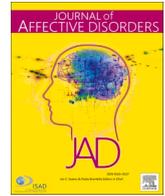




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Research paper

Rumination induction task in fMRI: Effects of rumination focused cognitive behavioral therapy and stability in youth

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ABSTRACT

Background: Rumination is implicated in the onset and maintenance of major depressive disorder (MDD). Rumination-Focused Cognitive Behavioral Therapy (RF-CBT) effectively targets rumination and may change resting-state brain connectivity and change in activation during a rumination induction task (RIT) post-intervention predicts depressive symptoms two years later. We examined brain activation changes during an RIT in adolescents with remitted MDD following RF-CBT and evaluated RIT reliability (or stability) during treatment as usual (TAU).

Method: Fifty-five adolescents ages 14–17 completed an RIT at baseline, were randomized to 10–14 sessions of RF-CBT ($n = 30$) or treatment as usual ($n = 25$) and completed an RIT at post-treatment or equivalent time delay. The RIT includes recalling negative memories (Rumination Instruction), dwelling on their meaning/consequences (Rumination Prompt), and imagining unrelated scenes and objects (Distraction). We assessed activation change in the RF-CBT group using paired-samples t -tests. We assessed reliability (or stability) via intraclass correlation coefficients (ICCs) of five rumination-related ROIs for TAU and RF-CBT separately across task blocks.

Results: Following treatment, participants receiving RF-CBT demonstrated increased activation of left precuneus during Rumination Instruction and of left angular and superior temporal gyri during Rumination Prompt blocks ($p < .01$). From baseline to post-treatment, across most ROIs and task blocks, the RF-CBT group demonstrated poor stability ($M = 0.21$, range = -0.19 – 0.69), while the TAU group demonstrated fair-to-excellent stability ($M = 0.52$, range = 0.27 – 0.86).

Conclusion: RF-CBT changes activation of rumination-related circuitry during state-induced rumination, offering exciting avenues for future interventions. The RIT has fair-to-excellent stability among individuals not explicitly treated for rumination, and as expected, RIT stability is disrupted by RF-CBT.

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Researchers have taken an increased interest in rumination or repetitive negative thinking as a transdiagnostic marker for psychopathology risk, especially for mood disorders (Ehring and Watkins, 2008; Watkins, 2008; Watkins and Roberts, 2020). Continued rumination after recovery from a major depressive episode is a significant risk factor for depression recurrence (Figueroa et al., 2019). Thus, rumination may be an important cognitive mechanism in both active and remitted psychopathology. Targeting rumination may be fruitful for enacting meaningful clinical change and reducing future psychopathology risk.

Treatments that specifically target rumination have illustrated promising short- and long-term benefits. One study found a 62% remission rate after just 12 sessions of Rumination-Focused Cognitive Behavioral Therapy (RF-CBT) in a phase II randomized controlled trial (Watkins et al., 2011). Another RF-CBT randomized controlled trial in adolescents with remitted major depressive disorder (rMDD) with pre- and post-intervention fMRI scans found reduced self-reported depression and rumination after 8 sessions (Jacobs et al., 2016). This study also showed a significant reduction in connectivity between the left posterior cingulate cortex (PCC) and the right inferior frontal gyrus (IFG) and bilateral inferior temporal gyri (ITG) during resting-state fMRI (Jacobs et al., 2016). Importantly, changes in self-reported depression and rumination were correlated with degree of change in connectivity, suggesting that differences in functioning involving the default mode network (DMN) and cognitive control network (CCN) are involved in rumination and depression. This connectivity and rumination correlation has recently been replicated in an independent sample by the same group (Langenecker et al., 2024), suggesting a common neural correlate for reductions in rumination.

In addition to resting-state fMRI, brain changes following RF-CBT in youth have also been examined in the context of an explicit and extensively validated rumination induction task. Based on findings from a cross-sectional study of adolescents with rMDD and controls using the rumination induction task (Burkhouse et al., 2017), Bessette and colleagues examined activation of two clusters, one of which was comprised of the posterior DMN, visual, and limbic regions, during rumination versus distraction conditions (Bessette et al., 2020). When comparing only baseline fMRI data across both RF-CBT and control groups, higher activation of the cluster including the posterior DMN for the rumination versus distraction contrast was associated with lower depressive symptoms at post treatment and at one- and two-year follow-up. Furthermore, across groups, greater change scores from pre- to post-treatment MRI during a rumination versus distraction contrast was associated with higher depressive symptoms at two-year follow-up. This work provides an important foundation for continuing to explore neurobiological changes that occur during induced rumination.

