; Garrett et al., 2013b; Waschke et al., 2021). Considering the proposed relationship between BOLD signal variability and adaptive cognition as well as network integration, it is possible that lower BOLD signal variability in these DMN and lateral prefrontal brain regions could contribute to maladaptive forms of rumination in depression. However, given that no studies to our knowledge have directly tested this hypothesis, it remains unclear whether resting-state BOLD signal variability would be associated with rumination in depression. Further, studies in healthy populations indicate that measures of BOLD signal variability may be distinct from other functional and structural imaging methods (Garrett et al., 2010, 2011; Guitart-Masip et al., 2016; Pur et al., 2019). For example, using the same fMRI task, researchers found that age was correlated with changes in the activity of different brain regions when using BOLD signal variability as compared with the average BOLD signal (Garrett et al., 2010). Other studies have shown that associations between age and BOLD signal variability remain significant after controlling for gray matter volume (Guitart-Masip et al., 2016; Pur et al., 2019). Together, these differences between neuroimaging measures suggest that examining resting-state BOLD signal variability in relation to rumination in depression may provide a unique contribution to the literature.

In the present study, we investigated the relationship between brooding and reflection rumination and resting-state BOLD_{SD} in a sample of women with different depression histories and symptom severities. First, we hypothesized that brooding and reflection rumination would be associated with distinct patterns of BOLD_{SD} in brain regions of interest (ROIs) previously implicated in rumination. Second, we predicted that BOLD_{SD} in these ROIs would be related to depression history. In particular, we expected that brooding rumination and depression would be associated with reduced BOLD_{SD}.

2. Material and methods

2.1. Participants and procedures

Participants were women ($n = 85$) who were recruited as part of a larger NIH funded study examining the effects of cortisol on cognitive and neural function in depression (Abercrombie et al., 2018; Gaffey et al., 2019; Rivera-Bonet et al., 2021; see Supplementary Materials for additional detail). Only women were recruited for the larger NIH study

due to the differential effects of cortisol on brain activity and negative memory bias in women versus men. Full neuroimaging data from the placebo day used in the current study were available for 79 participants, with ages ranging from 18 to 45 ($M_{age} = 27.6$, $SD_{age} = 7.0$). When participants were asked on each of the first and second visits what they thought had been administered, they did not perform above chance levels in distinguishing between CORT and placebo. Specifically, more than half of participants said they did not know what was administered (60% visit 1, 67% visit 2), and accuracies for participants that guessed were 52% for visit 1 and 38% for visit 2.

Participants were categorized into three separate groups based on their depression history and severity: (i) no history of depression ($n = 30$; NoDep); (ii) history of depression, but not currently depressed ($n = 15$; PastDep); and (iii) currently depressed, meeting the diagnostic criteria for a DSM-5 Depressive Disorder ($n = 34$; CurrentDep). With the exception of one subject who received a diagnosis of Social Phobia in partial remission during the SCID interview, participants in the NoDep group did not present with any other psychiatric conditions. See Table 1 for detailed demographic and clinical information.

All participants were screened for psychopathology using the Structured Clinical Interview for the DSM-IV, modified to assess DSM-5 criteria (SCID-I/P for DSM-IV-TR, First et al., 2002). Participants were not using antidepressants, other psychotropic medications, or illicit drugs at the time of the participation in the study. It is important to mention that participants did not receive psychotherapeutic treatment as part of this study nor was psychotherapy an exclusionary criterion. For a detailed description of exclusion criteria see Supplementary Materials.

Participants were recruited from the Madison, WI area via advertisements sent to counseling centers and clinics as well as paper and digital flyers posted at UW-Madison in the community. Participants provided written informed consent in accordance with the University of Wisconsin Health Sciences Institutional Review Board and were paid for their participation.

2.2. Rumination measure

We measured reflection and brooding rumination subtypes using the

Table 1
Demographic and clinical characteristics by depression group.

