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Whole-Brain Resting-State Functional Connectivity Patterns Associated With Pediatric Anxiety and Involuntary Attention Capture

Michael T. Perino,
School of Medicine, Washington University in St. Louis, St. Louis, Missouri

Michael J. Myers,
School of Medicine, Washington University in St. Louis, St. Louis, Missouri

Muriah D. Wheelock,
School of Medicine, Washington University in St. Louis, St. Louis, Missouri

Qiongru Yu,
Department of Psychology, San Diego State University, San Diego, California; Department of Psychiatry, University of California San Diego, San Diego, California

Jennifer C. Harper,
School of Medicine, Washington University in St. Louis, St. Louis, Missouri

Megan F. Manhart,
School of Medicine, Washington University in St. Louis, St. Louis, Missouri

Evan M. Gordon,
School of Medicine, Washington University in St. Louis, St. Louis, Missouri

Adam T. Eggebrecht,
School of Medicine, Washington University in St. Louis, St. Louis, Missouri

Daniel S. Pine,
Development & Emotion Branch, National Institute of Mental Health, Bethesda, Maryland.

Deanna M. Barch,
School of Medicine, Washington University in St. Louis, St. Louis, Missouri

Joan L. Luby,
School of Medicine, Washington University in St. Louis, St. Louis, Missouri

Chad M. Sylvester
School of Medicine, Washington University in St. Louis, St. Louis, Missouri

Abstract

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Address correspondence to Michael T. Perino, Ph.D., at mperino@wustl.edu, or Chad M. Sylvester, M.D., Ph.D., at chad.sylvester@wustl.edu.

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BACKGROUND: Pediatric anxiety disorders are linked to dysfunction in multiple functional brain networks, as well as to alterations in the allocation of spatial attention. We used network-level analyses to characterize resting-state functional connectivity (rs-fc) alterations associated with 1) symptoms of anxiety and 2) alterations in stimulus-driven attention associated with pediatric anxiety disorders. We hypothesized that anxiety was related to altered connectivity of the frontoparietal, default mode, cingulo-opercular, and ventral attention networks and that anxiety-related connectivity alterations that include the ventral attention network would simultaneously be related to deviations in stimulus-driven attention.

METHODS: A sample of children (n = 61; mean = 10.6 years of age), approximately half of whom met criteria for a current anxiety disorder, completed a clinical assay, an attention task, and rs-fc magnetic resonance imaging scans. Network-level analyses examined whole-brain rs-fc patterns associated with clinician-rated anxiety and with involuntary capture of attention. Post hoc analyses controlled for comorbid symptoms.

RESULTS: Elevated clinician-rated anxiety was associated with altered connectivity within the cingulo-opercular network, as well as between the cingulo-opercular network and the ventral attention, default mode, and visual networks. Connectivity between the ventral attention and cingulo-opercular networks was associated with variation in both anxiety and stimulus-driven attention.

CONCLUSIONS: Pediatric anxiety is related to aberrant connectivity patterns among several networks, most of which include the cingulo-opercular network. These results help clarify the within- and between-network interactions associated with pediatric anxiety and its association with altered attention, suggesting that specific network connections could be targeted to improve specific altered processes associated with anxiety.

Pediatric anxiety disorders are common, debilitating, and often indicative of future psychopathology (1). Evidence suggests that pediatric anxiety disorders are associated with disruptions in the connectivity of isolated brain regions from multiple functional brain networks (2,3). In parallel, pediatric anxiety disorders have been linked to attention alterations (4-7), including increased attention to threatening stimuli, increased stimulus-driven attention to salient stimuli more broadly (8), and increased activity in brain regions that are involved in directing stimulus-driven attention (9). Moreover, interventions that modify attention are effective in treating pediatric anxiety disorders (10). What remains unclear, however, is which specific network-network connectivity patterns are linked to specific altered cognitive processes (such as altered attention) in pediatric anxiety disorders. This study addressed these issues by characterizing network-level resting-state functional connectivity (rs-fc), using a functional brain network framework to explore altered within- and between-network connectivity patterns associated with pediatric anxiety severity and with stimulus-driven attention.

Functional brain networks are distributed sets of brain regions in which component regions demonstrate correlated activity at rest (11). Rs-fc can be measured by computing correlations in low-frequency brain activity, as measured with rs functional magnetic resonance imaging (rs-fMRI) (12). Prior work suggests that pediatric anxiety disorders involve altered rs-fc of isolated regions within the cingulo-opercular network (CON)

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(13), the frontoparietal network (FPN) (14), the default mode network (DMN) (15), and the ventral attention network (VAN) (16,17). One hypothesis is that patterns of altered connectivity relate to specific cognitive functions thought to be supported by these networks, such as CON with task-set maintenance, performance monitoring, and error detection (18-21); FPN with moment-to-moment adjustments of executive function (18,22,23); DMN with threat learning (15,24-26); and VAN with stimulus-driven attention (8,27,28).

