



Published in final edited form as:

*Am J Psychiatry*. 2024 March 01; 181(3): 201–212. doi:10.1176/appi.ajp.20220449.

## Cognitive behavioral therapy normalizes fronto-parietal activation in unmedicated patients with pediatric anxiety disorders

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### Disclosures

Dr. Kalin reports serving as a consultant to the Board of Scientific Advisors, Pritzker Neuropsychiatric Disorders Consortium; Skyland Trail National Advisory Board, CME Outfitters, LLC, Corcept Therapeutics Incorporated, and the Institute for Early Adversity Research External Scientific Advisory Board at the University of Texas-Austin. All other authors report no financial relationships with commercial interests.

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## Abstract

**Objective:** Anxiety disorders are among the most common psychiatric conditions in youth. Cognitive behavioral therapy (CBT) is an effective first-line treatment. The authors investigate the brain mechanisms associated with symptom change following CBT.

**Methods:** Unmedicated youth diagnosed with an anxiety disorder underwent CBT (12 weeks) as part of two randomized clinical trials testing the efficacy of adjunct computerized cognitive training. Across both trials, participants completed a threat processing task during functional magnetic resonance imaging pre- and post-treatment. Age-matched healthy comparison youth completed two scans over the same time span ( $M_{age}=13.20$ ,  $SD=2.68$ , 41% male, 69 anxious youth, 62 healthy comparison youth). An additional sample including youth at temperamental risk for anxiety was utilized to test stability of anxiety-related neural differences in the absence of treatment ( $M_{age}=10.51$ ,  $SD=0.43$ , 41% male). Whole-brain regional activation changes (thresholded at  $p<.001$ ) were examined using task-based blood-oxygenated level dependent response.

**Results:** At pre-treatment, patients with an anxiety disorder exhibited altered activation in fronto-parietal attention networks and limbic regions relative to healthy comparison children across all task conditions. Frontal-parietal hyperactivation normalized over the course of treatment, whereas limbic responses remained elevated post-treatment. Overlapping clusters emerged between regions showing treatment-related changes and regions showing stable associations with anxiety over time in the at-risk sample.

**Conclusions:** Activation in fronto-parietal networks may normalize following CBT in unmedicated pediatric anxiety patients. Limbic regions may be less amenable to acute CBT effects. Findings from the at-risk sample suggests that treatment-related changes may not be attributed solely to the passage of time.

## Introduction

Pediatric anxiety disorders are prevalent and highly impairing (1, 2). Cognitive behavioral therapy (CBT) is an effective first-line treatment (3). However, the neural mechanisms associated with CBT-related symptom change remain largely unknown (4, 5). Elucidating changes in brain function following CBT is a first step towards providing mechanistic insights, modifying treatment and improving clinical outcomes. Here, we use an established threat-processing task (6) to examine treatment-related changes in regional activation patterns, conducting a whole-brain analysis with fMRI data collected at pre- and post-CBT in a large, unmedicated sample of anxious youth.

Neurobiological models posit that pathological anxiety arises from dysregulated cognitive processes and defensive responses (5, 7, 8). Alterations in functional networks mediating this dysfunction include attention, salience and threat circuitry (5, 9–12), with hyperactivation of the amygdala, as well as dorsal and medial prefrontal regions (13–15) and fronto-parietal, and ventral attention networks. While identifying psychopathology-related

neural dysfunction is an important first step for developing targeted treatments (16), the malleability of these networks within the developing brain over the course of established treatments remains largely unknown.

CBT for anxiety disorders in youth emphasizes modifying behavioral and cognitive phenomena that maintain avoidance and dysfunctional thinking. The core components of CBT involve graded exposures to fear-provoking stimuli based on principles of extinction (17–19) and cognitive restructuring (20). Despite maturational neural changes in the developing brain including circuits underpinning emotion regulatory functions (21), the efficacy of CBT remains high in youth. More specifically, efficacy does not change as a function of age (22). Pathophysiologically, CBT engages executive processes, which are thought to enhance modulatory capacity in relation to limbic structures (23). Interventions at this critical developmental juncture have the potential for long-lasting therapeutic effects, given that circuits may be more malleable (24).

Functional magnetic resonance imaging (fMRI) can be used to examine neural correlates of clinical improvement (4). Only a handful of studies have examined threat-related brain-based indicators in relation to treatment outcome. Baseline variability in amygdala and prefrontal functioning and their connectivity during threat appraisal has been linked to CBT response in youth with pediatric anxiety disorders (13, 25, 26), and in adults with social anxiety disorder (27).

A recent meta-analysis (4) identified only two studies that used fMRI to assess the neural correlates of pre- to post-treatment change in youth with anxiety disorders (28, 29). Both were modest in sample size, and both included patients on medication, which complicates inferences about therapeutic effects related specifically to CBT. Thus, studying larger samples of unmedicated patients is needed.

Here, we use task-based fMRI to examine changes in brain activation during threat processing over 12 weeks from pre-to-post CBT in 69 unmedicated pediatric patients with a primary anxiety disorder (ANX). We further include a sample of 62 healthy comparison (HC) youth who provided fMRI data at matched time points to benchmark observed changes in activation and assess the reliability of different fMRI task contrasts. In an additional sample of youth at temperamental risk for anxiety, we test whether anxiety-associated differences remain stable over time in the absence of treatment. We anticipated that ANX youth would show hyperactivation pre-treatment in cortical and subcortical salience and attention control circuitry during the fMRI threat attention task (14). Because CBT primarily targets top-down regulatory processes through graded exposure and cognitive restructuring, we expected these neural networks to normalize following acute CBT treatment. Consistent with a two-system neuroscientific framework of anxiety (5), the effects of CBT on interrelated cortical and subcortical circuits may operate on different time scales; cortical circuits may be more responsive to CBT effects, while subcortical circuits may be less acutely affected, showing more protracted dysfunction.

## Methods

### Participants

A total of 74 treatment seeking, unmedicated youth with a primary anxiety disorder diagnosis (generalized anxiety, social anxiety, and/or separation anxiety disorder), as established by semi-structured clinical interview (KSADS-PL; 30, 31), completed a pre- and post-CBT fMRI scan. Sixty-nine participants ( $M_{\text{age}}=12.79$ ,  $SD=2.98$ , 33% male, see Table 1) generated usable data at both time points (days between scans:  $M_{\text{days}}=107.12$ ,  $SD=33.13$ ). Data were collected as part of two randomized controlled trials (RCTs) (13, 32) examining potential augmenting effects of 5–15 minutes of computerized attention training accompanying each CBT session. See Supplementary Materials for recruitment and enrollment, exclusion criteria, and additional information on each RCT including previously published data. An additional sample of 68 HC youth completed the same fMRI task twice at the same interval, with 62 HC youth generating usable data at both time points ( $M_{\text{age}}=13.66$ ,  $SD=2.23$ , 48% male, days between scans:  $M_{\text{days}}=84.1$ ,  $SD=35.38$ ).