While these preliminary data show promise in mapping brain related changes as they relate to rumination, we must also ensure that we are using reliable measures in effort to truly move the field forward. The reliability and utility of resting-state fMRI is well established at the level of brain networks (Zuo and Xing, 2014). However, fMRI tasks have been reported to have poor reliability upon retest. A meta-analysis by Elliott and colleagues demonstrated poor reliability across a variety of tasks, including picture naming, emotion identification and matching, button pressing, working memory, episodic memory, and reward (Elliott et al., 2020). Further, when examining tasks used in large imaging cohort studies (Dunedin Study and Human Connectome Project), aggregated reliability was again typically poor. One challenge of this work is that aggregated reliability values pertain to only a small subset of fMRI tasks available in the literature. There are many potential catalysts for poor reliability in fMRI tasks. This includes time pressures in the scanner (too few events), movement within the scanner (measuring different neural systems), and physiological sources of variability (heart rate). Yet, there are other sources of potential disruption to reliability. In the context of intervention work, we would expect and intend to see pre- to post-treatment changes in the targeted process (e.g., rumination) that might drive down reliability (or more appropriately, stability). Here,

lower stability in a randomized active treatment arm acts as a therapeutic intervention manipulation check, rather than an issue inherent to the fMRI measure being used. Further, task stability, or lack thereof, may highlight mechanisms of action (and brain locations) underlying therapeutic success. It is possible to use differential reliability or stability estimates in a treatment condition compared to a time matched comparison group to dissociate 1. stability of relevant neural circuits, and 2. pathways by which treatment induces change. This highlights the potentially unique importance of understanding the test-retest reliability or stability of an fMRI task—without good reliability it cannot be considered an important target for intervention.

In contrast to the summary by Elliott et al. (2020), studies have highlighted that fMRI task reliability may be dependent on brain regions of interest and the specific tasks that are used to elicit activation within those areas. Certain brain regions may be more likely to demonstrate task reliability over time. For example, researchers have consistently found good to excellent reliability in the occipital regions across fMRI tasks (Herting et al., 2018), and a recent meta-analysis synthesized fMRI findings from brain regions implicated in rumination (Zhou et al., 2020) and found that relevant brain regions demonstrated fair to high reliability. Further, one longitudinal study found that both adolescents and adults demonstrated fair to good reliability in bilateral precuneus, left inferior and superior parietal cortices, and right angular gyrus in a rule-switch task (Koolschijn et al., 2011). The middle temporal gyrus has also shown high test-retest reliability in an emotion regulation task (Berboth et al., 2021). Other research indicates that attentional switching ability, a cognitive process implicated in rumination, has moderate to high test-retest reliability and is fairly stable (Koster et al., 2013).

Taken together, findings suggest that brain regions and cognitive processes involved in rumination have moderate to high test-retest reliability. Thus, a rumination induction fMRI task (RIT) may also have adequate test-retest reliability, particularly in the absence of intervention. Indeed, one study found that a rumination induction task yielded reproducible findings across different scanners (Chen et al., 2020). The previously highlighted study by Bessette and colleagues demonstrated medium to large correlations of brain activation across blocks within the rumination induction task among adolescents (Bessette et al., 2020). However, assessment of test-retest reliability of RITs is still needed. While work has demonstrated significant changes in resting-state functional connectivity following an intervention that targets rumination, less work has evaluated neurobiological changes in response to fMRI tasks where rumination is explicitly induced.

The present study sought to 1. evaluate change in neurobiological responses to a common rumination induction task among adolescents who received RF-CBT, and 2. examine the reliability or stability of this RIT in the group of adolescents who were not randomized to the RF-CBT arm of this trial. While our approach can be considered an examination of test-retest reliability, stability is a more accurate term given the long duration between “tests”. These data are derived from a larger randomized controlled trial investigating the utility of RF-CBT for reducing rumination in a sample of adolescents with remitted MDD and high levels of self-reported rumination (to reduce likelihood of depression recurrence; Langenecker et al., 2024). Based on a prior meta-analysis of brain regions associated with rumination (Zhou et al., 2020), we specifically examined changes and stability in five regions of interest (ROIs): 1. left precuneus, 2. left superior temporal gyrus (STG), 3. left anterior cingulate cortex (ACC) and paracingulate, 4. left angular gyrus, and 5. left inferior frontal gyrus (IFG). These regions are involved in self-referential processing, memory retrieval, and emotional processing, which are all hypothesized to play a role in the ruminative habit (Andrews-Hanna et al., 2010; Frith et al., 2003; Nolen-Hoeksema, 1991). In this randomized control trial, participants completed MRI scanning and were either randomized to 10–14 sessions of RF-CBT or Treatment as Usual (TAU; Roberts et al., 2021). Participants then completed a second, post-intervention MRI. We anticipated that the RF-CBT group would demonstrate significant decrease in activation of these

five ROIs during the rumination induction task, and thus possibly poor stability between Time 1 and Time 2 fMRI. Conversely, we expected brain activation during the rumination induction task would show high stability between Time 1 and Time 2 in the TAU group. An earlier version of this manuscript was previously published as a preprint on medRxiv (Westlund Schreiner et al., 2023a).

1. Method

1.1. Participants

Data were collected as part of a larger RCT (Langenecker et al., 2024; Roberts et al., 2021; NCT03859297). We recruited adolescents with remitted major depressive disorder from Salt Lake City and surrounding areas through Facebook, radio, and community advertisements. Eligible participants were 14–17 years of age with a history of major depressive disorder (currently either in full or partial remission). Exclusion criteria consisted of lifetime history of mania or psychosis, suicide attempt in the past 6 months, current active suicidal plan or intent, a raw score above 45 on the Children's Depression Rating Scale-Revised (CDRS-R; Poznanski and Mokros, 1996), developmental disorders such as autism spectrum disorder and pervasive developmental delay, and MRI contraindications. As this was a clinical trial, exclusion criteria also included any CBT in the past six months and changes in psychiatric medications within 6 weeks prior to enrollment (with no dosage change in the prior 4 weeks). All participants were encouraged to maintain their medication and non-CBT treatment as usual for the duration of the study.