While suggestive, the full scope of altered network-level connectivity in pediatric anxiety, and how these alterations relate to cognitive functions, has not been well characterized. Prior work has focused on isolated regions of interest (ROIs) or a limited number of networks owing to concerns for low power and a difficulty in addressing multiple comparisons. Network-level analysis (NLA) (29) builds on techniques called enrichment that were adapted for genome-wide association studies (30) and provides one solution to these concerns. NLA identifies significant associations between behavioral measures and connectivity of all possible ROI pairs in the brain (29,31,32) and uses permutation testing to identify whether the observed number of significant brain-connectivity relations are disproportionately distributed among specific network pairs. NLA mitigates the issue of low power by looking within a reduced dimensional space (number of network pairs rather than the number of overall ROI pairs), while using permutation testing to provide a multiple comparison correction at the level of the whole brain. This study uses enrichment analyses to measure anxiety-related alterations in connectivity within and between all functional brain networks, providing one of the first comprehensive accounts of network-level pathophysiology.

An additional gap concerns whether alterations in specific network pairs relate to specific phenotypic features of anxiety disorders. Our own prior work has focused on increased stimulus-driven attention in pediatric anxiety (8), which has been linked to increased task-evoked activity in the VAN (9). We have hypothesized that rs-fc alterations in the VAN may underlie these processes (2), with indirect evidence linking behavioral inhibition, an early predictor of anxiety symptomology (33-35), with altered rs-fc (36) of specific VAN ROIs. The specific subset of network-network connectivity alterations linked to altered stimulus-driven attention, however, has not been well explored. Identifying alterations associated with specific features of anxiety disorders could facilitate the development of targeted treatments to address neurobiological alterations underlying specific symptoms or processes.

The goal of this study was twofold: 1) to characterize network rs-fc alterations associated with pediatric anxiety disorders and 2) to relate these network-level connectivity patterns to stimulus-driven attention in pediatric anxiety disorders. To accomplish these goals, we computed rs-fc among validated cortical regions (37,38), representing different functional networks (39) in 61 children (31 with a current pediatric anxiety diagnosis and 30 children without any psychiatric diagnosis). In a previous study with this same sample, we used a behavioral and fMRI task and observed that anxiety was related to increased stimulus-driven attention and increased attention-evoked VAN activity within the inferior frontal gyrus (9). In this study, we explored the relationship of anxiety and this attention alteration within the same sample to rs-fc networks using enrichment analysis. The rs-fMRI data evaluated in this study have not previously been studied. We hypothesized that 1) pediatric anxiety

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would be related to alterations in network-level connectivity, including the VAN, CON, DMN, and FPN, and 2) alterations in stimulus-driven attention would be associated with alterations in the subset of anxiety-related connectivity differences that include the VAN. Finally, in a series of post hoc analyses to examine specificity, we explored the differential associations of these functional connectivity patterns to anxiety accounting for comorbid psychopathology (depression, attention-deficit/hyperactivity disorder [ADHD]).

METHODS AND MATERIALS

Participants

Participants with and without anxiety disorders were recruited from the Greater St. Louis area. Children with clinically significant anxiety were recruited by advertising at informational talks about child anxiety directed at parents and delivered by the senior author (CMS). After the initial recruitment, exclusion criteria, including current use of a psychotropic medication, intellectual disability, autism, or a learning disability, were applied at screening. Of the 149 children preliminarily enrolled, 6 were later excluded owing to evidence of a disqualifying diagnosis during formal assessment. Additionally, 14 were excluded owing to poor performance on the attention task described below. The final behavioral sample consisted of 129 children (mean age = 10.56 years old; SD = 1.4; range = 7.7–13.5 years), of which 71 were invited to participate in a subsequent neuroimaging visit (see Recruitment in the Supplement). Participants in this study were previously characterized (9) using task-based fMRI. In the same MRI session, they completed resting-state scans, which have not previously been reported and are the focus of this study. Characteristics of the sample are presented in Table 1. The Institutional Review Board at Washington University School of Medicine approved all procedures. Informed consent was obtained from parents and assent was obtained from all child participants.

Clinical Measures

Parents and children were separately interviewed by master's level clinicians and assessed following procedures developed for the Research Unit on Pediatric Psychopharmacology Anxiety Study (40,41). Clinician-rated measures included the Kiddie Schedule for Affective Disorders (42) for DSM-5 psychiatric diagnoses and the Pediatric Anxiety Rating Scale (PARS) (41) for a dimensional measure of anxiety. To ensure reliability, periodic meetings—involving lectures, joint assessments, and weekly meetings between senior clinicians (CMS, JLL, DSP) and master's level clinicians—were enacted. Audiotapes of interviews were recorded and reviewed regularly by the senior author (CMS). Additionally, measures of depression (43) and ADHD (44) were collected.

