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Rumination-Focused Cognitive Behavioral Therapy Reduces Rumination and Targeted Cross-network Connectivity in Youth With a History of Depression: Replication in a Preregistered Randomized Clinical Trial

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ABSTRACT

BACKGROUND: Rumination-focused cognitive behavioral therapy (RF-CBT) is designed to reduce depressive rumination or the habitual tendency to dwell on experiences in a repetitive, negative, passive, and global manner. RF-CBT uses functional analysis, experiential exercises, and repeated practice to identify and change the ruminative habit. This preregistered randomized clinical trial (NCT03859297, R61) is a preregistered replication of initial work. We hypothesized a concurrent reduction of both self-reported rumination and cross-network connectivity between the left posterior cingulate cortex and right inferior frontal and inferior temporal gyri.

METHODS: Seventy-six youths with a history of depression and elevated rumination were randomized to 10 to 14 sessions of RF-CBT (n = 39; 34 completers) or treatment as usual (n = 37; 28 completers). Intent-to-treat analyses assessed pre-post change in rumination response scale and in functional connectivity assessed using two 5 minute, 12 second runs of resting-state functional magnetic resonance imaging.

RESULTS: We replicated previous findings: a significant reduction in rumination response scale and a reduction in left posterior cingulate cortex to right inferior frontal gyrus/inferior temporal gyrus connectivity in participants who received RF-CBT compared with those who received treatment as usual. Reductions were large (z change = 0.84; 0.73, respectively [$ps < .05$]).

CONCLUSIONS: This adolescent clinical trial further demonstrates that depressive rumination is a brain-based mechanism that is modifiable via RF-CBT. Here, we replicated that RF-CBT reduces cross-network connectivity, a possible mechanism by which rumination becomes less frequent, intense, and automatic. This National Institute of Mental Health-funded fast-fail study continues to the R33 phase during which treatment-specific effects of RF-CBT will be compared with relaxation therapy.

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Depression ranks as one of the top 2 most costly and the top 10 most deadly conditions globally (1,2). Many existing treatments are effective at reducing depression symptoms, and some can reduce the likelihood of recurrence. For example, combined cognitive behavioral therapy (CBT) and medication reduces the likelihood of recurrence by 20% to 45% (3–5). However, there is considerable scope for improvement in the effectiveness and longevity of treatments, with only up to 40% of patients achieving sustained long-term recovery.

In an effort to prevent recurrence, existing recommendations indicate that medication should be continued for at least 1 year after attaining remission in youth with depression (6–8), along with continuation of either structured or supportive therapy. Although these recommendations may delay recurrence and breakthrough in adolescents, up to 50% to 70% still experience recurrence, potentially leading to chronic illness and disability (9,10). Therefore, improved secondary prevention efforts that occur closer in proximity to illness onset are urgently needed. Furthermore, these efforts may be able to capitalize on the malleability of brain development and behavior during adolescence. Therefore, a better understanding of what and how to target and change risk factors and brain mechanisms for depression recurrence are needed for youth (11,12).

One key risk factor for both depression occurrence and recurrence is rumination. Rumination is a habitual response to

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difficulties and stressors and a thinking pattern in response to and focused on negative experiences that is repetitive, passive, and abstract (13). Notably, our view of rumination as a habit reflects the fact that the process often begins and continues outside conscious awareness and has a repetitive pattern. Rumination contrasts to more adaptive, concrete, and specific patterns of thinking (e.g., problem solving, emotional processing, or regulation) (14). Importantly, prior work has shown that rumination is associated with lower levels of treatment response, often remains elevated following remission from a major depressive episode, and prospectively predicts the severity and duration of depressive episodes in adolescents and adults [for a review, see (15)]. The role of the ruminative habit in these findings is that rumination is repetitive, long-lasting, and difficult to control (16–18); interferes with effective problem solving (19) and instrumental behavior (20); and prospectively predicts executive functioning impairments among adolescents (21).

Rumination-focused CBT (RF-CBT) emerged as an innovative approach to addressing treatment resistance and recurrence in depression (22). Early meta-analytic results suggest numerically greater effects (but underpowered significance) of RF-CBT in reducing rumination compared with other evidence-based treatments (22). Notably, multiple trials have demonstrated that 1) RF-CBT is superior in reducing rumination compared with treatment as usual (TAU) and other active treatments such as relaxation therapy, 2) RF-CBT may be superior in reducing depressive symptoms compared with active treatments such as antidepressants and standard CBT, and 3) RF-CBT is quite effective in adults (23). Reducing the frequency and intensity of habitual rumination while enhancing controllability is hypothesized to be an effective and efficient way to prevent recurrence of depression (13).