1.2. Measures

1.2.1. Clinical assessment

Participants and at least one parent or guardian completed a clinical assessment with a trained clinician. Assessments included the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997) to determine current and past psychopathology, and the CDRS-R to determine current depressive symptoms.

1.2.2. Neuroimaging

Participants completed MRI scanning at the Imaging and Neurosciences Center at the University of Utah, where we acquired simultaneous-multi-slice data (Feinberg and Setsompop, 2013). The scanning protocol included a high-resolution T1 structural image, which we used for registration of the task data. The T1 was acquired with the following parameters: field of view (FOV) = 256 mm, TE = 2500 ms, TR = 2500 ms, flip angle = 8 degrees, GeneRalized Autocalibrating Partial Parallel Acquisition (GRAPPA) acceleration factor = 2 (Griswold et al., 2002), multiband factor = 4, and voxel size = 0.8 mm isotropic.

Participants completed the Rumination Induction Task (RIT), which is a 9-min block design completed in a single run with rumination and distraction conditions. We recently published some of these data, which examined the association between brain activation and non-suicidal self-injury (Westlund Schreiner et al., 2023b). Our group has also used this task successfully with other adolescent samples (Bessette et al., 2020; Burkhouse et al., 2017). Before entering the scanner, participants are asked to generate four events from their own lives: a sad event, a frustrating event, a failure event, and a hurtful event. As these events are designed to elicit rumination, we had participants rate each event on a 9-point scale regarding how upset the event made them, both at the time it was happening, and at the current moment (1 = *Did not feel sad* and 9 = *Felt very sad*). When past or current ratings were rated as less than five, participants were encouraged to choose different memories to ensure sufficient potency to elicit rumination.

When in the scanner, participants were asked to bring one of the four memories to their mind in detail over a 25 s block (Rumination

Instruction). They were then directed to reflect on this past event using prompts over the course of 30 s (e.g., “Think about what your feelings mean”, “Think about why you reacted the way you did”, etc.; Rumination Prompt). These prompts, as well as the distraction prompts described below, were based on a well-established and extensively used experimental rumination manipulation devised by Nolen-Hoeksema and colleagues (Johnson et al., 2006; Lyubomirsky et al., 1998; Lyubomirsky and Nolen-Hoeksema, 1995, 1993; Morrow and Nolen-Hoeksema, 1990; Rusting and Nolen-Hoeksema, 1998). Following the Rumination Prompt blocks, participants were asked “How much are you focused on your feelings right now?” and “How sad do you feel right now?” using a scale of 1–5 (1 = *not focused on feelings/sad*, 5 = *very focused on feelings/sad*). This was followed by a 10–15 s block during which participants are instructed to “Rest” and then by a 30 s distraction prompt (e.g., “Think of a row of shampoo bottles”; Distraction). Participants completed ratings about how focused they were on their feelings and how sad they felt following each Distraction block. Participants completed a total of 4 repetitions of these conditions (one for each of the four negative memories generated by the participant) during the task (see Fig. 1).

1.3. Procedure

This project was approved by the Institutional Review Board at the University of Utah. Persons interested in enrollment first completed a brief phone screen to determine eligibility. If eligible, participants were scheduled for their initial visit where they completed informed written consent and assent. Following consent/assent, youth and their parent/guardian completed self-report measures and a clinical assessment with a trained independent evaluator to gather information regarding their current and past mental health symptoms. Youth participants completed the MRI scan at a separate visit, during which they completed the rumination induction task. As part of the randomized clinical trial, youth were randomized to either 10–12 sessions of RF-CBT or TAU. After completing RF-CBT (or after approximately 3–4 months for the TAU group), adolescents completed a second clinical assessment and MRI visit. Participants were compensated for their time for all non-treatment related visits.

1.4. Analyses

1.4.1. Neuroimaging preprocessing and analysis

We used tools from Anima (Voss et al., 2006) and Statistical Parametric Mapping 12 (SPM12; <https://www.fil.ion.ucl.ac.uk/spm/doc/>) for preprocessing and first- and second-level analyses. Consistent with recent work (Westlund Schreiner et al., 2023b) we completed preprocessing including echo-planar imaging (EPI) distortion correction, discarding the first 10 volumes of functional data, time-series realignment, high-resolution T1 co-registration, high-resolution T1 tissue segmentation, normalization of high-resolution and functional images to standard space (MNI), and 5 mm Gaussian smoothing. We used SPM12 to complete first-level whole-brain activation analyses with the rumination induction data. This included modeling key blocks of interest (Rumination Instruction, Rumination Prompt, and Distraction) and fixation, as well as including six motion parameters as covariates.