Stimulus-Driven Attention

Previously (9), participants from this exact sample completed a novel computerized Posner attention task to determine which components of attention processing (e.g., involuntary attention, inhibition of return) and cue types (e.g., faces, objects) were related to pediatric anxiety. Participants indicated whether a target arrow that appeared at one of two possible (left/right) screen locations was pointing up or down. The target was preceded in time by a cue (square box or a face) that was presented either in the same (valid) or opposite

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(invalid) location as the target. The cue-target stimulus-onset asynchrony was 200, 500, or 800 ms, designed to measure different temporal features of stimulus-driven attention (i.e., initial capture of attention, inhibition of return). Results from that study with this sample demonstrated that anxiety was related to attention processing; specifically, there was a significant relation between anxiety and the initial, involuntary capture of attention by square box cues and blood oxygen level–dependent (BOLD) activity in the VAN portion of the inferior frontal gyrus (9). In this study, we used the same sample and behavioral data as the previous study. Based on results from the prior study, we used the behavioral measure of involuntary attention capture (calculated as the difference in reaction times for targets preceded by invalid minus valid square box cues at the 200-ms stimulus-onset asynchrony, referred to throughout as stimulus-driven attention) to explore the relationship of these variables to rs-fc. Of note, while the relationship between anxiety and stimulus-driven attention has a similar effect size to our previous study, the value is not significant in the smaller scanning sample (see Behavioral Attention Task in the Supplement).

Imaging Protocols

Imaging was performed on a Siemens PRISMA 3T MRI scanner (Siemens Healthineers) with a 32-channel head coil. Structural images included a T1-weighted image (sagittal, 208 slices, 0.8-mm isotropic resolution, echo time = 2.22 ms, repetition time = 2400 ms, inversion time = 1000 ms, flip angle = 8°) and a T2-weighted image (sagittal, 208 slices, 0.8-mm isotropic resolution, echo time = 160 ms, repetition time = 3200 ms). Functional imaging was performed, including at least four resting-state runs (420 frames each), using a BOLD multiband echo-planar sequence (repetition time = 720 ms, echo time = 33 ms, flip angle = 52°, 2.4-mm isotropic resolution, multiband factor = 7). Two spin-echo field maps were obtained (one anterior to posterior and one posterior to anterior) during each session with the same parameters. FIRMM (45) was used during scanning to monitor real-time participant movement. Participants who completed the behavioral session and did not have contraindications (e.g., braces, retainers) were invited to scan, resulting in the recruitment of 71 participants (see Recruitment in the Supplement). Sessions were terminated if participants showed an inability to stay still during the scan, as determined by experienced clinical research assistants, resulting in 10 children being excluded for either excessive head motion or poor scan tolerance, leaving a final neuroimaging sample of 61 children (9).

rs-fc Preprocessing

Preprocessing included correction of intensity differences attributable to interleaved acquisition, bias field correction, intensity normalization of each run to a whole-brain mode value of 1000, linear realignment within and across runs to compensate for rigid body motion (46), and linear registration of BOLD images to a Talairach atlas template (47) via the T2- and T1-weighted images. Field map correction was performed by using the FSL TOPUP toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TOPUP). Atlas transformation, field distortion correction, and resampling to 3-mm isotropic atlas space were combined into a single interpolation (46,48).

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Following the initial preprocessing steps, the BOLD time series underwent the rs-fc processing pipeline. First, temporal masks were created to censor high-motion frames based on study-specific protocols described below. Then, censored frames were ignored as the data were processed with the following steps: 1) demean and detrend within run and 2) multiple regression with nuisance time series including white matter, ventricles, and whole brain (49), as well as 24-parameter Volterra expansion regressors derived from head motion (50-52) (see the Supplement for results obtained when excluding global signal regression). Then, we applied a first-order low-pass Butterworth filter (cutoff = 0.1 Hz) to each of the six head realignment parameters, which were summed to create a filtered framewise displacement trace. We censored frames from the filtered framewise displacement trace with values >0.08 mm to further reduce motion artifact (53). Functional runs with fewer than 130 frames were excluded. Only the 61 subjects with at least 670 remaining frames (8.04 min) were included in further analyses. Finally, retained data was interpolated into censored timepoints to allow bandpass filtering (0.009 Hz < f < 0.08 Hz).

FreeSurfer version 5.0.0 was used to generate surfaces for each subject and the volumetric rs-fc processed fMRI data were mapped to subject-specific surfaces using established procedures adapted from the Human Connectome Project as implemented in connectome workbench 1.2.3 (https://www.humanconnectome.org/). fMRI data were aligned across subjects in surface space using spherical registration. Time courses for surface data were smoothed with geodesic 2-dimensional Gaussian kernels (σ = 2.55 mm).

Cortical Parcellation

We applied a variation on a cortical parcellation scheme previously validated in an adult sample (37,54) that contained 333 unique cortical regions to create our connectivity matrix; specifically, we reapplied the Infomap community detection algorithm to a dataset of 120 adults (using 30-mm exclusion distance between parcels) across a range of matrix edge densities (0.3%–5%) while allowing for a minimum community size of 4 parcels. Next, we ran a network identification procedure that matched the observed networks to previously published networks (55). Finally, a consensus procedure was used to collapse the network assignments across edge density thresholds, giving each parcel the assignment it had at the sparsest possible threshold (see the Supplement for greater detail). Per convention with NLA, regions not assigned to any network (i.e., unassigned) were excluded from the matrix, leaving 292 regions representing 15 networks.

Potential Confounds

We conducted a series of analyses to determine if any confounds arose from our recruitment (Tables S1 and S2) or data approach (Table S3). Specifically, we ran zero-order correlations to test whether sample characteristics (age, days between sessions, rs-fc data characteristics) were significantly correlated with either anxiety or stimulus-driven attention in the scanning sample (see Sample characteristics in the Supplement and Table S3).