A secondary analysis on published data (33) was conducted to test whether anxiety-associated activation differences remain stable over time in the absence of treatment. A separate sample was drawn from a larger longitudinal community cohort of healthy children selected at 4 months of age based on criteria for high and low behavioral inhibition (BI), i.e., reactivity to novelty (34), a temperamental risk factor for anxiety (35). The at-risk (AR) sample included 87 participants who provided data at one of two time points: age 10 years ( $M=10.51$  years,  $SD=0.43$ ) and age 13 years ( $M=13.04$ ,  $SD=0.65$ ). 61 participants provided data at age 10 years (59% females) and 64 provided data at age 13 (67% females). For details on the cohort, exclusion criteria and procedure see Supplementary Materials.

### Treatment and measures

Twelve sessions of CBT for anxiety were delivered by a licensed clinical psychologist. All participants received standard CBT, which involved key components of cognitive and exposure-based therapies; the RCTs employed two different established manuals (36, 37). In early sessions this included introducing principles of CBT, psychoeducation, and self-monitoring of emotions, thoughts, and behaviors, while in later sessions this included in vivo exposures, cognitive restructuring exercises, and at-home practice skills. RCTs were primarily testing the efficacy of adjunct computerized cognitive training. All participants received either active or sham computerized attention bias modification training (ABMT), which was not further investigated here. The Pediatric Anxiety Rating Scale (PARS; 38) and Clinical Global Impressions Scale-Improvement (CGI-I; 39), clinician-rated measures of anxiety severity and clinical improvement respectively were administered. A PARS total score was created by summing items assessing symptom severity, frequency, distress, avoidance, and interference over the previous week. Patients with CGI-I ratings of  $\leq 3$  post-treatment are considered “treatment responders,” patients with scores  $>3$  are counted as “non-responders.” PARS and CGI-I ratings were collected weekly; pre- and post-CBT ratings were used to examine clinical improvement.

### Threat attention task

Participants completed a validated threat attention paradigm: the dot-probe task (40). See task schema and further details in the Supplementary Materials. Participants were instructed to respond via button press to indicate the direction of an arrow probe that followed a display of either angry-neutral or neutral-neutral face pairs of the same actor. The task had three conditions: 1) threat congruent trials, with probes presented in the angry face location of angry-neutral pairs; 2) threat incongruent trials, with probes presented in the neutral face location of angry-neutral pairs; and 3) neutral trials, with probes presented in either neutral face location of neutral-neutral pairs.

### fMRI data acquisition and preprocessing

fMRI data were collected on two 3T MR750 General Electric scanners (Waukesha, Wisconsin, USA) with an 8-channel or 32-channel head coil. Functional image volumes with 41 contiguous interleaved axial slices were collected with a T2\*-weighted echo-planar sequence (repetition time [TR] = 2300 ms, echo time [TE] = 25 ms, flip angle = 50°, field of view [FOV] = 240 mm<sup>2</sup>, matrix = 96 × 96, slice thickness 3 mm). For co-registration with the functional data, a high-resolution T1-weighted whole-brain volumetric scan was acquired during each scan session, with a high-resolution magnetization prepared gradient echo sequence (MPRAGE; TE = min full; TI = 425 ms; flip angle = 7°; FOV = 256 mm<sup>3</sup>; matrix = 256 × 256 × 256).

Data were analyzed using Analysis of Functional NeuroImages (AFNI; <http://afni.nimh.nih.gov/afni/>) (41) v18.3.03. Standard preprocessing included despiking, slice-timing correction, distortion correction, alignment of all volumes to a base volume, non-linear registration to the MNI template, spatial smoothing to 6.5 mm FWHM, masking, and intensity scaling. We used the `blur_to_fwhm` flag to assure that a similar smoothness was achieved across scanners and sessions, rather than adding a set blur kernel to acquired images that may vary in initial smoothness.

First-level models used a generalized least squares time series fit with restricted maximum likelihood estimation of the temporal autocorrelation structure with regressors for the three conditions (congruent, incongruent, neutral) and error trials per participant, modeled with a gamma hemodynamic response function.

Preprocessing and first-level general linear models (GLM) controlled for head motion. Six head motion parameters were included as nuisance regressors in the individual-level models. During preprocessing, any pair of successive TRs where the sum head displacement (Euclidean norm of the derivative of the translation and rotation parameters) between those TRs exceeded 1 mm were censored. TRs were also censored if more than 10% of voxels were timeseries signal outliers. Participants were excluded if the average motion per TR after censoring was more than 0.25 mm, or if more than 15% of TRs were censored for motion/outliers, or if behavioral performance was accuracy <70% ( $n=11$  excluded based on these thresholds).

## Data analyses

Changes in PARS total score over the course of treatment are reported. Mean reaction time per condition (congruent, incongruent, neutral) was computed. Age and cohort/headcoil were included as covariates in all analyses. Additional analyses controlling for sex assigned at birth can be found in the Supplementary Materials. The primary analysis examined change from pre- to post-CBT. Hence, the model of behavioral and imaging data compared change over time between ANX and HC youth. The model included group (ANX, HC) as a two-level, between-subjects factor and two within-subjects factors, one for condition with three levels (congruent, incongruent, neutral) and one for timepoint with two levels (first and second scan, pre- and post-CBT for ANX youth) with participant as a random factor. For the imaging data, the analyses were whole-brain voxel-wise linear mixed effects models (3dLMER in AFNI; 42). We focused on group differences, particularly the group-by-timepoint interaction. This approach is consistent with previous reports showing higher reliability estimates when assessing activation across all task conditions rather than using condition difference scores (e.g., 6).

Associations between pre-treatment activation patterns and symptom improvement in ANX youth undergoing treatment were explored using whole-brain voxel-wise multivariate models (3dMVM in AFNI; 43). Sixty-one (61) ANX youth had complete clinical data and were included in this analysis. Post-treatment PARS total scores were entered as a continuous variable with task condition (congruent, incongruent, neutral) as the within-subject variable, controlling for baseline anxiety using pretreatment PARS total score as a covariate. A second analysis examined voxel-wise correlations between change in PARS total score and change in activation patterns across the two timepoints. Complementary analyses using the CGI-I score can be found in the Supplementary Materials.

We also evaluated reliability of BOLD activation across the two sessions in HC and AR youth using voxel-wise Bayesian intraclass correlation coefficients (ICC[3,1]; 44, 45). These were conducted to confirm the most reliable task contrast and can be found in the Supplementary Materials alongside analyses assessing associations between reaction time and BOLD response.

Using AFNI's 3dClustSim, Monte-Carlo simulations were performed to correct for multiple comparisons within a whole-brain gray-matter mask (81,839 voxels), where at least 90% of individuals had data across the two time points. To estimate smoothness of the residual time series a Gaussian plus mono-exponential spatial autocorrelation function was used. Smoothness was estimated for each participant and then averaged, for an effective smoothness of 9.32 (acf parameters:  $a=0.589$   $b=3.429$   $c=10.759$ ). For group analyses, two-sided thresholding was used with first nearest neighbor clustering. All results were thresholded at a voxel-wise  $p$ -value of .001 and a cluster extent of  $k=21$  for a whole brain family-wise error correction of  $p<.05$ . Activity estimates were extracted per participant as an average from each significant cluster for post-hoc analyses and visualization.

