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Preschool Executive Function Predicts Childhood Resting State Functional Connectivity and ADHD and Depression

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ADHD and Depression

by
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Table of Contents

List of Tables

List of Figures

Acknowledgments

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ABSTRACT OF THE THESIS

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Background: Measures of executive function (EF), such as the Behavior Rating Inventory of

Executive Function, distinguish children with Attention-Deficit/Hyperactivity Disorder (ADHD)

from control children, but less work has examined relationships to depression or brain network

organization. This study examined whether early childhood EF predicted a new onset or

worsening of ADHD and/or depression, and examined how early childhood EF related to

functional connectivity of brain networks at school age. Methods: Participants were 247 children,

enrolled at ages 3-6, from a prospective study of emotion development. The BRIEF Global

Executive Composite (BRIEF-GEC) was used as the measure of EF in early childhood to predict

subsequent ADHD and depression diagnoses and symptoms across school age. Resting state

fMRI network analyses examined global efficiency in the frontal-parietal, cingulo-opercular,

salience, and default mode networks and six 'hub' seed regions selected to examine seed-based

connectivity. Results: Early childhood BRIEF-GEC predicted worsening and new onsets of

ADHD and depression across school age. Increasing EF deficits predicted increased global

efficiency in the salience network and altered connectivity with four regions for the dorsal

anterior cingulate hub and one region with the insula hub. This altered connectivity was related

to increasing ADHD and depression symptoms. Conclusions: Early executive deficits may be an early common liability for risk of developing ADHD and/or depression and were associated with altered functional connectivity in networks and hub regions relevant to executive processes. Future work could help clarify whether the same subtypes of EF deficits are implicated in the development of both disorders.

Introduction

Executive function (EF) deficits in young children may be an important marker for later development of mental disorders such as Attention-deficit/hyperactivity disorder (ADHD) or Major Depressive Disorder (MDD). EF involves the ability to regulate cognitive resources in order to engage in goal-directed behavior, especially in novel situations where more automatized responses are not feasible (1). Previous research provides mixed evidence on whether performance-based neuropsychological tasks that measure the cognitive processes of EF predict ADHD or depression (2). Despite the known limitations of parent report of child behavior, strong relationships between parent rating scales of EF and clinical outcomes have been shown with measures such as the Behavior Rating Inventory of Executive Function (BRIEF) (3). In children, the type of self-regulatory deficits assessed by the BRIEF may be related to disorders such as ADHD and depression as early as preschool. The BRIEF has been identified as a useful tool for assessing EF deficits in ADHD (4, 5) and has been shown to differentiate ADHD sub-types (6). However, less work has focused on the relationship between EF and mood disorders in young children, despite evidence of cognitive deficits in depression, which involve aspects of EF, and high rates of co-morbidity of ADHD and MDD (7–9). Research has frequently focused on commonalities between ADHD, other externalizing disorders, and anxiety, while less work has examined cognitive and neuroimaging correlates across ADHD and MDD. Thus, the goal of the current study was to examine whether parent-rated EF deficits in early childhood predicted new onsets or worsening of either ADHD and/or MDD at later developmental time points and to examine functional brain connectivity correlates of early childhood EF deficits.

1

EF begins to develop in early toddlerhood with important advances in the preschool period (10) and continued skill building through early adulthood. EF is theorized to consist of both common factors that contribute to performance on a range of tasks, as well as dissociable components. In individuals diagnosed with ADHD, EF has been shown to be developmentally delayed (11–13), with impairments consistently found in the inhibition, working memory, and set-shifting cognitive domains. Such EF impairments may contribute to a number of symptoms of ADHD, including difficulty with attention, distraction and the ability to complete goal-directed tasks. The presence of EF deficits across a range of domains suggests that clinically it may be useful to focus on EF deficits as a meta-construct, or an aggregate across specific EF domains. Further, while EF deficits occur during the early developmental stages of ADHD for many individuals, to our knowledge there have been no studies that have examined the prospective predictive utility of early childhood EF measured by the BRIEF and ADHD outcomes. Therefore, it remains unclear if EF deficits precede the development of ADHD and other disorders, and whether they might be an early risk for the development of a later diagnosis (13).