Enrichment Analyses

Fisher z-transformed Pearson correlation coefficients were computed for each of the possible ROI pairs, which were then grouped by network (15 × 15) for a 292 × 292 matrix and a

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total of 42,486 unique region-to-region connections. Figure 1 shows the parcellation scheme (Figure 1A) and average rs-fc of the scanning sample for each ROI pair, as organized by functional network (Figure 1B). As expected, rs-fc was highly correlated for within-network connections.

To test how the functional connectivity of participants was related to measures of clinical anxiety severity (PARS) and stimulus-driven attention, enrichment analyses were performed (29,56-58). Spearman rank correlations were computed between each ROI pair connectivity value and each of the two individual variables (PARS, stimulus-driven attention). Each connectivity-behavior correlation was then binarized based on statistical significance (uncorrected $p < .05$), and a hypergeometric test was conducted to examine if the number of significant connectivity-behavior relations within each network pair were significantly greater than expected. The hypergeometric statistic assessed the likelihood of observing a given number of strong correlations given the number of significant correlations observed overall and the number of possible hits for that network pair. Significance level for each of these tests was determined via permutation testing (1 million iterations) for each measure (PARS, stimulus-driven attention), providing statistical relations for network pairs that significantly outperformed the null distribution ($\alpha = 0.05$), were nonparametric, controlled familywise error-rates, did not make assumptions about the shape of the population distribution from the observed data, and adjusted to the degrees of correlations between tests. All enrichment analyses and visualizations were performed in MATLAB (release 2015a; The MathWorks, Inc.).

Post Hoc Analyses

To assess the strength and specificity of the rs-fc alterations linked with anxiety in comparison to other comorbid symptoms, we explored the strength of each ROI pair identified via enrichment when controlling for other psychopathology. We ran nonparametric partial correlations between anxiety severity and rs-fc, while controlling for individual metrics of comorbid psychopathology (depression, ADHD).

To assess for evidence of specificity for anxiety or stimulus-driven attention in the ROI pairs, we graphically displayed ROI pair connections that were only related to anxiety, only related to stimulus-driven attention, or related to both anxiety and stimulus-driven attention. To assess the strength of each variable (anxiety vs. stimulus-driven attention) in connections related to both, we conducted regressions where we simultaneously included both anxiety and stimulus-driven attention as independent variables relating to ROI pair connectivity. All post hoc statistical analyses were performed with SPSS (version 26; IBM Corp.).

RESULTS

rs-fc Patterns Related to Anxiety

Figure 2 illustrates the correlation between anxiety and each region-region connectivity value (Figure 2A), the specific connections in which the connectivity-anxiety relation was $p < .05$ (Figure 2B), and the specific network pairs in which there were a disproportionately high number of ROI pairs significantly correlated with anxiety (Figure 2C). Increased

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anxiety was related to increased connectivity (red lines) between the following network pairs: CON and DMN, CON and VAN. Additionally, increased anxiety was related to decreased connectivity (blue lines) between the following network pairs: CON and CON (within-CON connectivity), CON and visual network, CON and primary visual network, and motor mouth and primary visual network (Figure 2D). Treating anxiety categorically (current diagnosis; no diagnosis) led to very similar network-network patterns (Figure S4). Of the identified region-to-region connections that significantly related to anxiety from these 6 network pairs (n = 474 connections), approximately 95% (n = 449) were significant when controlling for at least one comorbid symptom, although it is worth noting variation in the number of connections surviving corrections (Tables S4-S6 for post hoc analyses).

rs-fc Patterns Related to Stimulus-Driven Attention

Figure 3 parallels Figure 2 but shows computed relations with stimulus-driven attention rather than anxiety. Increased stimulus-driven attention was related to increased connectivity between the following network pairs: FPN and DMN, CON and VAN. Additionally, increased stimulus-driven attention was related to decreased connectivity between the following network pairs: VAN and DMN, CON and premotor network, CON and medial parietal network, and CON and auditory network.

CON-VAN was the only network pair that was significantly related to both anxiety and stimulus-driven attention. Among the ROI pairs defining CON-VAN connectivity, 78 ROI pairs were significantly related to anxiety and 79 were significantly related to stimulus-driven attention; 24 of these ROI pairs were significantly related to both (Figure 4; Table S6).

DISCUSSION

This study suggests that pediatric anxiety disorders are associated with rs-fc alterations between at least six different brain network pairs. Most altered network pairs include the CON, which had altered within-network connectivity as well as altered between-network connectivity with the DMN, visual network, primary visual network, and VAN. Furthermore, some ROI pairs associated with anxiety severity survive analyses controlling for comorbid symptoms, suggesting the potential for improved specificity in brain-behavior associations. We found that variation in stimulus-driven attention was associated with altered connectivity among several networks but that only CON-VAN connectivity was associated with both anxiety and stimulus-driven attention. These results highlight the network-level interactions associated with pediatric anxiety disorders and are consistent with the hypothesis that specific disrupted processes in anxiety disorders may be linked to alterations in specific network pairs.