Because rumination can be conceptualized as a habit, the adolescent developmental period can be an optimal time to intervene. Learning effective habits before the rumination habit is entrenched can diminish the strength of this problematic mental behavior (24,25). A few recent pilot studies suggest that treating rumination in youth is effective, including in preventing the onset and recurrence of depression (12,26). Our pilot study demonstrated that RF-CBT was effective in reducing rumination, depression recurrence, suicide risk events, and anxiety, while also increasing behavioral activation (11,27). However, even within this exciting framework of risk reduction through rumination reduction (28), there are still many avenues for improving clinical interventions. Precision medicine with neuroimaging has been particularly promising because it may yield valuable information regarding treatment targets, evaluating the effectiveness of interventions, and how to facilitate lasting adaptive neurobiological changes (29). This neuromechanistic approach is particularly salient in youth because the brain is more amenable to change, allowing for establishing adaptive behaviors while evading the entrenchment of habits such as rumination. Understanding brain changes that are associated with the reduction of rumination affords a powerful interpretive framework for developing treatment modifications for RF-CBT and/or alternative intervention strategies to reduce rumination and risk for recurrent depression in adolescents.

At the level of brain function, multiple studies have indicated key nodes and networks involved in rumination, which serve as potential treatment targets. Both resting-state functional magnetic resonance imaging (rs-fMRI) and task-based approaches (including rumination induction paradigms) have been used to study the neural correlates of rumination among people with major depressive disorder (MDD) (30–40). In both adolescents and adults, default mode network (DMN) connectivity and activation have been implicated in rumination (39,41–49). The DMN is thought to support self-referential processing, passive waiting, and attention to the external environment. However, meta-analyses and a mega-analysis conflict in support for elevated versus reduced connectivity between DMN nodes in relation to depression and rumination (35,37,50,51). The cognitive control network (CCN) is another distinct network of distributed neural nodes that broadly supports integrative executive functions such as inhibitory control, working memory, and sustained attention. Our data and that of 2 other groups have illustrated elevated DMN to CCN connectivity (and relationships to rumination) in remitted MDD (rMDD), in active MDD, and in individuals who are at risk of MDD by virtue of having a family history of MDD [demonstrated and reviewed in (11,52)].

In addition to the clinical benefits highlighted above, our recent work using RF-CBT examined intervention-associated alterations in rs-fMRI networks in a sample of adolescents with rMDD (12). Results suggest stable increased activation in visual processing, somatosensory, and DMN regions during induced rumination, as well as reductions in DMN to CCN connectivity in youth who were receiving RF-CBT versus TAU (53). In the current study, we sought to replicate our previous findings of reduced rumination (measured via the Ruminative Response Scale [RRS] Questionnaire) (19) and rs-fMRI changes following RF-CBT compared with TAU (12). Specifically, we predicted that RF-CBT would result in reductions of rumination equivalent to a medium effect size decrease (>0.5 SD reduction) compared with a TAU control condition. This criterion was based on prior studies that have demonstrated that RF-CBT reduced rumination scores (measured in pre to post treatment changes in RRS) between 0.5 and 1 SD in clinical adult samples [e.g., (54)] and in our preliminary study, which demonstrated a 0.88 SD reduction in RRS scores in adolescents following RF-CBT. Additionally, we sought to replicate our finding of a reduction in cross-network left posterior cingulate cortex (PCC) connectivity with the right inferior frontal gyrus (IFG) and right inferior temporal gyrus in the RF-CBT group compared with the TAU group (12). We hypothesized a medium effect size (0.5 SD reduction). We also proposed an a priori unregistered, exploratory hypothesis that RF-CBT–derived improvements in RRS would mediate higher levels of global functioning measured using the Children's Global Assessment Scale (CGAS). Finally, in response to a reviewer suggestion, we evaluated an exploratory hypothesis (secondary post hoc, unregistered hypothesis) that degree of RRS reduction would be significantly correlated with degree of left PCC–right IFG/right inferior temporal gyrus connectivity reduction.

METHODS AND MATERIALS

Overview of the Clinical Trial

Rumination and seed-node resting-state connectivity were evaluated before and after 10 to 14 sessions of RF-CBT or TAU in a preregistered clinical trial.