Lastly, we completed conjunction analyses between the statistical maps showing changing activation patterns with treatment in the ANX/HC sample and the maps illustrating change and stability of anxiety-associated differences in the AR sample from the secondary

analysis. See Supplementary Materials for full results in the AR sample and additional region-of-interest analyses of amygdala activation across samples.

## Results

### Demographics and treatment effects

The ANX and HC groups did not differ significantly by sex and IQ (see Table 1). HC youth were marginally older than ANX youth. In addition to cohort, age was included as a covariate in all analyses. ANX youth showed significant improvement in PARS and CGI-I scores post-treatment (PARS<sub>change</sub>:  $M = -4.15$ ,  $SD = 4.19$ ,  $t(61) = -7.79$ ,  $p < .001$ ,  $d = .90$ ; 66% with clinically significant reduction, i.e. “responders” as defined by the CGI-I, see Figure 1A).

### Behavioral effects

A timepoint-by-group interaction ( $F(1,645) = 37.56$ ,  $p < .001$ ) was observed for mean task response time; the timepoint-by-group-by-condition interaction was not significant. At pre-treatment, ANX youth were significantly slower to respond across conditions relative to HC youth ( $\sim 69$  ms;  $t(129) = 4.578$ ,  $p < .001$ ), a difference that was larger compared to post-treatment ( $\sim 42$  ms;  $t(129) = 2.81$ ,  $p = .03$ , see Figure 1B; estimated difference  $\sim 27$  ms,  $\chi^2(1) = 37.56$ ,  $p < .001$ ).

### Whole brain analyses

**Pre- to post-treatment change**—For a summary of results including post-hoc statistical tests, see Table 2 and Figure 2A/B. No regions showed a significant group-by-condition-by-timepoint interaction. Thirty-seven (37) clusters emerged with a significant group-by-timepoint interaction. Thirteen of these regions showed activity normalization, i.e., ANX youth showed altered activity compared to HC pre-treatment and largely no differences post-treatment, while activation in HCs remained comparable at both time points. Regions that normalized with treatment included fronto-parietal network regions (bilateral supplementary motor area, middle frontal gyrus, and superior parietal lobule). Specifically, patients showed elevated activation in these regions pre-treatment compared to HCs across all task conditions, and these activation patterns declined to levels comparable or lower to those of HCs post-treatment. The remaining regions showing a significant group-by-time interaction suggests a potential treatment-induced compensatory mechanism. Specifically, regions in the temporal gyri (superior and inferior), bilateral inferior parietal lobule, and middle occipital gyrus, were characterized by no pre-treatment differences between ANX and HC youth; whereas at post-treatment, ANX patients showed significantly less activation compared to HC youth.

Eight regions showed a main effect of group across timepoints, including the bilateral motor cortex, the right amygdala/parahippocampal gyrus, and lateral anterior frontal areas. These regions showed hyperactivation in ANX relative to the HC youth; activation did not change significantly with treatment in ANX youth.

Lastly, a conjunction analysis between the group-by-time interaction (changing activation patterns with treatment) and the main effect of anxiety in the AR sample from the secondary analysis (anxiety-associated differences across two time points in development) illustrates some overlapping clusters in frontal and parietal cortex (Figure 2C). This provides preliminary evidence that changes observed in the main sample relate to treatment. In the AR, untreated sample, clusters reflect relations with anxiety that manifest across the two time points.

**Associations between activation patterns pre-treatment and treatment response**—No significant associations emerged between activation patterns at pre-treatment and improvement in PARS total score. Follow-up voxel-wise correlation analysis did not show relations between change in dimensional ratings of anxiety and change in activation patterns.

## Discussion

This study has four key findings. First, unmedicated, treatment-seeking youth with an anxiety disorder differed from HC youth at baseline in both reaction time and brain function. Second, reaction time and fronto-parietal activation normalized with CBT treatment. Third, a number of (sub)cortical regions, including the right amygdala, remained hyperactive in patients post-treatment. Fourth, in a sample including youth at temperamental risk for anxiety, anxiety-associated neural dysfunction remained relatively stable over time.

### Baseline differences in fronto-parietal networks

Prior to treatment, youth with an anxiety disorder showed widespread hyperactivation, including in fronto-parietal regions across all task conditions. This is consistent with prior research reporting frontal hyperactivation in pediatric anxiety patients relative to HC youth (for a recent meta-analysis, see 14). Additionally, network-based approaches examining activation and connectivity have reported aberrant frontoparietal network functioning in anxiety, suggesting cognitive control difficulties (46–48). In this study, hyperactivation emerged in the context of longer reaction times and reactivity in the right amygdala and frontal regions (inferior and middle frontal gyrus, precentral gyrus), indicating atypical functioning in this circuitry. Data in a separate, AR sample showed that youth at risk for anxiety also display atypical functioning in this circuitry across all task conditions.

Previous neuroimaging work with the dot-probe task has focused on threat specific trials or compared threat and neutral trials (13, 49). In contrast, our findings are not specific to a task condition and are consistent with neuroimaging findings in the dot-probe task demonstrating a higher level of test-retest reliability when estimating activation across all trial types (6). Our findings are also consistent with work demonstrating that neutral stimuli may be perceived as threatening for anxious youth (50), albeit a number of studies also report biases specific to threat-relevant stimuli in anxious populations (51, 52). Previous work employing non-emotional stimuli further suggests that the dysfunction observed in anxiety disorders may not be specific to threat processing. Instead, global changes in cognitive control and brain network functioning may characterize this population (46, 53). These general changes could either be secondary to a primary deficit in threat processing or may impact systems

involved in threat detection and appraisal. It is important to note that, albeit unlikely, we cannot rule out the possibility that changes across trial types reflect changes in brain activity during the unmodeled implicit baseline, or some combination of the modeled and unmodeled events.

### **Fronto-parietal networks and treatment-related change**

We found hyperactivation in fronto-parietal regions which characterized youth with anxiety disorders at pre-treatment normalized post-CBT, reaching levels comparable (or lower) to those observed in HC youth. Longitudinal data in an independent sample of youth at risk for anxiety showed stability of anxiety associated differences manifested across two years, without the changes seen in the treated patients. Reductions in activation in ANX youth may reflect more efficient engagement of cognitive control networks following CBT. Partially consistent with our findings, the two prior studies that examined pre- to post-treatment neural changes (28, 29) found frontal regional changes over the course of treatment, albeit in the opposite direction, with increased activation post-treatment. It is important to note, however, that those two studies included medicated patients and had smaller samples.

We also found that some patterns of hyperactivation, including several frontal regions and the right amygdala, did not change with treatment. This persistent pattern of altered circuit function after CBT may be understood within a two-system neuroscience framework of anxiety elicited by threats (5). The model posits that defensive response circuitry (e.g., amygdala), while directly involved in detecting threat, is only indirectly involved in generating signals that give rise to subjective fear. Subjective experiences of fear are mediated by higher order association cortex including lateral and medial prefrontal and parietal regions, supporting cognitive functions such as attention. While cognitive components of CBT may first reduce subjective feelings of fear or anxiety, defensive systems may demonstrate more persistent dysfunction. Speculatively, CBT may more effectively and efficiently target cortical circuitry, while subcortical dysfunction may lag in responsivity and/or might require more direct interventions to modulate exaggerated automatic, defensive reactions (54). Longer term follow-up of youth who complete CBT may reveal normalization of amygdala function, with CBT-affected cortical circuits regulating other cortical and subcortical functioning over time. Youth who continue to demonstrate aberrant prefrontal and amygdala functioning may be particularly relapse prone (55). In fact, many youth undergoing CBT, including those considered responders, maintain persistent symptoms of anxiety (56). Hence, two important avenues for future work are to examine the neural effects of CBT longitudinally, ideally in the context of dismantling designs to more directly link manualized components to changes in neural activation and to assess the effectiveness of complementary, adjunct treatments.