	NoDep ($n = 30$)	PastDep ($n = 15$)	CurrentDep ($n = 34$)
Age	27.1 (7.6)	28.0 (5.8)	27.9 (7.1)
Education Level^a			
High school diploma/ equivalent	0	1	0
Some college, no degree	12	4	10
Associate's degree	1	1	1
Bachelor's degree	7	6	11
Master's degree	8	3	10
Doctoral degree	2	0	2
Race^a			
White	22	13	25
Asian	5	2	6
African American	3	0	1
Unknown	0	0	2
BDI-II^b	0.9 (1.5)	1.3 (2.2)	20.3 (10.8)*
Reflection^c	9.7 (3.5)	11.3 (3.3)	14.2 (3.7)
Brooding^c	8.0 (1.8)	10.1 (2.6)	13.9 (3.7)

Notes.

^a There were no significant group differences in education level ($\chi^2(10) = 7.48$, $p > .6$) or race ($\chi^2(4) = 3.32$, $p > .5$).

^b BDI-II = Beck Depression Inventory-II; *expected group differences were found for depression severity ($F_{2,76} = 68.69$, $p < .001$).

^c Reflection and brooding rumination scores were derived from the Ruminative Responses Scale (Treyner et al., 2003); Reflection and brooding scores ranged from 6 to 20 across the sample.

22-item RRS (Treyner et al., 2003). An example item for brooding is “Think about a recent situation, wishing it had gone better” and for reflection an example item is “Go someplace alone to think about your feelings”. Participants rated their frequency of each item on a scale ranging from 1 (almost never) to 4 (almost always). We calculated scores separately for brooding and reflection rumination by summing up the responses for each subscale for each participant.

2.3. Depression measure

We assessed depression severity for all participants using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996). The BDI-II is 21-item self-report inventory used to measure depression-related symptom severity during the past two weeks. The BDI-II score collected during the placebo day fMRI scan visit was used for all analyses.

2.4. fMRI data acquisition

All participants were scanned using a 3T GE MRI scanner (Discovery MRI 750; GE Medical Systems, Waukesha, WI) equipped with an 8-channel radiofrequency coil array (GE Healthcare, Waukesha, WI). The resting-state fMRI data were collected using T2*-weighted Echo Planar Imaging (EPI) sequence (TR/TE/FA: 2150 ms/22 ms/79°, matrix: 64 × 64, FOV: 22.4 cm, slice thickness: 3.5 mm, voxel size: 3.5 mm × 3.5 mm × 3.5 mm, slices: 40 sagittal) using thin slices and short echo time in order to minimize signal dropout in the ventromedial prefrontal cortex. Each participant was instructed during the resting-state scan (~10 min) to remain “calm, still, and awake” with their eyes open fixating on a cross back-projected onto a screen via an LCD projector (Avotec, Stuart, FL). High-resolution T1-weighted structural imaging data were acquired using a weighted BRAVO pulse sequence (TI: 450 ms, TR/TE/flip angle (FA): 8.16 ms/3.2 ms/12°, matrix: 256 × 256 × 160, field of view (FOV): 215.6 mm, slice thickness: 1 mm, voxel size: 1 mm × 1 mm × 1 mm, slices: 156).

2.5. Preprocessing, motion analysis, and respiration for rs-fMRI data

The resting-state fMRI data were preprocessed using FSL tools (FMRIB software library; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>), AFNI (Cox, 1996) and ANTs (<http://stnava.github.io/ANTs/>). First, the following preprocessing steps were performed using FSL MELODIC: removal of the first five volumes, interleaved slice-time correction, MCFLIRT motion correction, and spatial smoothing with a 6 mm full-width half-maximum (FWHM) Gaussian kernel.