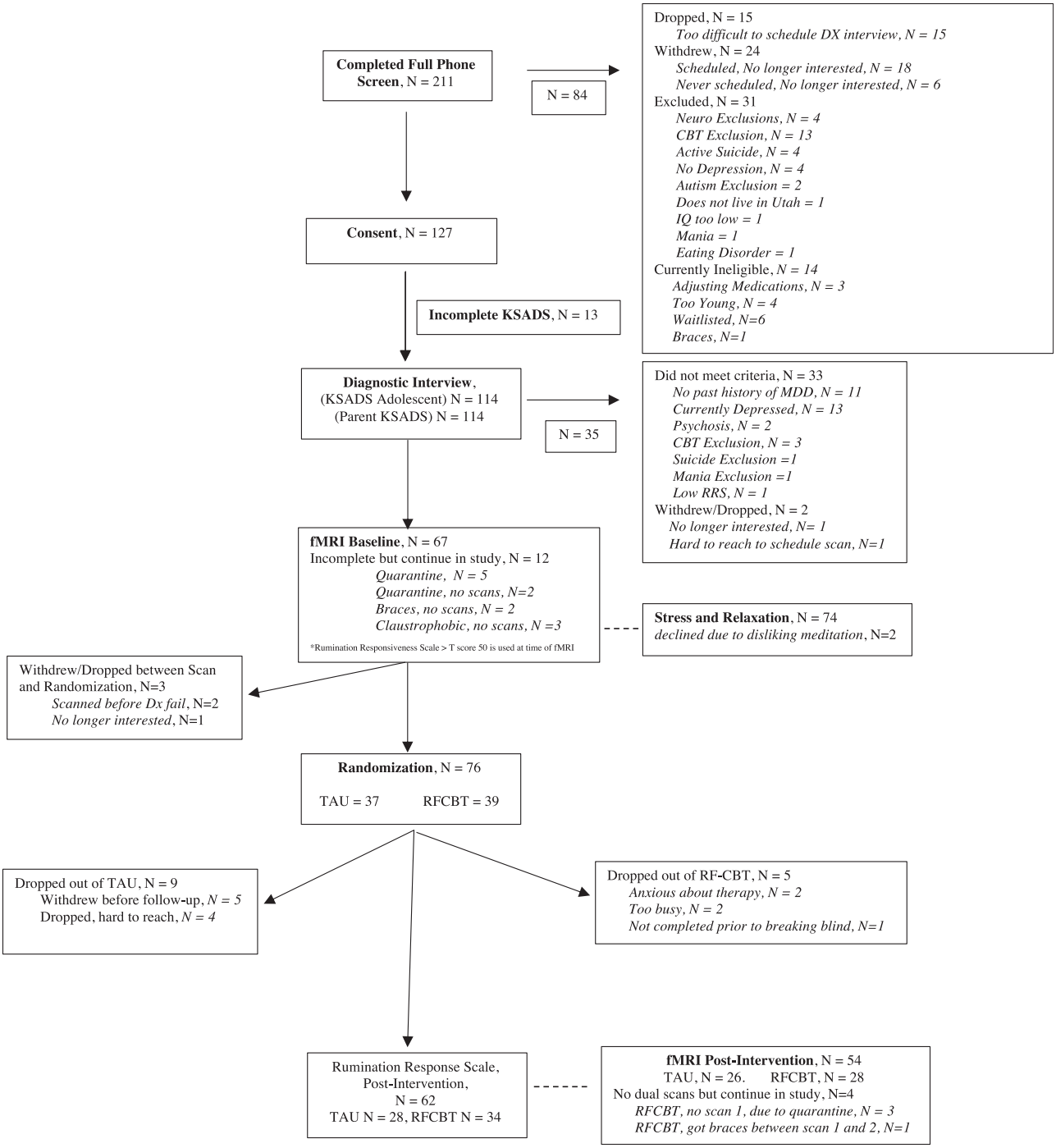

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram and study flow. The basic flow of the study, reasons for exclusions, numbers for dropouts, and group assignments are illustrated. CBT, cognitive behavioral therapy; DX, diagnostic; fMRI, functional magnetic resonance imaging; KSADS, Kiddie Schedule for Affective Disorders and Schizophrenia; MDD, major depressive disorder; RRS, Ruminative Response Scale; RF-CBT, rumination-focused CBT; TAU, treatment as usual.