For second-level analyses, we created the five ROIs using the coordinates independently derived and published by Zhou and colleagues (Zhou et al., 2020; see Table 1 and Fig. 2 for ROIs and MNI coordinates). We specified a radius of 10 mm for each region except for the angular gyrus, where we used a radius of 5 mm. We used MarsBaR within SPM12 to create the ROIs and extract values for the Rumination Instruction, Rumination Prompt, and Distraction blocks for all participants' Time 1 and Time 2 data (Brett et al., 2010). For the purposes of examining change in activation in response to treatment for the RF-CBT group, we also extracted values for the Rumination-Distraction contrast, which consisted of both Rumination Instruction and Prompt blocks minus the Distraction block.

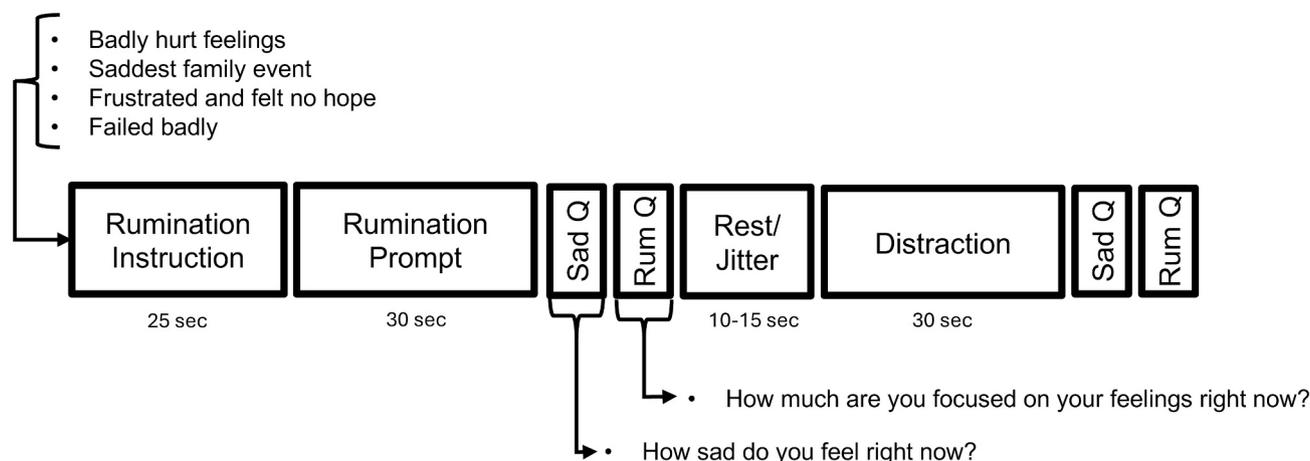


Fig. 1. Rumination Induction Task. Each full sequence completed 4 times (once for each Rumination Prompt). Each full sequence shown above is completed 4 times (once for each rumination prompt). For “Sad Q” and “Rum Q”, participants are asked to provide ratings using a response box on a scale from 1 to 5.

Table 1
Regions of interest and coordinates.

Region of Interest (ROI)	MNI Coordinates (X, Y, Z)
Left Anterior Cingulate Cortex (ACC)/Paracingulate	-2, 38, 12
Left Precuneus	-4, -58, 30
Left Superior Temporal Gyrus	-54, -24, 6
Left Angular Gyrus	-38, -70, 44
Left Inferior Frontal Gyrus and Pars Orbitalis	-30, 28, -18

1.4.2. Demographics and clinical characteristics

After we extracted the values from our five regions of interest, we combined these data with our demographic and clinical data. We used R to complete analyses, which include descriptive statistics for demographic and clinical data (R Core Team, 2022).

1.4.3. Treatment change and stability

To evaluate whether there were significant changes in brain activation during the rumination induction task following RF-CBT, we conducted paired-samples *t*-tests in the RF-CBT group. While we did not evaluate group-by-time interactions here, we do report these as exploratory analyses within the supplement. However, our group is currently conducting the R33 phase of the trial, which is designed and powered to conduct such analyses using an equivalent therapy group (Relaxation Therapy). We used the *irr* package in R to calculate intraclass correlation coefficients between the Time 1 and Time 2 data for the rumination induction task (Gamer et al., 2019; R Core Team, 2022). We

calculated ICCs under the assumption of a two-way mixed effects model (ICC(3,1); Shrout and Fleiss, 1979) using consistency in measurement (ICC(C,1)) as opposed to agreement in absolute values (McGraw and Wong, 1996) consistent with prior fMRI reliability research (Compère et al., 2021; Elliott et al., 2020; Flournoy et al., 2024; Fournier et al., 2014; Kennedy et al., 2022). We interpreted the ICC values based on previously established guidance in which ICC < 0.4 = Poor, 0.4 < ICC < 0.59 = Fair, 0.6 < ICC < 0.74 = Good, 0.75 > ICC > 1 = Excellent (Cicchetti, 1994; Cicchetti and Sparrow, 1981).