To extract and remove noise features from the data, including motion, ICA-FIX denoising was then applied to these data (Salimi-Khorshidi et al., 2014) as is common in BOLD signal variability preprocessing (e.g., Nomi et al., 2018). See the Supplementary Methods for additional details. We also calculated average root mean squared (RMS) displacement as a summary measure of subject motion to include in all BOLD signal variability analyses as a covariate (as in Nomi et al., 2018). Note, there were no significant differences in RMS motion between the three depression history groups ($F_{2,76} = 0.49$, $p = .61$). In addition, there was no correlation between RMS and depression symptom severity ($r = -0.14$, $p = .21$).

Subsequent preprocessing with the noise-cleaned data included realignment, co-registration to T1-weighted anatomical, normalization to MNI space using a symmetric normalization algorithm in ANTs (Avants and Gee, 2004), and despiking (3dDespike in AFNI). Cerebrospinal fluid (CSF), white matter (WM), and gray matter (GM) masks were segmented from normalized T1 anatomical images using FAST in FSL (Zhang et al., 2001). Lastly, CSF and WM masks were used in nuisance signal regression and data were bandpass filtered (0.01–0.10 Hz).

Respiratory data were acquired using a pneumatic belt placed around the participant's chest just above the level of the diaphragm (see

Supplementary Materials for further detail). Respiration volume per time (RVT) was computed as the (maxima – minima)/period at each TR (Birn et al., 2006). There were no significant group differences in RVT ($F_{2,75} = 2.77, p = .07$) and no correlation between RVT and depression symptom severity ($r = -0.11, p = .33$).

2.6. BOLD signal variability for brain regions of interest

We calculated BOLD signal variability for all subjects as the voxel-wise standard deviation (SD) of the BOLD signal across the entire time series (as in Pessin et al., 2022). We selected brain regions of interest (ROIs) based on previous neuroimaging research implicating these regions in rumination (Fox et al., 2005; Hamilton et al., 2011a; Satyshur et al., 2018). For the left and right amygdala, ACC, and PCC, we used the Harvard-Oxford atlases (Desikan et al., 2006). For the dlPFC and mPFC, we created 6-mm radius seed masks for each ROI using the MNI coordinates (Fox et al., 2005; Hamilton et al., 2011a). The average BOLD_{SD} for each seed ROI was then used in subsequent analyses for rumination subtype and depression group (see Supplementary Materials for additional detail).

2.7. Statistical analyses

2.7.1. Relationship between rumination subtypes and depression severity

To investigate the association between brooding and reflection rumination subtypes and depression severity, we conducted a linear regression analysis with brooding and reflection rumination subscale scores as the independent variables/predictors and BDI-II depression severity score as the dependent variable (version 27; SPSS/IBM, Chicago, IL).

2.7.2. Relationship between rumination subtypes and BOLD signal variability

To examine the association between rumination subtypes and BOLD signal variability, we conducted separate linear regression analyses with brooding and reflection rumination subscale scores as the independent variables/predictors and the average BOLD_{SD} for each seed ROI as the dependent variable (version 27; SPSS/IBM, Chicago, IL). RMS motion was also included as a covariate in these analyses (Martino et al., 2016; Nomi et al., 2017, 2018). Results were Bonferroni-corrected for multiple linear regression analyses (0.05/6 ROIs = $p < .008$). We also investigated whether results held when including depression severity in the model.

2.7.3. Group differences in BOLD signal variability in depression

In follow-up analyses, we investigated whether BOLD signal variability in ROIs associated with rumination subtypes was related to depression history. Specifically, we conducted separate linear regression analyses for any significant results from the rumination subtypes and BOLD signal variability analyses above with depression group (NoDep, PastDep, CurrentDep) as the independent variable/predictor and the average BOLD_{SD} for significant seed ROIs as the dependent variable (version 27; SPSS/IBM, Chicago, IL). RMS motion was also included as a covariate in these analyses (Martino et al., 2016; Nomi et al., 2017, 2018). We performed posthoc independent samples *t*-tests to examine any pairwise group differences (NoDep vs PastDep; NoDep vs CurrentDep; PastDep vs CurrentDep) for all significant results from the regression analyses with depression group. We also examined whether results remained significant when including brooding in the model.