Participants

The study was approved by the University of Utah Institutional Review Board and conducted at the university. Youths aged 14 to 17 years with a history of depression and their families were recruited primarily through radio and social media advertisements. Inclusion criteria required the youths to have been in remission from depression for at least 2 weeks prior to the assessment visit. Exclusion criteria included a current

depressive episode and a score above 45 on the Children's Depression Rating Scale-Revised (CDRS-R), consistent with the pilot study (12). Additional exclusion criteria included having an active suicidal plan or intent, psychosis outside the context of a mood episode, autism spectrum disorder, and substance abuse in the past 6 months. Current or recent (past 6 months) treatment with CBT was also exclusionary. Standard MRI safety exclusions also applied. See Figure 1 for CONSORT (Consolidated Standards of Reporting Trials) diagram and basic study flow procedures.

Clinical Measures

Rumination was assessed with the 22-item RRS questionnaire. Following informed consent and assent, a trained independent evaluator completed the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version and the CDRS-R with the youth and at least 1 parent or guardian. The independent evaluator also determined a score on the CGAS, which reflects the youths' current level of functioning, ranging from 0 (poor) to 100 (outstanding). This assessment procedure was repeated by a blinded independent evaluator at the post treatment follow-up visit (JAG, MP, Lucybel Mendez, Mallory Kidwell, Robyn Kilshaw). Participants completed the 22-item RRS to provide a self-report measure of rumination at pre- and postintervention.

Neuroimaging

MRI data were acquired at the Imaging Neuroscience Center at the University of Utah using a 3T Siemens Prisma scanner. A repetition time of 800 ms was used to acquire axial oblique images using multiband imaging (MB = 6). Four resting-state scans of 5 minutes, 12 seconds were acquired in the study. Two primary scans were acquired at the beginning of the scan and were the preferred resting-state scans for analyses. The field of view was 216 mm with 2.4 mm isotropic voxels. The flip angle was 52°, and echo time was 30. Field maps were acquired in reverse phase encode directions for the purposes of distortion correction. The first 10 images were discarded to reduce saturation effects.

Preprocessing of fMRI data included a pipeline of custom-built scripts (by RCW) using ANIMA, AFNI, ANTS, FSL, MATLAB, and SPM12 software packages (55,56). Preprocessing steps included reduction of outlier voxel signals (AFNI), realignment of time-series data (SPM12), coregistration of anterior to posterior and posterior to anterior field map to time series (ANIMA), echo-planar imaging distortion correction (ANIMA), coregistration of high-resolution T1 to time series (SPM12), normalization of high-resolution images to Montreal Neurological Institute space (ANTS), continued normalization of high-resolution images to Montreal Neurological Institute space (SPM), normalization of functional images to Montreal Neurological Institute space with (ANTS), and Gaussian smoothing using a 5-mm kernel (SPM12).

Consistent with recent literature, participant resting-state run scans were selected within movement thresholds of repetition time-to-repetition time <1 degree/mm or total scan drift <1.5 degree/mm ($n = 72$). When there were more than 2 runs that exceeded the total drift of 1.5 degree/mm threshold, a liberal threshold of total drift <3 degree/mm was accepted for inclusion, with preference given to the first 2 runs ($n = 36$). Of the 108 scans that were analyzed (across the pre- and postintervention periods), 95 scans were used from runs 1 and 2. Thirteen scans used alternate scans due to the excessive movement parameters described above. In total, 2 scans were used from runs 1 and 3, 2 scans were used from runs 1 and 4, 3 scans were used from runs 2 and 4, and 6 scans were used from runs 3 and 4. Preprocessing steps adjusting for movement, white matter signal, and cerebrospinal fluid signal, and first-level model building of individual connectivity matrices has been described in detail elsewhere and in the Supplement (12,57).

Randomization and RF-CBT Intervention

Participants were randomized to treatment in 5 sequential recruitment waves. Block randomization was used for waves 1 and 2. For waves 3 to 5, sequential random number string generation was used in Microsoft Excel with an adjustable proportionate cutoff score for randomization proportion (e.g., what proportion is randomized to RF-CBT), stratified by gender (i.e., male, female, and nonbinary/transgender), to achieve equal samples in each intent-to-treat arm. Randomization was designed by SAL, ERW, and RCW; implemented by RCW; and communicated by LT after baseline assessments (e.g., diagnostic, RRS, and MRI) to maintain investigator blindness (except RCW and LT).