Prior work is consistent with results from this study demonstrating CON disruptions in anxiety disorders. The CON includes the dorsal anterior cingulate and anterior insula and is associated with executive functions, including task-set maintenance, performance monitoring, and error detection (18). Most of the altered rs-fc patterns associated with anxiety included CON regions. We hypothesize that the CON may represent a final common pathway through which different types of processing deficits from other networks (VAN,

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DMN, visual) converge into a central executive function network. Recent large-scale meta-analyses suggest that CON deviations are features of many disorders (59,60). While post hoc analyses in this study suggest that some region-pair rs-fc alterations that included CON regions were linked with anxiety even when accounting for other psychopathology, future work is needed to clarify transdiagnostic versus disorder or symptom-specific rs-fc alterations.

Our findings are also consistent with research linking anxiety disorders to VAN disruptions. The VAN is associated with stimulus-driven attention, the involuntary orientation of attention to suddenly appearing stimuli, and includes the ventrolateral prefrontal cortex, the temporal–parietal junction, and portions of middle and superior temporal gyri (61,62). Capture of attention by threatening stimuli is thought to be central to the etiology of pediatric anxiety disorders (5). An unsettled question is whether the attention alterations observed in pediatric anxiety are threat specific or reflect involuntary attention capture by all salient stimuli (63,64). For example, anxiety is associated with hypervigilance, a state of readiness characterized by a broadly increased focus of attention to environmental stimuli cues independent of valence (6,65). Depression is generally linked with decreased involuntary attention capture (66,67), and ADHD is thought to be unrelated (68), which suggests that uncovering the neurobiology of attention mechanisms may help identify deviations specific to anxiety.

In addition to the CON-VAN connectivity, stimulus-driven attention was related to increased connectivity between the FPN and DMN and decreased connectivity between the VAN and DMN, CON and premotor network, CON and medial parietal network, and CON and auditory network. Notably, each of these network interactions linked to stimulus-driven attention included networks involved in executive control (FPN, CON) or directing attention (VAN). These results are consistent with both executive control and attention-orientating processes influencing the current locus of attention (69). However, future work is required to replicate these findings.

We previously reported that pediatric anxiety was associated with increased stimulus-driven attention and increased activity in VAN regions via a task that engaged stimulus-driven attention (9). Previous studies have also linked pediatric anxiety or specific anxiety risk factors to altered rs-fc that includes individual VAN regions (17,36,70). This study extends this prior work, suggesting that stimulus-driven attention alterations in pediatric anxiety are specifically linked to altered CON-VAN rs-fc. Prior work and these results are consistent with a hypothesized model in which stimulus-driven attention alterations in pediatric anxiety derive from alterations in evoked activity alterations in the VAN, and that altered VAN activity is communicated to the CON through altered CON-VAN connectivity. We also observed relations between anxiety and rs-fc of the CON with the following networks: DMN, visual network, and primary visual network. Previous models suggest that one function of the CON is to distribute information regarding salient stimuli to networks involved in both externally orientated attention and internally orientated processing (i.e., DMN) (71). One speculative possibility, therefore, is that altered connectivity between the CON and these various networks in pediatric anxiety relates to altered use of salient

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information to guide both externally driven (e.g., visual attention) and internally driven (e.g., rumination) psychological processes. Future work is needed to test these hypotheses.

An important implication of this study is that altered network-level connectivity patterns in pediatric anxiety disorders could be parsed into specific network pairs linked to specific cognitive processes or symptoms. Theoretically, altered interactions between specific network pairs could help explain the development of particular symptoms (i.e., altered attention), such that different symptoms may be explained by alterations in different network interactions (72). One possibility is that specific network pair connections could be targeted to determine if dysfunctional processes associated with functional impairment in anxiety (73,74) are malleable. For example, in the future, transcranial magnetic stimulation (75) or cognitive training (76) may target alterations in attention in anxiety disorders by remodeling CON-VAN connectivity.

This study focused on the relations among pediatric anxiety, stimulus-driven attention, and rs-fc; as such, the results from this study should be considered within the context of several limitations. This study was cross-sectional, and an important issue for future work is to describe longitudinal relations among disrupted network interactions, anxiety, and specific altered processes (i.e., attention). Future studies that have large sample sizes and assess multiple different domains of functioning, such as Adolescent Brain Cognitive Development (77), may be able to disambiguate the developmental sequence of these alterations. For example, such work could clarify whether the specificity of CON-VAN interactions relating to both stimulus-driven attention and anxiety is constant across development or whether variation in other network interactions that are related to attention (e.g., VAN-DMN) are additionally relevant to anxiety symptoms at different points in development. While age was not related to anxiety or stimulus-driven attention in this study, previous work has established links between age and various cognitive functions (78). Finally, future work should investigate whether manipulating network pairs (e.g., altering CON-VAN connectivity) through, for example, transcranial magnetic stimulation reduces anxiety and stimulus-driven attention to establish causal relations among the observed associations.