2. Results

2.1. Demographics and clinical characteristics

Fifty-five participants completed the rumination induction task at both time points. Thirty were randomized the RF-CBT condition and 25 were randomized to TAU. Table 2 provides additional information about the sample. Further information about the larger clinical trial can be found in Langenecker et al. (2024). There was no significant difference in number of days between scans for TAU (*M* = 188, *SD* = 43.3) and RF-CBT (*M* = 126, *SD* = 28.2), *t*(39.87) = -0.70, *p* = .49. Information about current psychotherapy or medication at the time of baseline for each group, in addition to TAU involvement in psychotherapy between Times 1 and 2, are shown in Supplemental Table 1.

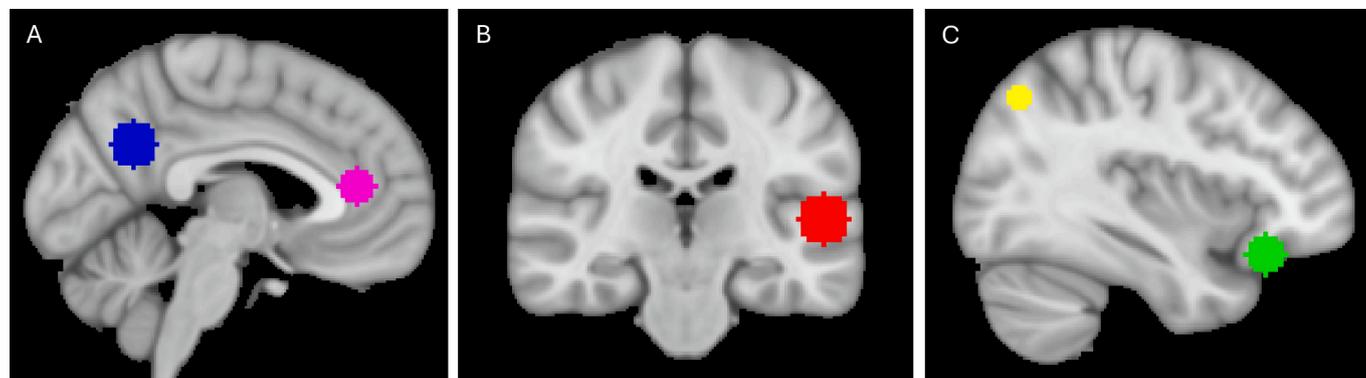


Fig. 2. Rumination-Related Regions of Interest. A) Sagittal slice depicting left precuneus (blue) and left anterior cingulate cortex (ACC)/paracingulate (fuchsia); B) Coronal slice depicting left superior temporal gyrus (red); C) Sagittal slice depicting left angular gyrus (yellow) and left inferior frontal gyrus and pars orbitalis (green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Demographic characteristics.

	TAU (N = 25)	RF-CBT (N = 30)	Overall (N = 55)
Mean age (SD)	16.1 (0.971)	15.8 (0.986)	16.0 (0.981)
Sex			
Male	8 (32.0 %)	8 (26.7 %)	16 (29.1 %)
Female	17 (68.0 %)	22 (73.3 %)	39 (70.9 %)
Gender			
Female (cisgender)	8 (32.0 %)	14 (46.7 %)	22 (40.0 %)
Male (cisgender)	2 (8.0 %)	8 (26.7 %)	10 (18.2 %)
Transgender male	1 (4.0 %)	0 (0 %)	1 (1.8 %)
Transgender female	0 (0 %)	1 (3.3 %)	1 (1.8 %)
Non-binary	2 (8.0 %)	2 (6.7 %)	4 (7.3 %)
Other	2 (8.0 %)	1 (3.3 %)	3 (5.5 %)
Missing	10 (40.0 %)	4 (13.3 %)	14 (25.5 %)
Sexuality			
Straight (heterosexual)	7 (28.0 %)	17 (56.7 %)	24 (43.6 %)
Gay	0 (0 %)	1 (3.3 %)	1 (1.8 %)
Lesbian	1 (4.0 %)	1 (3.3 %)	2 (3.6 %)
Queer	2 (8.0 %)	1 (3.3 %)	3 (5.5 %)
Pansexual	3 (12.0 %)	4 (13.3 %)	7 (12.7 %)
Asexual	1 (4.0 %)	0 (0 %)	1 (1.8 %)
Bisexual	1 (4.0 %)	2 (6.7 %)	3 (5.5 %)
Other	0 (0 %)	1 (3.3 %)	1 (1.8 %)
Missing	10 (40.0 %)	3 (10.0 %)	13 (23.6 %)
Race			
White	23 (92.0 %)	26 (86.7 %)	49 (89.1 %)
Black/African American	0 (0 %)	0 (0 %)	0 (0 %)
Asian	0 (0 %)	2 (6.7 %)	2 (3.6 %)
Native Hawaiian or Other Pacific Islander	0 (0 %)	0 (0 %)	0 (0 %)
American Indian or Alaska Native	0 (0 %)	1 (3.3 %)	1 (1.8 %)
Other	0 (0 %)	1 (3.3 %)	1 (1.8 %)
Missing	2 (8.0 %)	0 (0 %)	2 (3.6 %)
Ethnicity			
Hispanic or Latin(x)	3 (12.0 %)	5 (16.7 %)	8 (14.5 %)
Not Hispanic or Latin(x)	20 (80.0 %)	25 (83.3 %)	45 (81.8 %)
Missing	2 (8.0 %)	0 (0 %)	2 (3.6 %)
Mean Baseline CDRS Summary Score (SD)	34.5 (7.38)	35.7 (7.09)	35.2 (7.18)

CDRS = Children's Depression Rating Scale.