3. Results

In the behavioral analysis, regression results revealed a significant relationship between rumination subtypes and depression severity ($F(2,76) = 31.34, p < .001, f^2 = 0.82$, Table 2). Specifically, we found that higher levels of brooding were associated with greater depression

Table 2
Multiple Linear Regression for Rumination Subtypes and Depression Severity.

Variable	Depression Severity		<i>p</i>
	<i>B</i>	SE <i>B</i>	
(Constant)	-12.15	3.29	<.001
Brooding	2.11	0.35	<.001
Reflection	-0.13	0.34	.70

Notes. Only brooding rumination was significantly associated with depression severity ($p < .001$).

severity across the sample ($t(76) = 6.03, p < .001, f^2 = 0.32$). There was no significant association between reflection and depression severity ($t(76) = -0.39, p = .70$). In addition, we found a significant correlation between rumination subtypes ($r = 0.69, p < .001$). Collinearity statistics were within normal limits for our regression model, VIF = 1.89, tolerance = 0.53.

In the analyses with rumination and BOLD signal variability, we found a significant relationship between rumination subtype and BOLD_{SD} in the dlPFC ($F(3,75) = 4.68, p = .005, f^2 = 0.19$, Table 3). Specifically, greater levels of brooding were associated with lower BOLD_{SD} in the dlPFC ($t(75) = -2.61, p = .01, f^2 = 0.09$, Fig. 1). There was also a trend-level association between rumination subtype and variability in the PCC, with greater levels of brooding related to lower BOLD_{SD} (Table S1). There were no other significant relationships between rumination subtype and BOLD_{SD} for the amygdala, ACC, or mPFC ($ps = .17-.92$).

Follow-up analyses indicated that depression history was related to BOLD_{SD} in the dlPFC ($F(2,76) = 6.73, p = .002, f^2 = 0.18$). Posthoc analyses further revealed that BOLD_{SD} was lower in those with current depression as compared with no history of depression ($t(61) = -2.44, p = .018$, Fig. 2). There were no significant differences in dlPFC BOLD_{SD} between either past depression and no history of depression groups ($p = .12$) or between past depression and current depression groups ($p = .87$).

Finally, we explored whether these findings for BOLD_{SD} in the dlPFC were driven by either depression severity or brooding rumination. When controlling for depression symptoms in the model with rumination subtypes, the relationship between brooding and lower BOLD_{SD} in the dlPFC remained significant ($t(74) = -1.99, p = .05, f^2 = 0.03$). By contrast, when brooding was included as a covariate in the model with depression history, the association between depression history and BOLD_{SD} in the dlPFC was no longer significant ($p = .16$).

4. Discussion

The aim of the current study was to investigate whether rumination subtypes were correlated with distinct patterns of resting-state BOLD signal variability in women with different depression histories and severities. We also examined whether BOLD signal variability was related to depression. We found novel relationships between both brooding and depression and BOLD_{SD} in the dlPFC.

Our findings indicated that only brooding was associated with lower BOLD_{SD}, specifically in the dlPFC. The results remained significant after

Table 3
Multiple Linear Regression for Rumination Subtypes and BOLD signal variability in dlPFC.

Variable	BOLD signal variability, dlPFC		<i>p</i>
	<i>B</i>	SE <i>B</i>	
(Constant)	20.67	2.30	<.001
Reflection	0.23	0.15	.14
Brooding	-0.42	0.16	.01
RMS	-0.06	0.02	.003

Notes. dorsolateral prefrontal cortex, dlPFC; average root mean squared motion, RMS.