### **Pre-treatment activation patterns and treatment response**

We did not find pre-treatment activation patterns associated with treatment response. A handful of studies have examined threat-related brain-based indicators as predictors of treatment outcome (13, 25, 26). Although these studies do not directly address mechanisms of therapeutic change, they indicate subtypes of potential responders with specific alterations in threat circuit functioning (13). Previous work in anxious youth has shown greater

activation in prefrontal regions to angry faces predicts better treatment response across CBT and pharmacological treatment (26). Methodological differences between studies (e.g., explicit vs. implicit emotion processing tasks, medication use) may explain inconsistent results. Given the mixed findings, further work is needed.

### Strengths and Limitations

Results should be interpreted in light of several limitations. First, we were unable to include a patient control arm of medication-free, anxious youth since our institution's review boards will not permit delay of treatment for those youth on ethical grounds. However, in a separate adolescent sample at temperamental risk for anxiety who were not receiving treatment, we showed that some frontal and parietal hyperactivation is consistently associated with increased anxiety over time. Second, heterogeneity and potential noise in the clinical and fMRI data may have been introduced by collapsing data from participants across two different manualized CBT protocols and across adjunct ABMT. Given the similarity of stimuli employed in the fMRI task and adjunct treatment, repeated exposure to these stimuli and practice effects could impact both response time and BOLD response in the treatment-receiving group. Findings on the efficacy of ABMT in youth are mixed, with studies reporting positive effects in the small (57–60) to medium range (61–63) with the largest RCT finding no effect of ABMT on anxiety symptoms (64). Therefore, even if the findings of the current study were positive, questions would remain about the efficacy of adjunct ABMT. Our study is well powered to examine symptom and neural changes with CBT, because the effects are likely larger, and the sample size doubled compared to examining adjunct ABMT subgroups. Third, while we applied established whole-brain procedures to examine task activation patterns, recent advances in network-based analytical techniques mapping connectivity across the brain open up new and important avenues for future work. Techniques such as connectome-based predictive modeling (65) and functional connectome fingerprinting (66) may facilitate additional predictive modeling of treatment response. Finally, although we added a sample including youth characterized by an early childhood inhibited temperament with a higher risk for developing an anxiety disorder (67), very few of the youth in the enriched group met criteria an anxiety disorder at the time of the scan. However, prior research on behavioral inhibition (33) suggests that the relations between neural functioning and dimensional measures of anxiety severity remain, even when the symptom level does not reach the stricter threshold of an anxiety disorder.

Despite these limitations, this study provides evidence in a large sample of unmedicated anxious youth for the circuitry and potential putative mechanisms of manualized CBT. While CBT is the current gold standard intervention for pediatric anxiety (3, 22), response rates are variable (68), leaving a large portion of treated youth with significant symptoms following treatment (56). The moderate success rate may be due, in part, to limited understanding of the mechanisms catalyzing immediate and long-term neural changes in CBT. Clinical outcomes may be improved via targeting fronto-parietal attention circuits and complementing CBT with adjunctive interventions directly impacting subcortical structures (54).

## Conclusions

CBT is an effective first-line treatment for anxiety disorders (3), which are among the most common psychiatric conditions in youth. However, success rates are limited (1), with high rates of relapse (3, 55). The current data reveal neural mechanisms that change following the acute effects of CBT for pediatric anxiety, as well as potential subcortical and cortical targets that remain dysfunctional following 12 weeks of CBT. Future work may benefit from directly targeting subcortical, automatic, and biased processing to enhance CBT treatment response.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

We thank Dr. Daniel S. Pine for insightful discussion and comments on earlier drafts. This work utilized the computational resources of the NIH HPC Biowulf cluster (<http://hpc.nih.gov>).

## Funding/Support:

This research was supported by project ZIAMH002781 (Dr. Pine) and ZIA MH002969 (Dr. Brotman) from the Intramural Research Program of the National Institute of Mental Health, National Institutes of Health, and was conducted under Clinical Study Protocol 00-M-0192 ([clinicaltrials.gov](https://clinicaltrials.gov) identifiers [NCT00018057](#) and [NCT03283930](#)).