2.2. Rumination task manipulation check

We performed analyses to ensure that the task was eliciting the intended behavioral responses (e.g., rumination blocks will elicit feelings of sadness) and aligned with the theoretical model (e.g. focusing on feelings may engage the ROIs within the DMN). Specifically, we used two-tailed paired *t*-tests to evaluate the sadness and focus on feelings ratings that were provided following each of the rumination and distraction blocks. At baseline, sadness ratings following rumination blocks ($M = 3.88$, $SD = 0.73$) were significantly higher than distraction blocks ($M = 2.88$, $SD = 0.92$), $t(54) = 10.89$, $p < .001$. Focus on feelings ratings were also significantly higher following rumination blocks ($M = 4.04$, $SD = 0.67$) than distraction blocks ($M = 3.22$, $SD = 0.87$), $t(54) = 10.14$, $p < .001$. Similarly, at post-treatment, sadness ratings following rumination blocks ($M = 3.45$, $SD = 0.66$) were significantly higher than distraction blocks ($M = 2.59$, $SD = 0.71$), $t(54) = 12.28$, $p < .001$. Focus on feelings ratings were also significantly higher following rumination blocks ($M = 3.83$, $SD = 0.63$) than distraction blocks ($M = 3.02$, $SD = 0.85$), $t(54) = 7.90$, $p < .001$. For exploratory purposes, we examined group by time interactions for each of the four ratings. There was no significant group by time interaction on sadness ratings following distraction ($p = .91$) nor was there a main effect of group ($p = .28$) or time ($p = .05$). There was also no significant interaction on sadness ratings following rumination ($p = .27$) nor was there a main effect of group ($p = .15$). However, there was a main effect of time on sadness ratings following rumination ($p < .001$), in which ratings were lower for the second MRI scan compared to baseline. There was no significant

group by time interaction on focus on feelings ratings following distraction ($p = .61$) nor was there a main effect of group ($p = .53$) or time ($p = .13$). There was no significant interaction on focus on feelings ratings following rumination ($p = .51$) nor was there a main effect of group ($p = .60$). However, there was a main effect of time on focus on feelings ratings following rumination ($p = .02$), in which ratings were lower for the second MRI scan compared to baseline.

2.3. Brain activation change during rumination induction following RF-CBT

The RF-CBT group demonstrated significant increases in activation following treatment across multiple ROIs. During both the Rumination Instruction and Rumination Prompt blocks, post-treatment activation values were higher in the left angular gyrus, precuneus, and STG (see Table 3). When using a Bonferroni-corrected *p*-value threshold of 0.01 (accounting for five ROIs), activation differences for the left precuneus during the Rumination Instruction blocks and the left angular gyrus and superior temporal gyrus during the Rumination Prompt blocks remained significant. There were no significant changes over time for activation during the Distraction blocks. There were also no significant activation changes over time for the Rumination-Distraction contrast that withstood Bonferroni-correction.

2.4. Task stability

Task stability intraclass correlation coefficients are reported in Table 4. Consistent with our expectations the TAU group demonstrated fair to excellent stability across nearly all ROIs and task blocks. The Rumination Instruction blocks demonstrated the highest stability. During Rumination Instruction, activation of the left angular gyrus demonstrated excellent stability, followed by the left precuneus which demonstrated good stability. The remaining three ROIs demonstrated fair stability. For the Rumination Prompt and Distraction blocks, the left angular gyrus demonstrated good stability and the left precuneus demonstrated fair stability. The left ACC and paracingulate demonstrated fair stability during the Rumination Prompt and good stability during Distraction. The left STG demonstrated fair stability during the Distraction blocks and poor stability during the Rumination Prompt. The left IFG demonstrated poor stability for both Rumination Prompt and distraction blocks.

Reduced stability, potentially associated with intentional treatment change, was observed in the RF-CBT group. The poor stability in RF-CBT was observed for most ROIs and task blocks. Indeed, only the left angular gyrus and IFG showed fair stability during Rumination Instruction and the left angular gyrus showed good stability during Rumination Prompt blocks. This is consistent with our hypotheses as we anticipated that specifically targeting the ruminative habit would lead to changes in rumination related neural activation, and reductions in stability for these key regions. Supplemental Figs. 1–3 show mean activation values for each of the task blocks at the first and second scans for each of the two groups.

3. Discussion

The present study provides three encouraging and potentially provocative results. First, we provide evidence that there is acceptable fMRI stability of the rumination induction task in activation of key regions associated with rumination derived from prior empirical studies. Second, strong stability in these rumination-related regions is observed specifically among youth who did not receive a treatment that was intended to change the rumination habit. In contrast, stability was poor in those who specifically did receive a treatment developed to change the rumination habit and related brain activation. Third, activation in rumination-associated brain regions significantly increased during tasks designed to induce rumination following RF-CBT.