RF-CBT was completed in-person for wave 1 and then moved to telehealth (predominantly via Zoom and rarely by phone) due to safety precautions during the COVID-19 pandemic (waves 2–4). During wave 5, participants were offered a hybrid of in-person and telehealth based on the preferences of the youths and their families. Treatment was implemented by SEC, MWS, KLB, SAL, and RHJ. Local supervision was conducted by SEC, and primary supervision and training were coordinated and led by ERW and DJ via weekly (or more frequent) teleconference. A description of the intervention is available upon request [manual by ERW, (58)]. The Supplement includes more details on implementation and fidelity assessments. The comparison arm was TAU (individuals were encouraged to pursue any treatment, and 3 had new and 10 had continuation psychotherapy) other than RF-CBT. Twenty-eight percent in the RF-CBT group and 22% in the TAU group were taking medication at study enrollment.

Preregistered Statistical Plan for Analyses

We conducted analyses of hypotheses for NCT03859297, preregistered at https://clinicaltrials.gov/ct2/show/NCT03859297. The described analyses for RRS and rs-fMRI are consistent with 1) the prior pilot RF-CBT trial, 2) clinical significance, and 3) instructions for R61/R33 trial with clarity in Go/NoGo milestones (https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-17-604.html). A paired-samples t test using z score changes codified the meaningful psychometric change. Conservatively, we identified a 0.5 SD reduction in RRS in the RF-CBT group versus the TAU group in our sample as a marker of the Go criteria (medium effect size clinical change), consistent with the fast-fail methodology in the R61 portion of the study. Resting-state analyses mirrored those for RRS to understand symmetry in analytic strategy, SD change, and interpretability of any brain changes. Based on our

Table 1. Demographic and Clinical Information for the Intent-to-Treat Sample

Demographic Characteristics	TAU, n = 37	RF-CBT, n = 39	Group Comparison
Age, Years	16.00 (0.91)	15.67 (1.13)	$t_{72.17} = 1.42$, $p = .16$
Female	25 (67.57%)	26 (66.67%)	$\chi^2_1 = 0.007$, $p = .93$
Race/Ethnicity			
American Indian	2 (5.4%)	1 (2.6%)	–
Asian	0 (0%)	1 (2.6%)	
Black/African American	0 (0%)	0 (0%)	
Hispanic	3 (8.1%)	6 (15.3%)	
Other	0 (0%)	1 (2.6%: Asian/White)	
Pacific Islander	0 (0%)	0 (0%)	
White	32 (86.5%)	30 (76.9%)	
Family Income			
<$21,000	2 (5.4%)	1 (2.6%)	–
$21,000–$40,999	0 (0%)	2 (5.1%)	
$41,000–$60,999	3 (8.1%)	4 (10.3%)	
$61,000–$80,999	4 (10.8%)	4 (10.3%)	
$81,000–$100,000	4 (10.8%)	12 (30.8%)	
>$100,000	20 (54.1%)	15 (38.5%)	
Response missing	4 (10.85%)	1 (2.65%)	
Clinical Characteristics			
Baseline RRS total	54.19 (11.24)	59.87 (12.03)	$t_{73} = 2.11$, $p = .04$[a]
Baseline RRS brooding	12.42 (3.71)	14.28 (3.28)	$t_{73} = 2.31$, $p = .02$[a]
Baseline RRS reflection	12.00 (3.14)	12.18 (3.56)	$t_{73} = 0.23$, $p = .82$
Baseline CDRS	33.61 (8.29)	36.54 (7.89)	$t_{73} = 1.57$, $p = .12$
Baseline SCARED	35.17 (16.30)	39.03 (15.27)	$t_{71} = 1.04$, $p = .30$

Values are presented as mean (SD) or n (%).

CDRS, Children's Depression Rating Scale; RF-CBT, rumination-focused cognitive behavioral therapy; RRS, Ruminative Response Scale; SCARED, Screen for Child Anxiety Related Disorders; TAU, treatment as usual.

[a]28% of the RF-CBT group and 22% of the TAU group were receiving medication treatment at time of trial onset.

prior work (14), our neuroimaging Go criterion for the R61 was demonstrating reduced cross-network connectivity between the left PCC/precuneus (dorsal DMN) and left inferior frontal and temporal gyri (i.e., the CCN). The sample size was chosen so that we would have sufficient power for these directional tests of the hypotheses.

Exploratory Analyses

In addition to our a priori hypotheses, further analyses used mixed-methods linear models with relevant covariates of interest (for baseline CDRS-R and baseline RRS, see the Supplement). We also conducted unregistered exploratory analyses to examine global functioning as measured by the CGAS and Youth Quality of Life Instrument in SAS using mixed linear model. We also conducted unregistered post hoc exploratory analyses based on a reviewer suggestion; we conducted exploratory correlation coefficient analyses of dose relationships of RRS change as it relates to connectivity change. The study sample size was not determined with sufficient power for any of the exploratory analyses.