EF deficits are not unique to ADHD, and have been observed in depression (14, 15). Impairments in attention and concentration are common in depression, and may relate to underlying EF deficits. These deficits likely contribute to challenges disengaging attention to negative emotional salient information and subsequent emotion regulation (16). While some associations between EF and depression have been shown in adults (17–19), fewer studies have focused on early childhood. EF deficits in preschool-aged children, as measured by the BRIEF, have been previously associated with depression and anxiety in later childhood (20). Children experiencing depression often have symptoms of inattention and increased irritability (21),

suggesting that ADHD and depression may share some overlapping diagnostic features in early childhood. Comorbidity is also common, occurring in approximately 20-30% of child and adolescent cases (8, 9, 22). As such, EF deficits that may be shared across ADHD and depression deserve further exploration, as they may be a common liability for assessing risk of later development of both disorders (13, 19).

Understanding how early EF deficits relate to neural network organization in childhood could help clarify the pathway by which EF deficits may be related to ADHD and/or depression, particularly if common alterations in connectivity are found. To examine network organization, we assessed established functional brain networks (23–25), which are considered to be relatively adult-like by age two (26). Of particular interest were the cingulo-opercular (CON) and fronto-parietal (FPN) networks, thought to be involved in top-down control processes that support goal directed behavior (27). We were also interested in the default mode network (DMN), which shows suppression in activation during novel and demanding tasks (28, 29). Lastly, we were interested in the salience network (SAL), thought to be important for mediating responses to important internal or external signals, and switching between DMN and FPN networks (30).

We used a graph theory approach to understand network organization in relation to EF deficits assessed by the BRIEF. Graph theory quantifies complex networks of information and generates metrics that can be used to describe the functional connections between brain regions (31). To examine the strength of the connections among regions within our networks of interest, we examined global efficiency, thought to represent the functional integration of a given network. In addition, we examined specific "hub" regions within these networks to assess connectivity between networks. Hub regions are highly-connected brain regions thought to integrate information across multiple distinct networks that are thought to be particularly

vulnerable to disease states (34, 35). Previous work has illustrated the importance of flexible

hubs for EF and adaptive task control (32, 33), and disruptions of hub connectivity have been

associated with cognitive dysfunction, including EF deficits (36).

Normative developmental maturation of brain networks has been shown to be disrupted

in disorders such as ADHD, particularly in the organization of the frontal-parietal and cingulo-

opercular networks (37, 38). There has also been some work on the relationship between

neuropsychological tasks that assess EF and resting-state functional connectivity in children. For

example, Marek et al. (2015) (25), found that integration of a cingulo-opercular/salience network

predicted performance on a task thought to measure aspects of EF. Additionally, previous work

has shown atypical connectivity of the DMN in children with preschool onset depression (39).

However, to our knowledge, no studies have examined the relationship between parent reported

EF in early childhood, connectivity profiles, and later ADHD and/or MDD at school age.

Given the research reviewed above, we predicted that preschool-aged children with EF

deficits who had never been diagnosed with ADHD or MDD would exhibit increasing MDD and

ADHD symptoms across development and would be more likely to meet diagnostic criteria at

school age. We expected early childhood EF deficits would show some specificity to later

ADHD and MDD, and would not predict the development of any future disorder. In addition, we

hypothesized that children with EF deficits would exhibit altered functional connectivity in

specific networks and hubs associated with executive control at school age. A limited number of

networks and hubs involved in aspects of EF were selected a priori to maintain a hypothesis-

driven approach and limit corrections for multiple comparisons. Specifically, we expected early

childhood EF to be associated with reduced global network efficiency in the FPN, CON, and

SAL networks, increased global efficiency in the DMN, and altered functional connectivity

patterns with hub regions selected a priori in the SAL/CON and FPN networks. Lastly, we predicted that the altered connectivity associated with early childhood EF would also be associated with ADHD and/or MDD symptoms across school age.