This study highlights that anxiety disorders are associated with alterations in connectivity of many network pairs, most of which include the CON. Alterations in CON-VAN connectivity are associated with both increased anxiety and increased stimulus-driven attention. These results inform the pathophysiology of pediatric anxiety, provide specific connectivity patterns that may be used as biomarkers, and suggest that specific symptoms can be associated with alterations in a specific subset of the full scope of connectivity alterations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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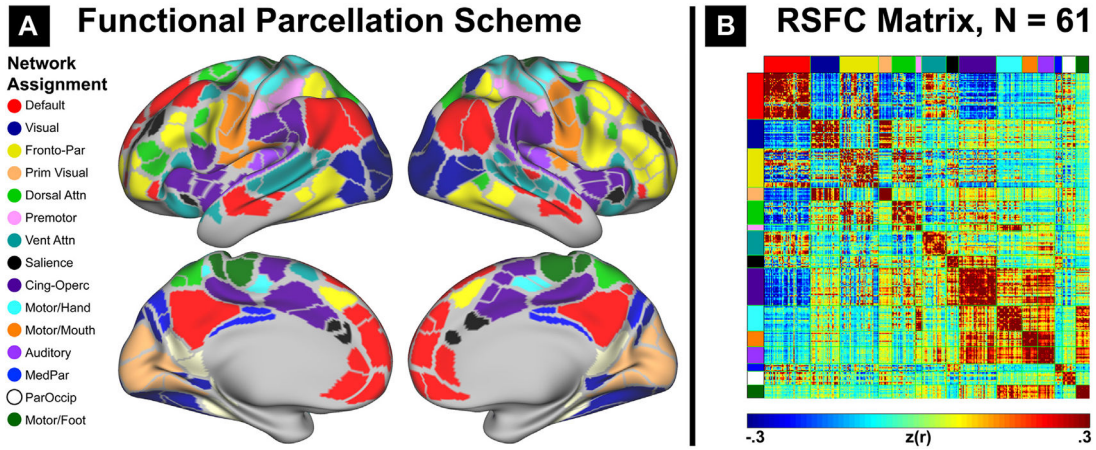

Figure 1.

Functional network assignment and resting-state functional connectivity (RSFC) correlation matrix. **(A)** We used a variation of a validated functional network cortical parcellation scheme (37,54). After removing cortical regions that were unassigned, 292 regions reflecting 15 different functional networks remained for enrichment analyses. **(B)** The average resting-state functional connectivity matrix for all region-of-interest pairs (292 × 292) were organized by functional network assignment. The blocks of color on the top and left side of the matrix indicate the functional brain network assignments of associated regions, with the color key identical to **(A)**. As expected, regions from the same network tended to be more strongly correlated than regions from different networks.

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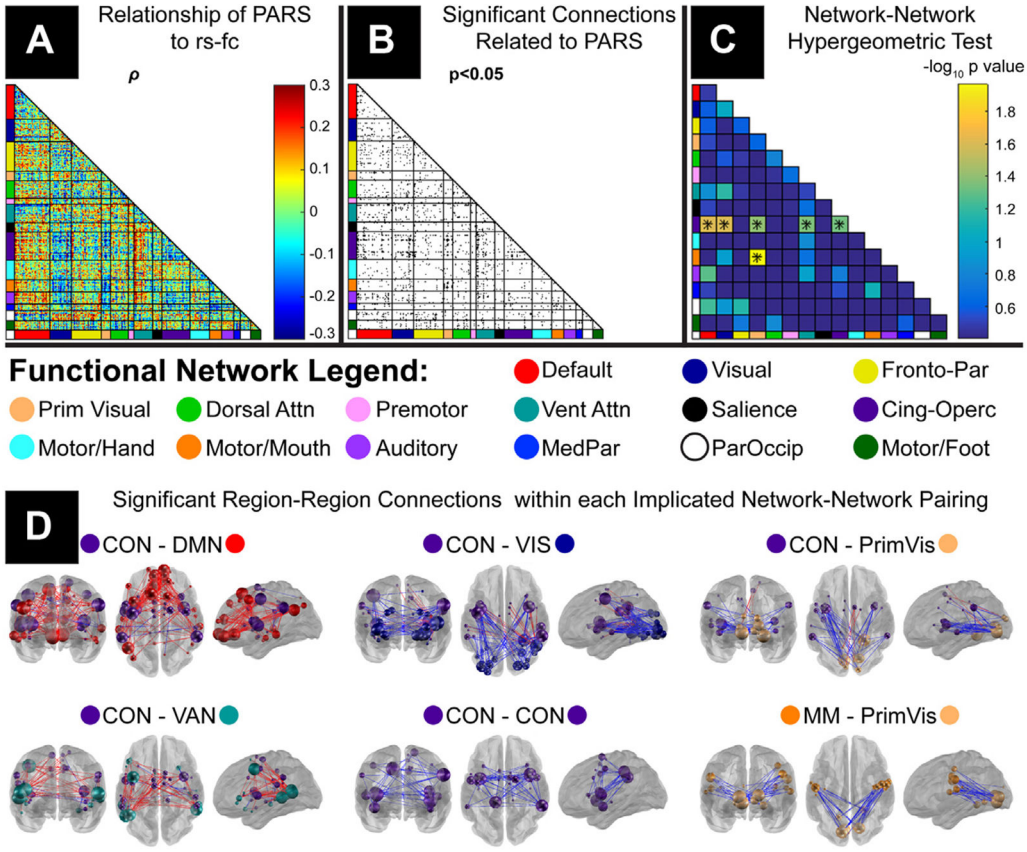

Figure 2.