Table 3
Pre- versus post-treatment activation in RF-CBT Group.

Condition	ROI	Pre-RF-CBT	Post-RF-CBT	
Rumination instruction	Left ACC & Paracingulate	0.08 (0.32)	0.14 (0.34)	t(29) = -0.72, p = .48
	Left Angular Gyrus	-0.17 (1.01)	0.26 (0.85)	t(29) = -2.56, p = .02
	Left Inferior Frontal Gyrus	-0.03 (0.29)	0.52 (0.35)	t(29) = -1.31, p = .20
	Left Precuneus	0.20 (0.31)	0.49 (0.42)	t(29) = -3.32, p < .01 ^a
	Left Superior Temporal Gyrus	-0.14 (0.39)	0.11 (0.35)	t(29) = -2.36, p = .03
Rumination prompt	Left ACC & Paracingulate	0.06 (0.31)	0.11 (0.37)	t(29) = -0.63, p = .53
	Left Angular Gyrus	-0.47 (0.81)	0.04 (1.01)	t(29) = -3.86, p < .001 ^a
	Left Inferior Frontal Gyrus	0.01 (0.29)	0.11 (0.33)	t(29) = -1.58, p = .12
	Left Precuneus	0.04 (0.30)	0.26 (0.42)	t(29) = -2.43, p = .02
	Left Superior Temporal Gyrus	-0.06 (0.36)	0.21 (0.33)	t(29) = -2.92, p < .01 ^a
Distraction	Left ACC & Paracingulate	-0.08 (0.30)	-0.03 (0.30)	t(29) = -0.77, p = .45
	Left Angular Gyrus	-0.23 (0.78)	-0.29 (0.97)	t(29) = -0.37, p = .71
	Left Inferior Frontal Gyrus	0.08 (0.28)	0.08 (0.31)	t(29) = -0.03, p = .98
	Left Precuneus	-0.27 (0.39)	-0.15 (0.54)	t(29) = -1.21, p = .24
	Left Superior Temporal Gyrus	-0.08 (0.40)	0.14 (0.38)	t(29) = -2.07, p = .05
Rumination-Distraction ^b	Left ACC & Paracingulate	0.15 (0.41)	0.16 (0.40)	t(29) = -0.06, p = .95
	Left Angular Gyrus	-0.10 (0.87)	0.44 (1.02)	t(29) = -2.42, p = .02
	Left Inferior Frontal Gyrus	-0.09 (0.39)	0 (0.41)	t(29) = -1.18, p = .25
	Left Precuneus	0.39 (0.40)	0.52 (-0.50)	t(29) = -1.27, p = .21
	Left Superior Temporal Gyrus	-0.02 (0.31)	0.02 (0.31)	t(29) = -0.40, p = .69

^a Below Bonferroni-corrected p-value threshold of 0.01.

^b Includes both Rumination Instruction and Prompt blocks minus Distraction contrast.

The present study found that compared to activation pre-treatment, youth with remitted MDD (and elevated rumination) who completed RF-CBT showed increased activation of the angular gyrus, precuneus, and STG during the rumination induction blocks. As brain activation is a relative measure in the context of fMRI tasks, there is more than one potential interpretation for these findings. While an increase in activation of rumination-related brain regions would seem antithetical to RF-CBT, it is possible that this is instead a reflection of a greater contrast

between blocks in which participants are ruminating and blocks during which they are not given explicit instruction (i.e., Rest blocks). This is partially supported by an early study of memory retrieval which found that, for individuals with elevated symptoms of depression, rest appeared to act as an uninstructed rumination condition, producing a similar pattern of performance to an explicit self-focus task, and an active distraction task was required to interrupt rumination (Hertel, 1998). In this case, results would suggest that following RF-CBT, participants were able to better disengage from rumination during non-rumination task blocks. A body of literature suggests that rumination persistence may relate to diminished ability to switch or inhibit mental sets, which could be related to difficulty disengaging relevant neural circuitry (Hilt et al., 2014; Whitmer and Banich, 2007). The increase and positive activation in rumination relevant regions during rumination blocks following RF-CBT suggests that RF-CBT may be facilitating greater dynamic range in and flexible engagement of these rumination-related nodes.

Given recent concerns regarding the reliability and stability of fMRI tasks, we found it necessary and valuable to evaluate the stability of the RIT. This is especially critical in the context of longitudinal and interventional studies as it facilitates more confident interpretations when attributing task activation changes to either treatment or a particular characteristic, rather than fMRI noise. Using the TAU group of this clinical trial as a benchmark, results indicate fair stability of the RIT, with certain brain regions showing higher stability than others. In particular, the angular gyrus and precuneus had good to excellent stability during the Rumination Instruction blocks. Since RF-CBT specifically targets rumination, we also examined whether the stability of the rumination induction task was poor within the RF-CBT group.