Methods and Materials

Study Sample: The full sample included 247 children, ages 3-6 at time of recruitment, from a longitudinal study of emotion development that oversampled for preschool depression. Families were recruited through community child care sites and primary care clinics using a caregiver completed screening checklist, The Preschool Feelings Checklist (PFC) (40). Detailed recruitment methods, exclusion criteria, and participant details have been described previously (21). Children and primary caregivers participated in 1-7 waves of behavioral assessments. A subset of these children participated in a longitudinal imaging component, completing up to three waves of resting state scans. Only the first scan was included in this study, as this was the most proximal scan to the early childhood BRIEF. This imaging sample included 83 children who were 6-12 years old at the time of their first scan (see Table 1).

Measures: The BRIEF, an 86 item, well-validated rating scale, was completed by the primary caregiver as a measure of childhood EF (3). The BRIEF includes eight clinical scales designed to assess subdomains of EF which form an overall score, the Global Executive Composite (GEC) t-score, where higher scores are more clinically significant EF impairments. The BRIEF-GEC was used as an overall marker of early EF in this study. The BRIEF was first collected at the second wave of behavioral assessments, when the children were between ages 4 and 7, and a combination of the BRIEF and the preschool version (BRIEF-P) (41), was used based on the child's age (cut-off is age 5 for BRIEF-P), herein referred to as the early childhood

BRIEF. Diagnoses of psychopathology were generated at each annual visit using age appropriate psychiatric interviews (Preschool Age Psychiatric Assessment (PAPA): age 3-7 (42), Child and Adolescent Psychiatric Assessment (CAPA): age 8 and up (43). Symptom counts for ADHD and MDD at each annual visit were averaged after the early childhood BRIEF visit and used as the outcome variable in dimensional analyses. Diagnostic status across all annual visits after the early childhood BRIEF visit was generated as the outcome variable in categorical analyses.

Data Analysis for Clinical Variables: We conducted a series of regressions in R Studio v0.99.465 to address our hypotheses. Multivariate linear regression was used to examine whether early EF deficits predicted increased MDD and ADHD symptoms measured dimensionally across time, over and above symptom levels assessed in preschool. Binomial logistic regression was used to examine whether early EF deficits predicted a diagnosis of MDD or ADHD over time to assess new onsets in undiagnosed preschoolers. Age, sex, and socioeconomic status were used as control variables. Specificity analyses were completed using the same methods for anxiety, conduct disorder (CD), and oppositional defiant disorder (ODD) to determine whether the BRIEF was a non-specific predictor of broader psychopathology. Further, since ADHD and MDD symptoms are known to be correlated, we were interested in whether the BRIEF predicted either ADHD or MDD because of their association with each other. To test this, cumulative average symptom scores for ADHD and MDD were added to the regression model of the other disorder to test whether comorbidity accounted for the variance explained.

Imaging Methods: A subset of children were scanned on a Siemens 3.0-T Tim Trio and completed up to three annual waves. The scanning protocol included two T1 structural scans and two resting state fmri (rsfMRI) scans (~6.8 mins, TR=2.5, 4mm^3 voxels, 164 frames). Standard preprocessing methods, including global signal regression, were used to reduce motion artifact

and other confounds (see supplement for details). Children who completed scan 1 were included in this study if there were at least 110 frames remaining after motion scrubbing (FD 0.2mm). To further control for potential individual differences in movement, each subject's average pre-scrub FD was included as a covariate in imaging analyses.

Network Analyses: To examine the strength of the connections among regions in particular networks we used the graph theory metric global efficiency, which represents the average inverse shortest path length of all node pairs in a network, and is thought to represent a network's functional integration. Efficiency metrics were calculated at 1-10% tie-density thresholds, preserving the strongest 1-10% of correlations, in 1% increments. Although there is no "correct" threshold (23), we tested an average of the top 1-5% and 6-10% of the strongest correlations. Global efficiency in our four a priori networks in relation to EF was examined using multivariate linear regression in R Studio v0.99.465 and Bonferroni multiple comparison corrections were performed.