RESULTS

The basic flow of participant enrollment is illustrated in Figure 1 (CONSORT diagram). Of 78 participants who were randomized with intent to treat, 56 to 58 had fMRI and/or RRS data available for pre-post analyses. Ten participants who were randomized to TAU did not complete follow-up RRS scores or scans. Five participants who were randomized to RF-CBT did not complete follow-up RRS scores or scans. Seven youths missed their pre- or postscan due to COVID safety precautions.

Results of the participant randomization was effective in obtaining intent-to-treat samples that were equivalent in CDRS scores and key demographic variables (gender, age, socioeconomic status [SES], race) (Table 1). The RF-CBT group had higher baseline RRS scores.

Planned Clinical Outcome Change in Rumination

The RF-CBT group demonstrated a significant reduction in RRS scores during the intervention period equivalent to

Table 2. *z* Score Difference and Cohen's *d* and SD Changes in RRS From Baseline to Follow-up, by Group

Group	RRS Baseline, Mean (SD)	RRS Postintervention, Mean (SD)	Mean Difference in Change (95% CI)	Cohen's *d*	*z* Score
TAU (28 of 36, 78% "Completers")	53.64 (11.66)	52.65 (14.01)	9.77 (2.77–16.77)	0.71	0.84[a]
RF-CBT (35 of 39, 89% "Completers")	60.8 (12.13)	50.02 (12.95)			

Here, completers' baseline scores are reported, such that 8 of 36 TAU and 4 of 39 RF-CBT did not complete RRS scores in the postintervention period.
RF-CBT, rumination-focused cognitive behavioral therapy; RRS, Ruminative Response Scale; TAU, treatment as usual.
[a]Exceeds the preregistered threshold of change (0.5 SD) and aligns with pilot study, Jacobs *et al*. (12).

0.92 SD, 0.84 SD greater than the TAU group. Note that 13 of the TAU participants who completed post treatment evaluations had continuing or new treatment, with a nominal decline in RRS scores (mean = 1.6, SD = 15.3). The Cohen's *d* difference of changes in RRS was 0.71. The *z* change (SD) and Cohen's *d* score changes for each group are presented in Table 2.

Planned Neural Outcome Reduction in Cross-network Brain Connectivity

Paired tests were conducted to identify the means and standard deviations of the primary outcome (left PCC–right IFG/right inferior temporal gyrus connectivity) at baseline and later time points. The *z* score difference, or SD difference, in change of the brain connectivity score difference between groups was −0.73. Figure 2 illustrates the changes in the target brain regions. A follow-up analysis for spatial robustness is described and included in the Supplement, with the significance in spatial overlap illustrated in Figure 3. Additional post hoc results for extracted connectivity values are also included in the Supplement.

Exploratory Analyses

For exploratory analyses, there was nonsignificantly greater improvement in Youth Quality of Life Instrument for RF-CBT versus TAU (*z* = 0.37) and no difference for CGAS (*z* = 0.01).

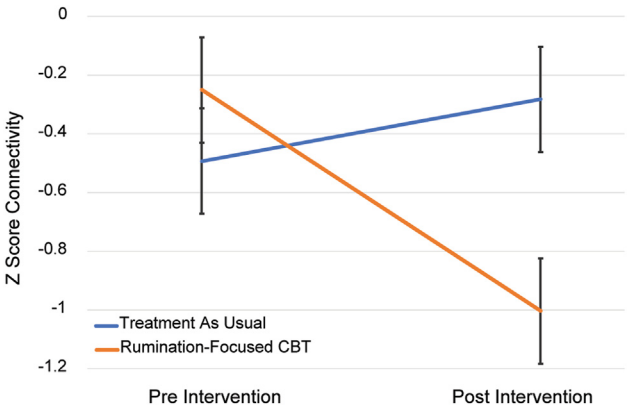

Figure 2. Pre to post treatment change in temporal connectivity for the primary seed-edge blood oxygen level–dependent signal of left posterior cingulate cortex with the average of the right inferior frontal gyrus and inferior temporal gyrus blood oxygen level–dependent signal. Error bars are standard error of estimate. The y-axis is the mean *z* score of connectivity along these edges. CBT, cognitive behavioral therapy.

Reliable change, attrition, and treatment analysis details are included in the Supplement.

In exploratory analyses of the relationship of rumination reduction to connectivity reduction, there was no significant relationship between the change measures ($r = -0.21$, $p = .10$).