Significant relations of anxiety to resting-state functional connectivity (rs-fc). **(A)** To perform enrichment analyses, Spearman's correlation between anxiety and every region-region connectivity value were computed. **(B)** Connections determined to be significant ($p < .05$) were identified and binarized to provide a numerical representation of the number of significant connections within each network pair. **(C)** Hypergeometric tests were run to identify network pairs that had a statistically significant number of region-region connections associated with anxiety, with the color scale providing $-\log_{10} p$ values (corresponding to a ceiling of $p < .01$). **(D)** Elevated anxiety was related to increased network-network connectivity of the following network pairs: cingulo-opercular network (CON) to default mode network (DMN), and CON to ventral attention network (VAN). Elevated anxiety was related to decreased network-network connectivity of the following network pairs: CON to visual (VIS), CON to primary visual (PrimVis), CON to CON, and motor mouth (MM) to PrimVis. Each spherical node is centered at the parcel centroid, with larger nodes reflecting a greater number of connections related to anxiety. PARS, Pediatric Anxiety Rating Scale.

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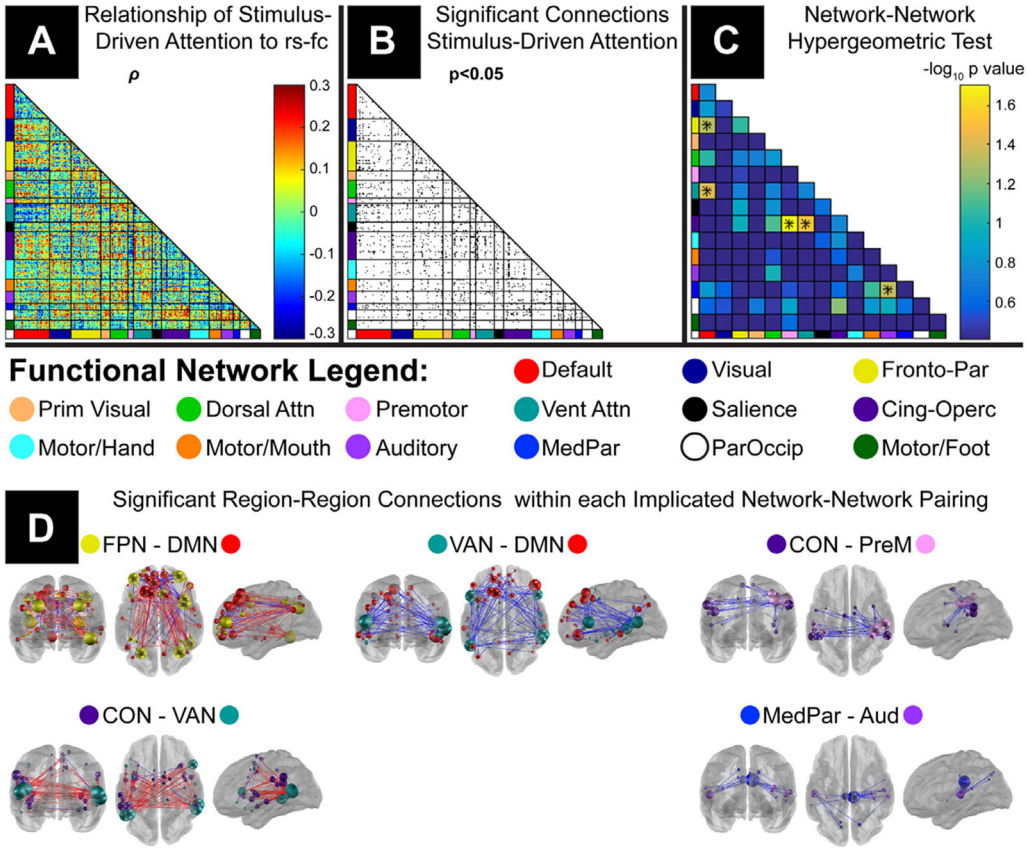

Figure 3.

Significant relations of stimulus-driven attention to resting-state functional connectivity (rs-fc). **(A)** The relationship of stimulus-driven attention to the rs-fc matrix was assessed using Spearman's correlations. **(B)** Connections determined to be significant ($p < .05$) were identified and binarized to provide a numerical representation of the number of significant connections within each network pair. **(C)** Hypergeometric tests were run to identify network pairs that had a statistically significant number of region-region connections associated with stimulus-driven attention, with the color scale providing $-\log_{10} p$ values (corresponding to a ceiling of $p < .01$). **(D)** Elevated stimulus-driven attention was related to increased network-network connectivity of the following network pairs: frontoparietal network (FPN) to default mode network (DMN) and cingulo-opercular network (CON) to ventral attention network (VAN). Elevated stimulus-driven attention was related to decreased network-network connectivity of the following network pairs: VAN to DMN, CON to premotor (PreM), and medial parietal (Med-Par) to auditory (Aud). Each spherical node is centered at the parcel centroid, with larger nodes reflecting a greater number of connections related to stimulus-driven attention.