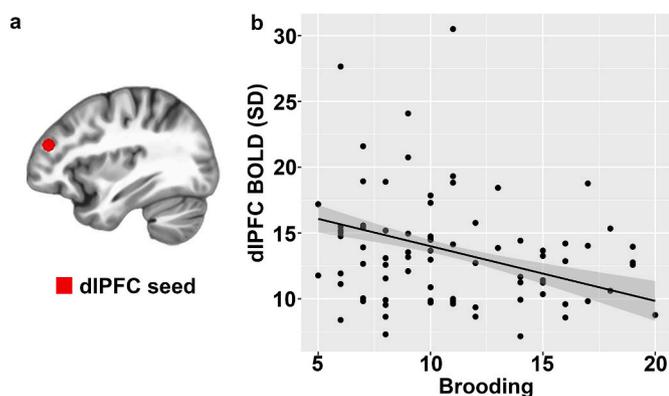


Fig. 1. Brooding is associated with BOLD signal variability in dlPFC. (a) Left dlPFC seed region of interest in red ($x = -31, y = 46, z = 23$). (b) Raw data points (in black) are plotted along with the regression line showing the relationship between brooding rumination and the standard deviation of the BOLD signal in the dlPFC across the sample. Error bands represent 1 standard error (SE) above and below the point estimate of the model (in gray).

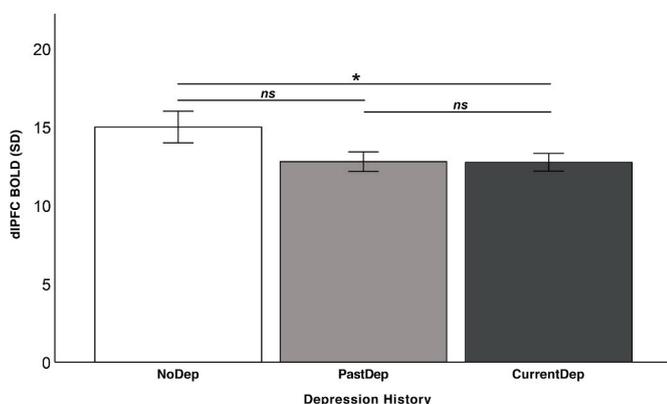


Fig. 2. Depression history is related to BOLD signal variability in dlPFC. Bar graphs plot the mean standard deviation of the BOLD signal in the left dlPFC seed during the rs-fMRI scan for NoDep (white), PastDep (light gray), and CurrentDep (dark gray) depression history groups and error bars correspond to ± 1 standard error. Lines above the bar graph show the pairwise comparisons of BOLD signal variability between depression history groups, * = $p < .05$ and ns = non-significant ($p > .05$).

controlling for depression severity, suggesting that this relationship with BOLD_{SD} may be driven more by brooding. These findings are consistent with previous research linking brooding with altered dlPFC structure and function in healthy and depressed participants (Sin et al., 2018; Stange et al., 2017; Vanderhasselt et al., 2011; Wang et al., 2015; Yuan et al., 2020). For example, studies have reported correlations among brooding, depressed mood, and gray matter volume in the dlPFC in individuals with and without depression (Sin et al., 2018; Wang et al., 2015; Yuan et al., 2020). Further, an fMRI study in healthy participants found that high brooders exhibited greater activity in dlPFC when disengaging from negative emotional stimuli (Vanderhasselt et al., 2011). This finding indicates that the dlPFC may need to work harder in individuals with higher levels of brooding to successfully shift attention away from negative emotional information. During resting-state fMRI, another study found that reduced connectivity between the dlPFC and cognitive control brain regions predicted greater brooding in individuals with remitted major depressive disorder (Stange et al., 2017). Together with the current findings, this research suggests that reduced volume, altered activity and connectivity, as well as reduced variability in dlPFC function may contribute to brooding by disrupting the ability to flexibly disengage from sad thoughts and mood in depression. More broadly, our

results may be relevant to other forms of repetitive negative thinking, including worry, which have also been associated with changes in dlPFC structure and function (Demnitz-King et al., 2021; Servaas et al., 2014; Steinfurth et al., 2017).