There are several reflections and limitations relevant to this work. First, it is notable that the RIT is a block design, which tends to have stronger test-retest reliability or stability than event-related designs. Second, the task was developed after a strong base of clinical studies demonstrating psychological and clinical validity (Cooney et al., 2010; Johnson et al., 2006; Lyubomirsky and Nolen-Hoeksema, 1993). Thus, conversion to fMRI conditions was predicated on knowledge that the task was already valid and reliable. Third, this is a relatively homogeneous sample of teens with higher levels of rumination and history of depression. While such homogeneity might be expected to reduce range and variability, thus constraining reliability, that was not observed here. Fourth, this is a relatively modest sample size for stability. It is, however, relatively large compared to similar intervention studies in youth with neuroimaging. Additional limitations of the study include the substantial duration of time between the two MRI scans (approximately six months on average for TAU) and restricting our ROIs to those identified in a prior meta-analysis (Zhou et al., 2020). A whole-brain or DMN network-based analysis may yield important information regarding other ROIs as well as the overall pattern of network functioning. Further, the ROIs from the Zhou et al. (2020) meta-analysis were all located within the left hemisphere, which may be related to the relation between language and rumination (Şimşek, 2013; Watkins and Roberts, 2020), and may be of interest for further exploration. Future work will also benefit from examining the influence of different model specifications (such as autocorrelation within fMRI data) as well as potential fluctuations in clinical characteristics and interventions on the reliability or stability of fMRI tasks.

In conclusion, we found strong stability for the brain regions where we expected stable activation and poor stability across ROIs and task blocks where we intended to elicit poor stability, in alignment with our hypotheses. Therefore, RF-CBT appears to specifically change activation of rumination-related circuitry during state-induced rumination, offering exciting avenues for future work that integrates neuroimaging and intervention. It also appears to be the case that the RIT is likely measuring aspects of both state (amenable to treatment-related change) and trait (not amenable to treatment-related change) rumination. With our team's ongoing collection of a larger sample of youth who are

Table 4
Intraclass Correlation Coefficients (ICCs) for Rumination Induction Task.

Condition	ROI	TAU ICC	Interpretation	RF-CBT ICC	Interpretation
Rumination instruction	Left ACC & Paracingulate	0.52 (0.16–0.75)	Fair	0.18 (–0.19–0.50)	Poor
	Left Angular Gyrus	0.86 (0.70–0.94)	Excellent	0.51 (0.19–0.73)	Fair
	Left Inferior Frontal Gyrus	0.51 (0.15–0.75)	Fair	0.41 (0.07–0.67)	Fair
	Left Precuneus	0.69 (0.42–0.85)	Good	0.15 (–0.22–0.48)	Poor
	Left Superior Temporal Gyrus	0.40 (0.02–0.68)	Fair	–0.19 (–0.51–0.17)	Poor
Rumination Prompt	Left ACC & Paracingulate	0.51 (0.16–0.75)	Fair	0 (–0.36–0.35)	Poor
	Left Angular Gyrus	0.61 (0.29–0.81)	Good	0.69 (0.45–0.84)	Good
	Left Inferior Frontal Gyrus	0.33 (–0.07–0.64)	Poor	0.36 (0.00–0.63)	Poor
	Left Precuneus	0.48 (0.11–0.73)	Fair	0.08 (–0.28–0.43)	Poor
	Left Superior Temporal Gyrus	0.27 (–0.13–0.60)	Poor	–0.05 (–0.39–0.32)	Poor
Distraction	Left ACC & Paracingulate	0.60 (0.27–0.80)	Good	0.32 (–0.04–0.61)	Poor
	Left Angular Gyrus	0.72 (0.46–0.87)	Good	0.39 (0.04–0.66)	Poor
	Left Inferior Frontal Gyrus	0.31 (–0.09–0.62)	Poor	0.09 (–0.27–0.43)	Poor
	Left Precuneus	0.50 (0.14–0.74)	Fair	0.29 (–0.08–0.58)	Poor
	Left Superior Temporal Gyrus	0.46 (0.09–0.72)	Fair	–0.14 (–0.47–0.23)	Poor

receiving either RF-CBT or Relaxation Therapy, we can further explore this relation (NCT03859297; R33MH116080). Other longitudinal studies of youth with multiple time points may further support the use of this task as a reliable measure of rumination.

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CRediT authorship contribution statement

Mindy Westlund Schreiner: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Anna M. Jacobsen:** Writing – review & editing, Formal analysis, Data curation. **Brian W. Farstead:** Writing – review & editing, Investigation, Data curation. **Raina H. Miller:** Writing – original draft. **Rachel H. Jacobs:** Writing – review & editing, Methodology, Conceptualization. **Leah R. Thomas:** Writing – review & editing, Writing – original draft, Investigation. **Katie L. Bessette:** Writing – review & editing, Writing – original draft, Investigation. **Myah Pazdera:** Writing – review & editing, Project administration, Investigation. **Sheila E. Crowell:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Conceptualization. **Erin A. Kaufman:** Writing – review & editing, Writing – original draft. **Daniel A. Feldman:** Writing – review & editing, Formal analysis, Data curation. **Henrietta Roberts:** Writing – review & editing, Methodology. **Robert C. Welsh:** Writing – review & editing, Writing – original draft, Software, Resources, Methodology, Data curation. **Edward R. Watkins:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Scott A. Langenecker:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

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Appendix A. Supplementary data

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