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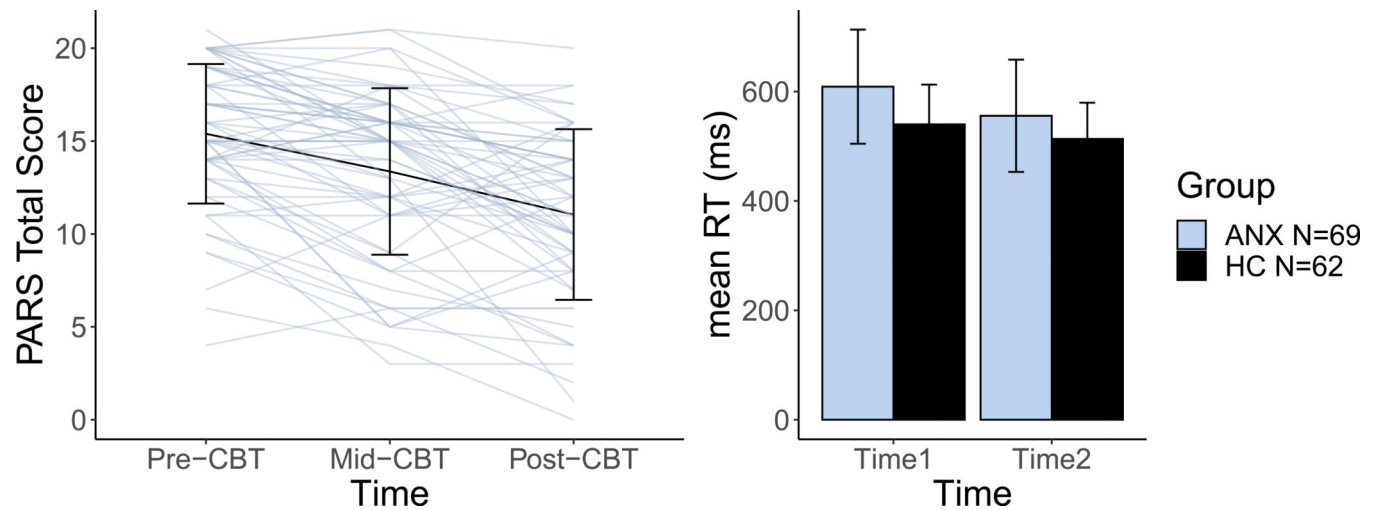
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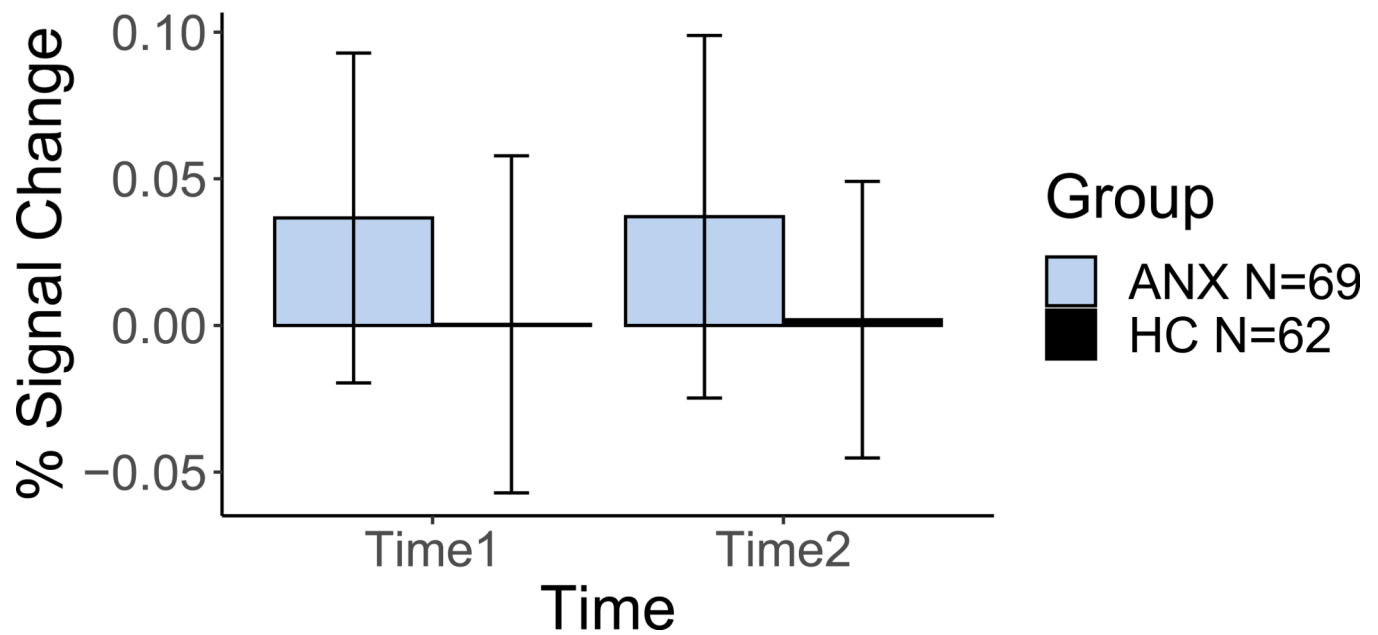
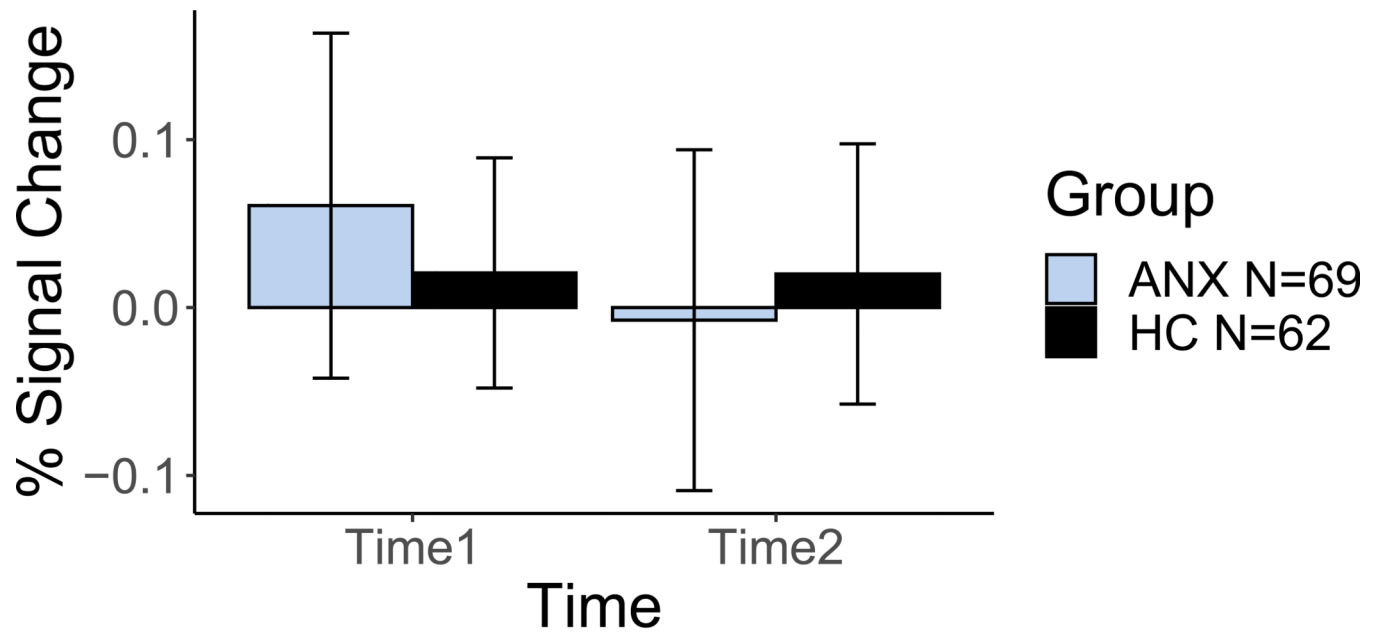
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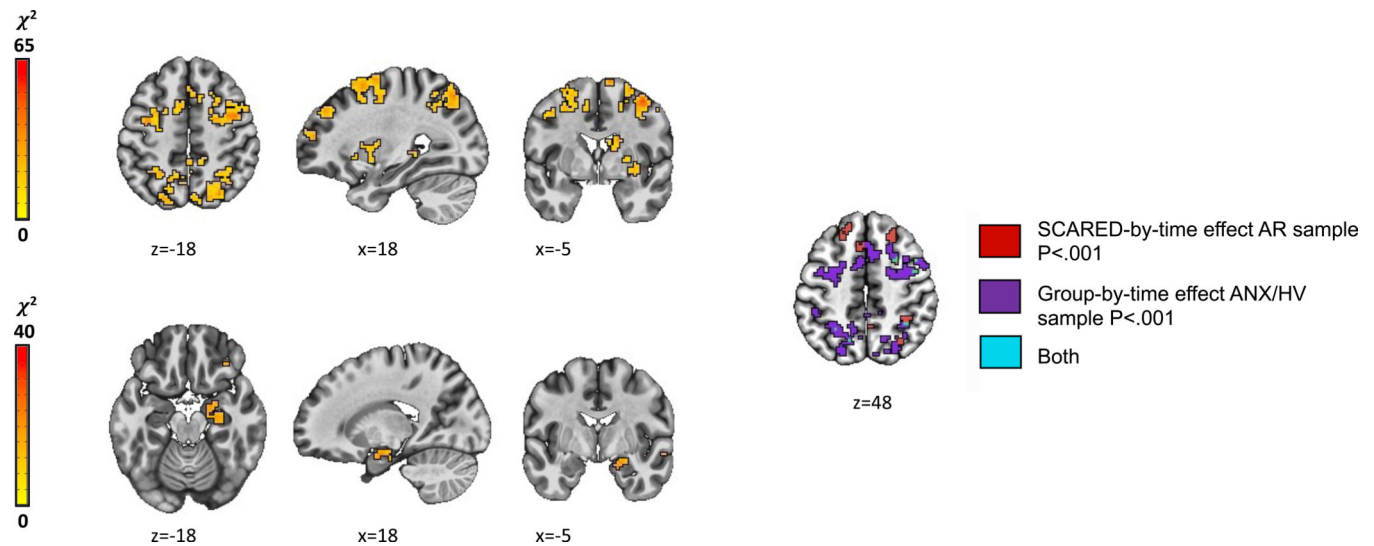
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**Figure 1.**