Seed Based Analyses: Six 'hub' like seeds were selected based on high participation coefficients and previous association with executive function from the list of nodes in the Power 264 set (23). Three seeds were selected in the CON/SAL network in the right and left insula, and the dorsal anterior cingulate. Two seeds were selected in the Dorsal Attention network in the middle frontal gyrus and precuneus. The final seed was in the middle frontal gyrus of the FPN (see supplement Table S1 for coordinates). These seeds were used to create functional connectivity seed maps for each child of the correlations between each of these seeds and all the other voxels in the CON/SAL and FPN networks. Linear regression using an in-house software (FIDL analysis package, http://www.nil.wustl.edu/labs/fidl/index.html) was used to examine whether early childhood EF impairments were related to variation in connectivity between the

hub regions and any voxels in the CON or FPN networks. To reduce the search space, a mask was applied for only these two networks, both thought to be involved in top-down control (27). Spherical ROIs were drawn around coordinates published by Power et al. (23), for the CON and FPN networks to create this mask. Significance thresholds were set using AFNIs 3dclustsim (Version AFNI_16.2.09) at p=.005, z=2.83, and 27 contiguous voxels for a whole-brain false positive rate of 0.05.

To further explore the interrelationships between early childhood EF, functional connectivity, and ADHD/MDD symptoms, we conducted Pearson product-moment correlations between ADHD/MDD symptoms and the global efficiency and hub connectivity metrics predicted by BRIEF-GEC.

Results

ADHD and EF: <u>Dimensional</u>**:** Multivariate linear regression showed that early childhood BRIEF-GEC predicted increased cumulative ADHD symptoms across the study over and above current ADHD symptoms (Figure 1a), controlling for age, gender, IQ, and SES at the early childhood BRIEF visit [β=0.18, 95% CI (0.06, 0.07), p=.003]. Since ADHD and MDD symptoms are known to be correlated, and were strongly correlated in this sample (r=.65, n=260, p<.001), cumulative MDD symptoms were added to the final model, and the results remained significant (p=.006). <u>Categorical:</u> Utilizing logistic regression to examine diagnostic outcomes in children who did not have a diagnosis of ADHD, early childhood BRIEF-GEC predicted new onsets of categorical ADHD diagnoses at school age [Odds ratio=1.05, 95% CI (1.020, 1.086), p=.001], when controlling for current ADHD symptoms, the aforementioned control variables (p=.02), and MDD symptoms (p=.04).

8

MDD and EF: <u>Dimensional:</u> Multivariate linear regression showed that early childhood BRIEF-GEC predicted increased cumulative MDD symptoms across the study over and above current MDD symptoms (see Table 1b), controlling for age, gender, IQ, and SES at the early childhood BRIEF visit [β=0.02, 95% CI (0.01, 0.03), p<.001]. These results remained significant (p=.03), when including cumulative ADHD symptoms. <u>Categorical:</u> Logistic regression showed that the early childhood BRIEF-GEC also predicted a new onset of a categorical MDD diagnosis at school age in children who did not meet criteria for MDD, [Odds ratio=1.05, 95% CI (1.03, 1.08), p<.001], when controlling for current MDD symptoms and the aforementioned control variables (p=.037), but did not remain significant when controlling for ADHD symptoms (p=.60).

To further examine diagnostic specificity, binomial logistic regression analyses were conducted examining ODD, CD, and anxiety as outcomes. Although some basic models were significant, none remained significant when control variables were added (see supplemental Table S2). In addition, since a few children included in the sample had estimated IQ scores below 80 (11 subjects) or were taking psychotropic medications during testing visits (8 subjects), all behavioral analyses were run again with those subjects removed as a follow-up analysis and all results remained significant.

Network Analyses: Higher early childhood BRIEF scores, indicating worse EF, predicted increased global efficiency in the salience network at an average threshold of 1-5% [β=0.003, t(81)=3.36, p=.001, η^2=.003]. This result remained significant when controlling for age, gender, and average FD at the time of scan 1 (p=.002), and when correcting for multiple comparisons using the Bonferroni adjusted alpha level of .0125 (.05/4). However, global

efficiency was not significantly associated with early childhood BRIEF in any other a priori networks.