In our follow-up analyses with depression, we found that BOLD_{SD} in the dlPFC was significantly lower in individuals with current depression as compared with no history of depression. Our results are aligned with studies in depressed populations that have reported reduced dlPFC activity (Baxter et al., 1989; Bench et al., 1992; Davidson et al., 2009; Koenigs and Grafman, 2009; Zhong et al., 2016) and BOLD signal variability (Wang et al., 2012). One possible explanation for these findings is that reduced activity and variability in dlPFC may contribute to aberrant large-scale functional connectivity in depression. In line with this hypothesis, several studies have revealed diminished resting-state functional connectivity of dlPFC with cortical and subcortical brain regions in depression (Avissar et al., 2017; Kaiser et al., 2015; Mulders et al., 2015; Ye et al., 2012). In addition, lesion studies have found that damage that affects the dlPFC or connectivity with the dlPFC is associated with higher levels of depression (Koenigs et al., 2008; Padmanabhan et al., 2019). Given the role of the dlPFC in emotion regulation and attentional control (Buhle et al., 2014; Cole et al., 2014; Dosenbach et al., 2007; Frank et al., 2014; Kohn et al., 2014; Ochsner and Gross, 2008; Vincent et al., 2008), altered signal variability in dlPFC in depression could further impair the ability to regulate sadness or to shift attention away from current negative thoughts and emotions. However, our findings for depression did not remain significant after controlling for brooding. Additional research will be needed to characterize the relationships among dlPFC BOLD_{SD}, functional connectivity, depressive symptoms, and rumination in depression. Future research could specifically address whether the relation between dlPFC BOLD_{SD} and depression is driven by ruminative cognitive processes, such as brooding.

Besides the dlPFC, we did not find any significant relationships between brooding or reflection and BOLD_{SD} of the amygdala, ACC, or mPFC. This is inconsistent with prior task-based and resting-state fMRI studies implicating these brain regions in rumination in both healthy and depressed populations (Burkhouse et al., 2017; Cooney et al., 2010; Lydon-Staley et al., 2019; Makovac et al., 2020; Zhang et al., 2020; Zhou et al., 2020). One potential explanation for our null findings may relate to specific associations between the dlPFC and cognitive flexibility as well as BOLD signal variability. For instance, previous research has found that greater activity in the dlPFC and non-invasive stimulation to the dlPFC are associated with improved cognitive flexibility (Asgharian Asl and Vaghef, 2022; Dajani and Uddin, 2015; Metuki et al., 2012). In addition, researchers have proposed that moderate levels of BOLD signal variability may support greater cognitive flexibility (Easson and McIntosh, 2019; Garrett et al., 2011; Waschke et al., 2021). Thus, it is possible that reduced dlPFC BOLD_{SD} may be associated with brooding and depression due to deficits in cognitive flexibility. However, given that altered BOLD signal variability in amygdala, ACC, and mPFC have been reported in individuals with depression (Guo et al., 2015; Song et al., 2017; Wang et al., 2012; Zheng et al., 2020), future work in larger samples will be needed to confirm these null findings.

Our results are further relevant to clinical interventions designed to target rumination or the neural circuits associated with rumination in depression. For instance, clinical research has found that rumination-focused cognitive behavioral therapy and other treatments that focus on persistent negative thought patterns are effective in reducing depressive symptoms and ruminative cognition (Besette et al., 2020; Spinhoven et al., 2018; van Aalderen et al., 2012; Watkins and Roberts, 2020). Interestingly, there is some evidence that therapeutic interventions designed to address ruminative thought could increase dlPFC activity (Baeken et al., 2021) and normalize connectivity between DMN and cognitive control regions, including the dlPFC (Jacobs et al., 2016). Other studies using brain stimulation techniques to target the dlPFC have also shown some promise in depressed and healthy