<sup>a</sup> Panel A shows PARS total score pre- mid- and post-treatment in youth with an anxiety disorder, both individual trajectories and the average trajectory with associated standard deviations at each time point. Panel B shows mean RT and associated standard deviations across all task conditions pre- and post-treatment in youth with an anxiety disorder benchmarked against a group of healthy control youth who completed the task at a matched time interval. Error bars represent standard deviation.





**Figure 2.**

<sup>a</sup> Panel A shows clusters with a significant group-by-timepoint interaction alongside mean percent signal change and associated standard deviations for a cluster in the right superior parietal lobule for each time point and group. Panel B shows a significant main effect of group in the right amygdala alongside mean percent signal change in this cluster and associated standard deviations for each time point and group. Panel C shows a conjunction map illustrating the overlap in brain regions that showed increased stable activation with anxiety across the two developmental time points (main effect of anxiety, cluster-corrected) in the absence of treatment and those regions that changed with treatment in the treatment seeing group (group-by-time interaction, cluster-corrected). Error bars represent standard deviation.

Table 1.

Participant characteristics

|                                             | ANX (n=69) |              | HC (n=62) |          | Statistic | P-Value | Effect Size |
|---------------------------------------------|------------|--------------|-----------|----------|-----------|---------|-------------|
|                                             | n          | Mean (%)     | n         | Mean (%) |           |         |             |
| Male, n (%)                                 | 23         | (33.33%)     | 30        | (48.39%) | X=2.48    | 0.12    | OR=1.87     |
| Age (y), mean (SD)                          |            | (2.98)       |           | (2.23)   | t=1.91    | 0.06    | d=.33       |
| IQ, mean (SD)                               |            | (13.79)      |           | (12.02)  | t=-1.16   | 0.25    | d=-.20      |
| Race <sup>1</sup> , n (%)                   |            |              |           |          |           |         |             |
| Asian                                       | 1          | (2%)         | 3         | (5%)     |           |         |             |
| American Indian or Alaskan Native           | 1          | (2%)         | 0         | (0%)     |           |         |             |
| Black or African American                   | 1          | (2%)         | 14        | (23%)    |           |         |             |
| Multiple Races                              | 10         | (14%)        | 6         | (10%)    |           |         |             |
| Native Hawaiian or Other Pacific Islander   | 1          | (2%)         | 0         | (0%)     |           |         |             |
| White                                       | 50         | (73%)        | 19        | (31%)    |           |         |             |
| Unknown or Undeclared                       | 5          | (8%)         | 19        | (31%)    |           |         |             |
| Ethnicity, n (%)                            |            |              |           |          |           |         |             |
| Latino or Hispanic                          | 9          | (13%)        | 2         | (3%)     |           |         |             |
| Not Latino or Hispanic                      | 56         | (81%)        | 42        | (68%)    |           |         |             |
| Unknown or Undeclared                       | 4          | (6%)         | 18        | (29%)    |           |         |             |
| Combined family income, n (%)               |            |              |           |          |           |         |             |
| < \$25,000                                  | 5          | (7%)         | 3         | (5%)     |           |         |             |
| \$25,000 – \$39,999                         | 1          | (2%)         | 3         | (5%)     |           |         |             |
| \$40,000 – 59,999                           | 1          | (2%)         | 4         | (7%)     |           |         |             |
| \$60,000 – 89,999                           | 5          | (7%)         | 2         | (3%)     |           |         |             |
| \$90,000 – \$179,999                        | 26         | (38%)        | 18        | (29%)    |           |         |             |
| > \$180,000                                 | 29         | (42%)        | 11        | (18%)    |           |         |             |
| Unknown or Undeclared                       | 2          | (2%)         | 21        | (34%)    |           |         |             |
| PARS total score pre-treatment, mean (SD)   |            | 15.40 (3.75) |           |          |           |         |             |
| CGI-I total score post-treatment, mean (SD) |            | 3.12 (0.88)  |           |          |           |         |             |
| Current diagnoses, n (%)                    |            |              |           |          |           |         |             |
| Generalized Anxiety                         | 55         | (78%)        | -         |          |           |         |             |

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|                    | ANX (n=69) |      |       | HC (n=62) |      |     | Statistic | P-Value | Effect Size |
|--------------------|------------|------|-------|-----------|------|-----|-----------|---------|-------------|
|                    | n          | Mean | (%)   | n         | Mean | (%) |           |         |             |
| Social Anxiety     | 43         |      | (62%) | -         | -    |     |           |         |             |
| Separation Anxiety | 19         |      | (28%) | -         | -    |     |           |         |             |
| Specific Phobia    | 20         |      | (30%) | -         | -    |     |           |         |             |
| Panic Disorder     | 1          |      | (2%)  | -         | -    |     |           |         |             |

*Note.* ANX: Treatment-seeking youth with an anxiety disorder; HC: Healthy Controls; PARS: Pediatric Anxiety Rating Scale; CGI-I: Clinical Global Impressions Scale – Improvement  
<sup>1</sup>Children’s race and sex assigned at birth is based on parents’ report. Race categories are based on the US Office of Management and Budget Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity.

**Table 2.**  
Summary of group-level activation for main effect of group and the group-by-timepoint interaction.

| Region                           | K  | mm3  | CM LR | CM PA | CM IS | Mean  | SEM  | Anx-HC difference value | t(127) | p-value  |
|----------------------------------|----|------|-------|-------|-------|-------|------|-------------------------|--------|----------|
| R Precentral Gyrus               | 93 | 1453 | 40.9  | -20.8 | 55.6  | 17.39 | 0.30 | 0.06                    | 4.73   | $p<.001$ |
| L Precentral Gyrus               | 88 | 1375 | -35.1 | -28   | 62.9  | 16.21 | 0.23 | 0.06                    | 4.70   | $p<.001$ |
| R Parahippocampal Gyrus/Amygdala | 76 | 1188 | 23.3  | -11.6 | -18.8 | 16.92 | 0.28 | 0.04                    | 6.44   | $p<.001$ |
| R Superior Temporal Gyrus        | 40 | 625  | 56.1  | -9.3  | -10.8 | 18.20 | 0.47 | 0.06                    | 4.93   | $p<.001$ |
| L Postcentral Gyrus              | 30 | 469  | -46   | -18.9 | 50    | 16.53 | 0.42 | 0.05                    | 4.74   | $p<.001$ |
| L Middle Frontal Gyrus           | 24 | 375  | -26.8 | 51.4  | 8.6   | 16.18 | 0.41 | 0.03                    | 4.64   | $p<.001$ |
| R Inferior Frontal Gyrus         | 22 | 344  | 35.9  | 32.6  | -13.4 | 17.47 | 0.57 | 0.04                    | 5.08   | $p<.001$ |
| R Inferior Frontal Gyrus         | 21 | 328  | 45.4  | 19.5  | 26    | 16.26 | 0.37 | 0.05                    | 4.44   | $p<.001$ |