DISCUSSION

RF-CBT is a developmentally appropriate treatment and is effective at reducing the rumination habit among youth and facilitating change in network interactions between the DMN and CCN. The large effect sizes that we observed are consistent with those observed among adults. Moreover, acceptability and retention were also high (89% completion rate of RF-CBT). Indeed, a recent meta-analysis, although underpowered to detect between-group effects, did suggest that RF-CBT and adolescent interpersonal therapy may be two of the most effective treatments for this age range (5,59). In addition, RF-CBT is readily adaptable across late adolescent development and to a teletherapy context.

Importantly, compared with TAU, RF-CBT resulted in both clinical improvement in rumination and co-occurring reductions in network crosstalk between the posterior DMN and several anterior and lateral CCN nodes. Such changes could be interpreted in different and potentially contrasting ways about potential processes that co-occur with rumination reduction during RF-CBT. Because the sample consists of formerly depressed teens, the increased cross-network connectivity could reflect 1) the process of sustaining remission (e.g., a compensation framework such as increased effort to damp down habitual rumination), 2) abnormally elevated rumination (e.g., illness framework—looping or chatter, such as rumination hijacking problem solving), or 3) some rumination- or illness-aligned disease process that declines with treatment (third variable, comorbidity). A compensation framework hypothesis implies that increased CCN-DMN connectivity occurs in real time for these teens to prevent deterioration. In the pilot work by Jacobs *et al.* (12), we demonstrated that cross-network connectivity was elevated in adolescents with rMDD compared with healthy teens and that RF-CBT reduced this observed increase in cross-network connectivity. Here, we did not have a non-rMDD comparison group, and the change post treatment was also toward reduced connectivity. Thus, this treatment-associated reduction in connectivity may be indicative of increased within-network coherence in both networks and could indicate a reduction in the need for compensation.

If the reduction in rumination-associated crosstalk between networks reflects a reduction in looping or "chatter" in neural networks, this would be consistent with the desired

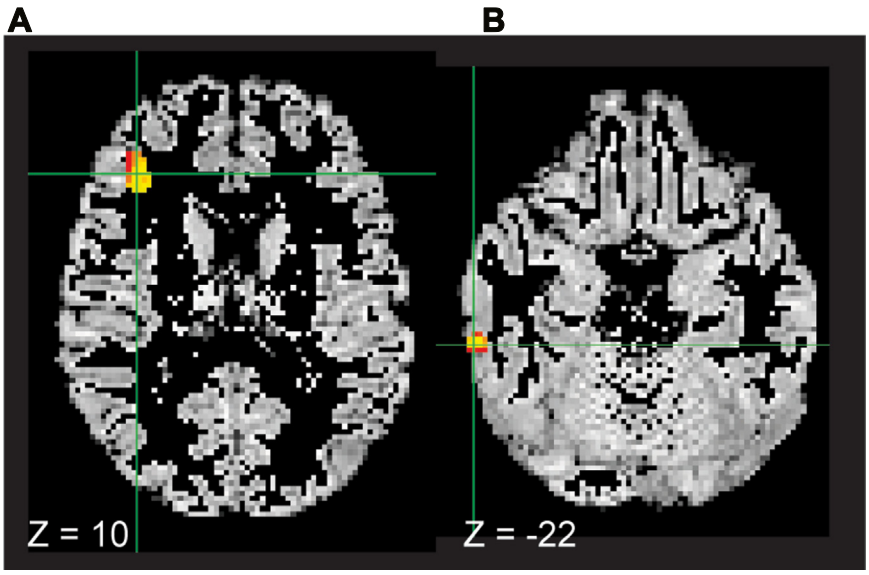

Figure 3. (**A**) Right inferior frontal gyrus map of overlapping significant areas of treatment-associated changes in connectivity with left posterior cingulate cortex seed(s), mapped onto the average gray matter (segmented) signal for all individuals in the trial. (**B**) Right inferior temporal gyrus map of overlapping significant areas of connectivity with left posterior cingulate cortex seed(s).

mechanistic modeling intended for R61 mechanisms. This chatter could reflect atypically merged signals between self-reflective (i.e., DMN) and regulatory (i.e., CCN) processes such that task-focused processing slips into habitual rumination. While our current data do not enable us to distinguish clearly between these processes, future studies can attempt to disentangle 1) the specificity of this change to rumination reduction, 2) the specificity of how such reduction occurs (e.g., a skill taught by RF-CBT such as learning to shift out of rumination into adaptive, concrete, and approach-oriented styles), 3) whether the change is sustainable over time, and 4) whether the change reflects a neurodevelopmental, treatment-induced shift point that has dividends for long-term life functioning. Our R33 phase has begun and can address some of these questions, and we intend to continue parsing putative mechanisms in future studies.