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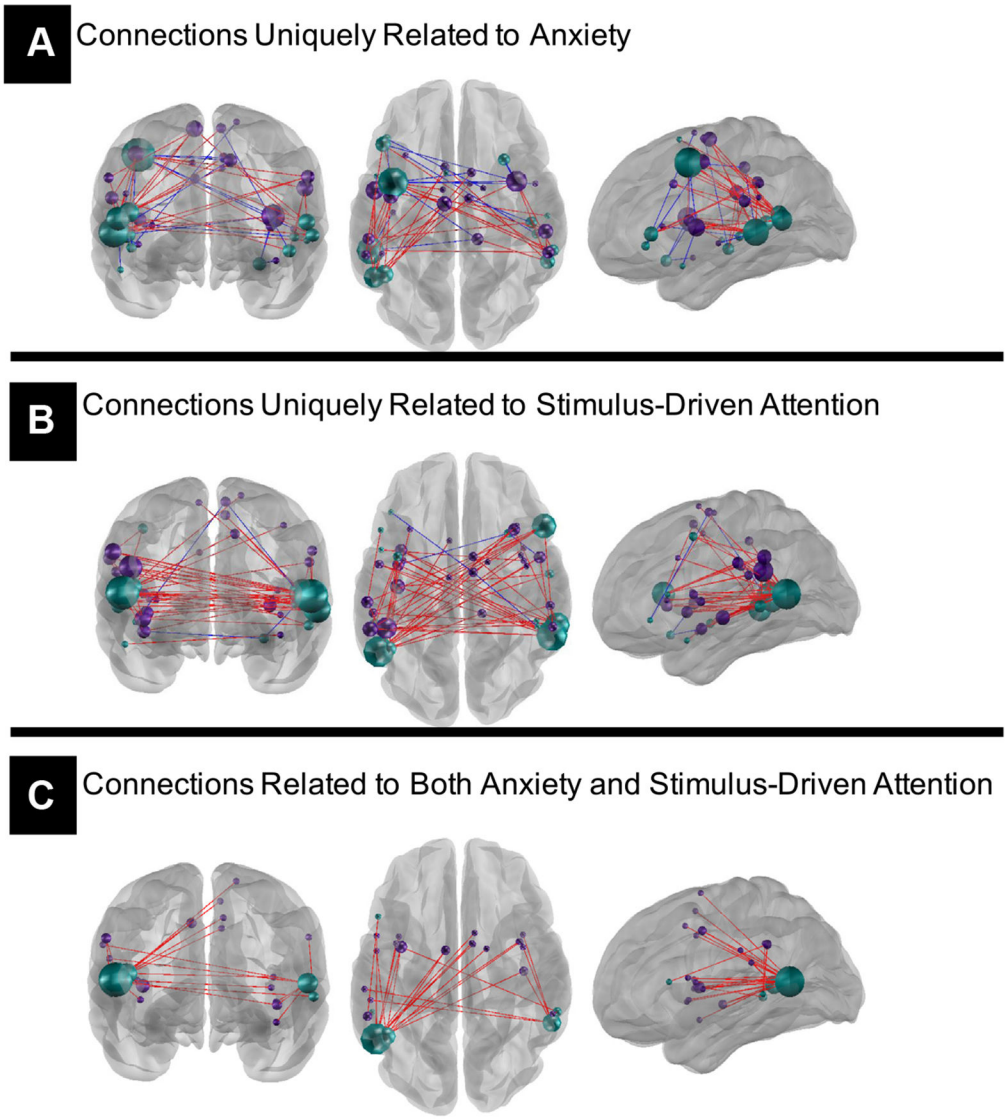

Figure 4.

Unique and shared connections between cingulo-opercular network (CON) and ventral attention network (VAN) related to anxiety and stimulus-driven attention. **(A)** The 54 CON-VAN region-of-interest pairs significantly related to anxiety but not stimulus-driven attention. **(B)** The 55 CON-VAN region-of-interest pairs significantly related to stimulus-driven attention but not anxiety. **(C)** The 24 CON-VAN region-of-interest pairs significantly related to both anxiety and stimulus-driven attention. These 24 connections in **(C)** primarily consist of bilateral posterior superior temporal sulcus regions in the VAN connecting to disparate CON regions. Node size reflects the number of significant connections related to each region. Line color indicates the direction of the relation (red = positive connectivity; blue = negative connectivity).

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Table 1.

Descriptive Statistics of Demographic, Behavioral, Clinical, and Resting-State Functional Connectivity Data

	n	Mean	SD
Demographic Characteristics (*n* = 61)			
Sex			
Female	31		
Male	30		
Race			
White	50		
Black	3		
Asian	1		
Biracial/multiracial	7		
Age, Years		10.48	1.33
Clinical Psychopathology Measures			
PARS severity sum scores		15.20	8.96
CDI-Child total		5.85	5.23
CDI-Parent total		8.56	6.25
Connors-3: Hyperactivity		2.18	2.87
Connors-3: Inattention		2.46	2.34
RS-fMRI Characteristics			
Days between sessions		41.61	45.10
Mean filtered FD, mm		0.029	0.008
Retained frames per subject		1760.62	832.44
Retained data per subject, min		21.13	9.99

CDI, Children's Depression Inventory; FD, framewise displacement; PARS, Pediatric Anxiety Rating Scale; RS-fMRI, resting-state functional magnetic resonance imaging.