| Region                     | k   | mm3  | CM LR | CM PA | CM IS | Mean  | SEM  | ANX: Time 1-2 |         | HC: Time 1-2 |         | ANX>HC Time 1 | ANX>HV Time 2 | p-value | t(127) | p-value  |
|----------------------------|-----|------|-------|-------|-------|-------|------|---------------|---------|--------------|---------|---------------|---------------|---------|--------|----------|
|                            |     |      |       |       |       |       |      | t(127)        | p-value | t(127)       | p-value |               |               |         |        |          |
| R Lingual Gyrus            | 535 | 8359 | 3.6   | -77.8 | 10.2  | 21.42 | 0.30 | -0.03         | -4.07   | $p<.001$     | 0.04    | 4.95          | $p<.001$      | -0.02   | -0.98  | 0.76     |
| R Middle Frontal Gyrus     | 434 | 6781 | 33.3  | 2.2   | 53.5  | 22.07 | 0.40 | 0.04          | 8.50    | $p<.001$     | -0.01   | -2.24         | 0.11          | 0.03    | 3.91   | $p<.001$ |
| R Superior Parietal Lobule | 264 | 4125 | 19.2  | -69.2 | 53.4  | 19.85 | 0.31 | 0.07          | 10.25   | $p<.001$     | 0.00    | 0.09          | 1.00          | 0.04    | 2.90   | 0.02     |
| R Superior Temporal Gyrus  | 256 | 4000 | 55.7  | -41.8 | 20.8  | 22.61 | 0.59 | 0.05          | 10.75   | $p<.001$     | 0.00    | -0.82         | 0.84          | 0.03    | 3.30   | 0.01     |
| R Inferior Temporal Gyrus  | 215 | 3359 | 43.7  | -64.4 | -7.9  | 19.08 | 0.31 | 0.06          | 11.09   | $p<.001$     | 0.00    | 0.40          | 0.98          | 0.03    | 2.06   | 0.17     |
| L Precentral Gyrus         | 189 | 2953 | -31.5 | -1.4  | 53.9  | 18.96 | 0.35 | 0.04          | 8.76    | $p<.001$     | -0.01   | -1.26         | 0.59          | 0.02    | 1.88   | 0.24     |
| L Inferior Parietal Lobule | 180 | 2813 | -21.7 | -55.2 | 47.7  | 21.35 | 0.53 | 0.03          | 9.19    | $p<.001$     | -0.01   | -2.03         | 0.18          | 0.01    | 1.30   | 0.56     |
| L Middle Occipital Gyrus   | 171 | 2672 | -46.4 | -70.3 | 2.2   | 19.87 | 0.33 | 0.06          | 10.57   | $p<.001$     | 0.01    | 1.43          | 0.48          | 0.03    | 2.12   | 0.15     |
| L SMA                      | 135 | 2109 | 1.3   | 10.6  | 46    | 18.93 | 0.40 | 0.03          | 5.44    | $p<.001$     | -0.02   | -3.46         | 0.00          | 0.03    | 2.55   | 0.06     |
|                            |     |      |       |       |       |       |      |               |         |              |         |               |               | -0.03   | -4.31  | $p<.001$ |
|                            |     |      |       |       |       |       |      |               |         |              |         |               |               | -0.03   | -1.79  | 0.28     |
|                            |     |      |       |       |       |       |      |               |         |              |         |               |               | -0.03   | -2.60  | 0.05     |

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| Region                     | k   | mm3  | CM LR | CM PA | CM IS | Mean  | SEM  | ANX: Time 1-2 |        | HC: Time 1-2 |        | p-value | t(127) | ANX>HC Time 1 | p-value | ANX>HV Time 2 | t(127) | p-value |        |
|----------------------------|-----|------|-------|-------|-------|-------|------|---------------|--------|--------------|--------|---------|--------|---------------|---------|---------------|--------|---------|--------|
|                            |     |      |       |       |       |       |      | Time 1        | Time 2 | Time 1       | Time 2 |         |        |               |         |               |        |         |        |
| R Putamen                  | 123 | 1922 | 31.1  | 8     | -0.7  | 19.37 | 0.38 | 0.02          | 4.51   | p<.001       | -0.19  | -4.64   | p<.001 | 0.02          | 3.46    | 0.00          | -0.02  | -2.56   | 0.06   |
| L Middle Occipital Gyrus   | 98  | 1531 | -28   | -72.2 | 29.1  | 20.71 | 0.62 | 0.04          | 8.30   | p<.001       | 0.00   | -0.11   | 1.00   | 0.01          | 1.01    | 0.74          | -0.03  | -2.48   | 0.07   |
| R Caudate Nucleus          | 89  | 1391 | 15    | -5.1  | 17.5  | 20.84 | 0.55 | 0.02          | 2.78   | 0.03         | -0.04  | -5.71   | p<.001 | 0.05          | 4.69    | p<.001        | -0.01  | -1.11   | 0.68   |
| R Middle Frontal Gyrus     | 61  | 953  | 29.6  | 44.3  | 34.3  | 19.40 | 0.57 | 0.01          | 1.89   | 0.23         | -0.04  | -6.23   | p<.001 | 0.03          | 3.67    | 0.00          | -0.02  | -1.76   | 0.30   |
| L Middle Frontal Gyrus     | 57  | 891  | -35.8 | 48.8  | 2     | 19.29 | 0.65 | -0.03         | -4.94  | p<.001       | 0.02   | 3.28    | 0.01   | -0.01         | -0.97   | 0.77          | 0.04   | 4.82    | p<.001 |
| L Middle Cingulate Cortex  | 54  | 844  | -10.1 | 12.7  | 36.1  | 18.80 | 0.63 | 0.02          | 4.07   | p<.001       | -0.02  | -3.81   | p<.001 | 0.03          | 3.27    | 0.01          | -0.01  | -1.77   | 0.29   |
| R Middle Occipital Gyrus   | 53  | 828  | 34.1  | -68.7 | 36.5  | 18.75 | 0.49 | 0.04          | 7.94   | p<.001       | 0.00   | -0.11   | 1.00   | 0.03          | 3.36    | 0.01          | -0.01  | -1.43   | 0.48   |
| R Precuneus                | 53  | 828  | 6.8   | -44.1 | 53.3  | 19.33 | 0.75 | 0.01          | 2.39   | 0.08         | -0.04  | -5.66   | p<.001 | 0.04          | 3.52    | 0.00          | -0.01  | -0.59   | 0.93   |
| R Inferior Parietal Lobule | 52  | 813  | 31.7  | -54.4 | 47.6  | 16.75 | 0.35 | 0.05          | 9.64   | p<.001       | 0.01   | 2.06    | 0.04   | 0.01          | 1.02    | 0.74          | -0.03  | -2.74   | 0.04   |
| R Rolandic Operculum       | 49  | 766  | 46.4  | -12.6 | 12.3  | 18.41 | 0.62 | -0.04         | -7.07  | p<.001       | 0.01   | 1.80    | 0.28   | -0.01         | -0.59   | 0.93          | 0.05   | 4.72    | p<.001 |
| L Superior Parietal Lobule | 43  | 672  | -21   | -73   | 45.8  | 20.46 | 0.80 | 0.05          | 7.74   | p<.001       | 0.00   | -0.74   | 0.88   | 0.03          | 1.72    | 0.32          | -0.03  | -1.78   | 0.29   |
| L Precuneus                | 42  | 656  | -14.4 | -71.4 | 59.1  | 21.68 | 1.15 | 0.08          | 8.44   | p<.001       | -0.01  | -0.65   | 0.92   | 0.02          | 1.10    | 0.69          | -0.06  | -3.14   | 0.01   |
| R Thalamus                 | 40  | 625  | 6.6   | -26.6 | 16.2  | 16.97 | 0.47 | 0.02          | 2.34   | 0.09         | -0.04  | -5.20   | p<.001 | 0.04          | 3.33    | 0.01          | -0.02  | -1.55   | 0.41   |
| R Middle Occipital Gyrus   | 40  | 625  | 36.7  | -77.9 | 18.7  | 19.24 | 0.70 | 0.05          | 8.35   | p<.001       | 0.00   | 0.49    | 0.96   | 0.02          | 1.58    | 0.40          | -0.03  | -1.79   | 0.28   |
| R Superior Frontal Gyrus   | 38  | 594  | 28.4  | 56.7  | 15.1  | 19.96 | 0.77 | 0.02          | 3.22   | 0.01         | -0.04  | -4.51   | p<.001 | 0.05          | 3.93    | p<.001        | -0.01  | -0.63   | 0.92   |
| L Superior Temporal Gyrus  | 37  | 578  | -59.2 | -45.7 | 19.4  | 19.55 | 0.59 | 0.04          | 7.71   | p<.001       | -0.01  | -2.22   | 0.12   | 0.03          | 3.85    | 0.00          | -0.01  | -1.44   | 0.48   |
| Cerebellar Lobule VIIa     | 36  | 563  | -1    | -74.9 | -39.8 | 19.81 | 0.79 | 0.04          | 6.55   | p<.001       | -0.02  | -2.17   | 0.13   | 0.04          | 3.25    | 0.01          | -0.02  | -1.83   | 0.27   |
| L Inferior Occipital Gyrus | 34  | 531  | -24   | -95.9 | -6.1  | 21.00 | 1.01 | 0.04          | 4.23   | 0.00         | -0.04  | -4.04   | p<.001 | 0.07          | 2.90    | 0.02          | -0.01  | -0.44   | 0.97   |