populations. Specifically, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) applied to the dlPFC has demonstrated efficacy in attenuating depressive symptoms in individuals with depression (Avissar et al., 2017; Cash et al., 2019; Cole et al., 2020; Fox et al., 2012; Jog et al., 2019; Liston et al., 2014; Rezaei et al., 2021; Salehinejad et al., 2017; Weigand et al., 2018). In particular, it has been suggested that TMS to the dlPFC may reduce depressive symptoms by normalizing connectivity between the dlPFC and sgACC/ventral mPFC (Cash et al., 2019; Fox et al., 2012; Liston et al., 2014; Weigand et al., 2018). In addition, tDCS to the dlPFC has been shown to reduce state ruminative self-focus, primarily in healthy populations (Baeken et al., 2017; De Raedt et al., 2017; Hoebeke et al., 2021). However, future studies will be necessary to examine whether dlPFC stimulation is associated with reduced brooding and depressive symptoms and whether these reductions are mediated by the modulation of dlPFC variability and connectivity in depression.

There are some important limitations in the present study to consider. First, although the sample size was relatively large for a study with a clinical population, the smaller sample size and unequal number of participants in each depression group could influence the reproducibility of our findings (Marek et al., 2022). Thus, these results should be replicated in a larger sample. Second, we used one resting-state scan to calculate BOLD_{SD} as opposed to multiple scans, which could limit the reliability of our findings (Zuo et al., 2019). That being said, previous studies using BOLD signal variability measures have found high test-retest reliability for both BOLD_{SD} and ALFF (Garrett et al., 2013a; Månsson et al., 2022; Zuo et al., 2010). Future research is warranted to directly investigate test-retest reliability of resting-state BOLD signal variability in depression. Third, some research suggests that the psychometrics of the RRS may differ for depressed compared to healthy individuals. For example, it may be difficult to use non-transformed rumination subtype scores, since the original analysis of brooding and reflection on the RRS forced these factors to be anticorrelated (Treyner et al., 2003). In addition, a recent factor analysis of the RRS found less evidence for a two-factor model, including reflection, in depressed participants (Whitmer and Gotlib, 2011). Given that we had individuals with current depression in our study, this may help explain why we did not find significant effects for reflection. Furthermore, experimental manipulation of rumination could provide evidence beyond relations between self-reported rumination and BOLD_{SD}. Fourth, our sample included women with moderate depression, which could limit the generalizability of our results to men or those with extremely severe depression. Further, our sample was relatively homogeneous in terms of other demographic factors, including race. Therefore, additional research including both men and women, participants of different racial and ethnic groups, as well as individuals with more severe depression will be necessary to confirm our findings.

5. Conclusion

Our findings demonstrated that self-reported brooding was associated with lower BOLD_{SD}, specifically in the dlPFC, and this result remained significant when controlling for depression severity. We also found that BOLD_{SD} in the dlPFC was lower in participants with current depression, but this effect was no longer significant when controlling for brooding. We speculate that the relationship with BOLD_{SD} in the dlPFC may be driven more by brooding than by depression symptoms, which should be addressed further in future research. Our results align with previous task-based and resting-state neuroimaging research and provide novel support for the neural correlates of maladaptive rumination in depression. Broadly, the study findings are relevant to psychotherapy and non-invasive brain stimulation approaches used to treat depression that target ruminative cognition and the neural circuits implicated in rumination.

Contributors

Carissa L. Philippi: Conceptualization, methodology, data curation, software, formal analysis, writing - original draft, writing - reviewing & editing, & supervision. Katie Leutzinger: Conceptualization, formal analysis, writing - reviewing & editing. Sally Pessin: Data curation, software, formal analysis, writing - reviewing & editing. Alexis Cassani: Writing - original draft, writing - reviewing & editing. Olivia Mikel: Writing - original draft, writing - reviewing & editing. Erin Walsh: Project administration, methodology, investigation, data curation, writing - review & editing. Roxanne M. Hoks: Project administration, methodology, investigation, data curation, writing - review & editing. Rasmus M. Birn: Methodology, investigation, data curation, writing - review & editing. Heather C. Abercrombie: Funding acquisition, methodology, investigation, data curation, writing - review & editing.

Data availability statement

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

Declaration of competing interest

The authors report no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

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