RF-CBT results in significant, treatment-specific declines in rumination for people with a history of depression, although some challenges remain. For instance, there were still a number of youths in our study who showed no meaningful reduction in RRS scores or clinical improvements in CGAS functioning. The R33 portion of this trial, which has now begun, is intended to expand on individual differences in response, dose-response effects, and effects in relation to treatment fidelity. Our clinical observation was that youth with low awareness of their triggers and process of rumination had difficulty sticking with the therapy. Adolescents who were younger tended to have less awareness of the ruminative habit, which tended to make experiential practice in the therapy difficult. This treatment may be less well suited to individuals with poor metacognition. In contrast, teens with high levels of awareness of their rumination and willingness to engage in the experiential exercises tended to report large reductions in rumination.

There were several additional limitations of the current study. RF-CBT was effective among minority and under-represented youth in middle and upper SES strata, but we did observe lower enrollment in all youth and families from lower SES groups and even lower enrollment for minorities within these low SES groups. Therefore, we cannot speak to whether this therapy may be effective among youth with higher levels of familial and environmental stress. We observed a pattern wherein male participants who enrolled in the study seemed to have lower recognition of their thinking patterns and were more likely to drop out of the study. We intentionally focused on targeted replications of the brain connectivity results that were reported in Jacobs *et al.* (12) and as such did not have sufficient power to conduct a whole-brain connectivity analysis (planned analyses for the R33 with 50/cell). We note that a recent study suggested that both mindfulness-based CBT and emotion regulation CBT were effective in reducing the ruminative habit in teens with social anxiety (60). Conducting comparative intervention studies to address the specificity of rumination reduction as a potential brain-based mechanism is an exciting avenue for future research. Finally, there are contrasting publications showing elevated rumination as being related to increased within-DMN network connectivity (51) or increased cross-DMN-CCN connectivity (50). We did not have a healthy control group that would allow us to directly address this question, but our data continue to support a cross-network pattern related to elevated rumination. Resting-state scan length can adversely affect reliability. We included 2 5-minute rest scans, using the ABCD sequences and durations for comparability, but note that reliability with 10 minutes of scan time may not be optimized. The trial used random assignment, but unfortunately, participants in the RF-CBT arm had higher initial RRS scores. It is possible that regression to the mean or expectancy effects distorted the actual effects of the therapy. However, we note that both groups mean RRS scores start at nearly 2 SDs above the age-respective means, making it less likely that regression to the mean would only happen in 1 group. As for expectancy effects, it is possible that

such effects account for the specific change only in the RF-CBT group. The R33 phase has a strong comparator therapy in relaxation therapy, which is designed to have no effect on rumination, so that we can test this hypothesis more clearly. An additional consideration that was pointed out to us during the review process was that our conceptualization of rumination as a habit did not align with our preregistered choice of networks and seeds for analysis (e.g., there is no hypothesized subcortical "habit" framework). Future work with larger samples can target such mechanisms and hypotheses with sufficient sample sizes to test comparative frameworks.

We made substantial adjustments to the model to accommodate youth developmental stages (e.g., maturity, framing the intervention), teletherapy because of COVID, and family factors. These changes are currently being codified in a modified treatment manual, which will be made available to interested parties. Given the scope, acceptability, and effectiveness of this treatment with youth, we will continue to pursue opportunities to increase access and evaluate effectiveness and generalizability. One surprising and exciting result was that the intensive process-focused elements of RF-CBT could be conducted effectively via teletherapy. These elements included functional analysis and experiential practice in-session. Many youths reported being pleased with the modality, and many engaged in the sessions using tablet computers in the comfort of their bedrooms. Longitudinal follow-up will continue for at least 1 year and can evaluate the sustainability and long-term clinical effectiveness of this intervention (including reductions in depression relapse suicide risk with parallel increases in functioning and quality of life).

Conclusions

In summary, the current results included a planned, registered replication of change in reduction of the ruminative habit and cross-network resting-state connectivity. Amid recurring concerns about the clinical viability of fMRI as a metric of brain change, this replication stands as a representative example of how an R61 study can have clear, measurable Go criteria and inform mechanistic clinical insights into how a therapy works and how to improve a therapy.

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