| Region                    | k  | mm3 | CM    |       |       | Mean  | SEM  | ANX: Time 1-2 |        |        | HC: Time 1-2 |        |        | ANX>HV Time 2 | t(127) | p-value | t(127) | p-value |        |
|---------------------------|----|-----|-------|-------|-------|-------|------|---------------|--------|--------|--------------|--------|--------|---------------|--------|---------|--------|---------|--------|
|                           |    |     | LR    | PA    | IS    |       |      | Time 1        | Time 2 | t(127) | p-value      | Time 1 | Time 2 |               |        |         |        |         | t(127) |
| Cerebellar Vermis (4/5)   | 31 | 484 | 1.8   | -61.1 | -14.9 | 20.15 | 1.17 | 0.02          | 5.41   | p<.001 | -0.01        | -2.75  | 0.03   | 0.02          | 3.04   | 0.02    | -0.01  | -1.85   | 0.25   |
| R SMA                     | 30 | 469 | 11    | 0.4   | 72.4  | 21.00 | 1.11 | 0.06          | 8.20   | p<.001 | 0.00         | -0.41  | 0.98   | 0.04          | 2.76   | 0.03    | -0.02  | -1.31   | 0.56   |
| R Superior Temporal Gyrus | 29 | 453 | 45.1  | -31   | 13.7  | 23.76 | 1.44 | -0.04         | -5.90  | p<.001 | 0.02         | 2.52   | 0.06   | 0.00          | -0.16  | 1.00    | 0.06   | 4.63    | p<.001 |
| R Middle Cingulate Cortex | 29 | 453 | 6.6   | 24.1  | 30.8  | 16.46 | 0.42 | 0.02          | 2.95   | 0.02   | -0.03        | -3.83  | p<.001 | 0.03          | 2.80   | 0.30    | -0.02  | -1.72   | 0.32   |
| R Postcentral Gyrus       | 29 | 453 | 46.4  | -34.9 | 59.8  | 19.21 | 0.77 | 0.07          | 6.66   | p<.001 | -0.01        | -1.17  | 0.65   | 0.06          | 2.77   | 0.03    | -0.02  | -0.99   | 0.76   |
| R Hippocampus             | 28 | 438 | 24.4  | -32.9 | 6.2   | 20.11 | 0.99 | 0.01          | 4.14   | p<.001 | -0.02        | -4.83  | p<.001 | 0.03          | 5.38   | p<.001  | 0.00   | -0.90   | 0.81   |
| R Fusiform Gyrus          | 27 | 422 | 43.3  | -39.3 | -18.3 | 20.79 | 0.92 | 0.04          | 7.34   | p<.001 | -0.01        | -0.99  | 0.76   | 0.03          | 3.32   | 0.01    | -0.01  | -0.88   | 0.82   |
| L Superior Temporal Gyrus | 26 | 406 | -41.6 | -37.4 | 19.3  | 19.09 | 0.83 | -0.03         | -3.93  | p<.001 | 0.02         | 3.57   | 0.00   | -0.01         | -1.04  | 0.73    | 0.04   | 3.28    | 0.01   |
| L Lingual Gyrus           | 22 | 344 | -8.5  | -67.2 | -3    | 22.03 | 1.64 | -0.05         | -4.12  | p<.001 | 0.03         | 2.82   | 0.03   | -0.04         | -1.47  | 0.46    | 0.04   | 1.38    | 0.51   |
| Cerebellar Vermis (8)     | 21 | 328 | -0.9  | -57.8 | -29.2 | 19.98 | 1.29 | -0.03         | -3.85  | p<.001 | 0.03         | 4.24   | p<.001 | -0.04         | -4.37  | p<.001  | 0.02   | 1.89    | 0.24   |

*Note.* Cluster-corrected voxel-wise linear mixed-effects model results are presented here summarizing regions showing a main effect of group and those showing a group-by-timepoint interaction. k=number of voxels in cluster, mm3=cluster volume, CM=center of mass of cluster, SEM=standard error of the mean, LR=left-right (x), PA=posterior-anterior (y), IS=inferior-superior (z), anatomical locations: Eickhoff-Zilles macro labels from N27 (MNI\_ANAT space)