Hub Based Analyses: As shown in Figure 2, early childhood BRIEF-GEC significantly predicted connectivity with four regions for the left dACC hub seed region. Worse (higher) early childhood BRIEF-GEC scores predicted stronger positive connectivity between the dACC and bilateral anterior insula. Higher BRIEF-GEC scores also predicted stronger negative connectivity between the dACC and DLPFC, as well as the posterior precuneus. In addition, higher early childhood BRIEF-GEC scores predicted stronger negative connectivity between the insula hub seed region and a superior parietal region (Figure 3).

Seed region distributions were graphed as density and scatter plots to visualize the patterns of the results. All children showed positive connectivity between the dACC seed and the bilateral anterior insula regions (Figure 2). When these distributions were binned by quartiles, children in each quartile exhibited connectivity between these regions that was significantly greater than zero (see Figure S1, A and B), regardless of their level of EF deficits on the BRIEF, though the magnitude of this positive connectivity was higher in children with greater EF deficits. However, for the dACC seed and regions in the DLPFC, and posterior precuneus (Figure S1, C and D), some children showed positive connectivity and some showed negative connectivity. All quartiles were significantly different from zero except for the 3rd quartile of the dACC to the posterior precuneus (p=.78). Thus, children with greater EF deficits showed significant negative connectivity between the dACC and both DLPFC and posterior precuneus, while children with minimal EF deficits showed significant positive connectivity.

Next, we asked whether global efficiency and hub connectivity metrics predicted by early childhood BRIEF scores were also correlated with ADHD and/or MDD symptoms through school age. As shown in Table 2, both ADHD and MDD symptoms were significantly correlated with almost all hub metrics predicted by the early childhood BRIEF, but not SAL GE. Interestingly, all metrics correlated with ADHD remained significant when controlling for MDD symptoms (*ps<.05)*, except for the dACC to right insula. However, none of the correlations with MDD remained significant when controlling for ADHD symptoms.

Discussion

In this study, early childhood EF deficits predicted increased cumulative ADHD and depressive symptoms across childhood, over and above symptoms at baseline, age, gender, IQ, and SES. The robustness of this correlation suggests that EF is predicting some unique variance of later symptoms of ADHD and MDD independently. Examining categorical diagnoses, we found that children with EF deficits who did not meet baseline diagnostic criteria for ADHD in early childhood were more likely to be diagnosed with ADHD in later childhood, even when controlling for cumulative MDD symptoms. We found a similar result for MDD, though this result did not remain significant when controlling for cumulative ADHD symptoms. Thus, dimensional symptoms of depression showed greater evidence of prediction by early childhood BRIEF independent of ADHD than did categorical diagnoses of MDD. These results suggest that early EF deficits may be a common liability for the later development of ADHD and/or MDD symptoms. Further, these robust relationships were not found for ODD, CD, or anxiety in this sample, indicating that early EF deficits did not just indiscriminately predict later psychopathology.

11

This work complements and extends previous research with children and adolescents implicating the predictive power of EF deficits in early childhood for two later childhood disorders. Previous research on EF deficits in adult ADHD suggests that cognitive processing deficits may be a risk factor for depression (14), and it is plausible that the distress caused by difficulty implementing goal-directed behavior may represent a risk factor as well. Research has also shown that difficulty shifting attention away from negative emotional stimuli, which may partially reflect EF deficits, might contribute to the risk of developing depression (17, 44). Therefore, early childhood EF deficits could be an important precursor in the development of ADHD and/or MDD. As such, it is important to understand how these behavioral measures of EF relate to alterations in functional connectivity and whether these factors are linked in this risk trajectory between early EF and later ADHD and depression.

In this sample, *EF deficits* predicted increased global efficiency in the salience network. The direction of this finding was somewhat unexpected, as we had predicted *better EF* to be associated with increased global efficiency, since the salience network is thought to be involved in guiding the ability to switch between tasks and regulate attentional fluctuations. The lack of association between EF and global efficiency in the FPN, CON, and DMN may reflect the need to examine more specific aspects of EF in relation to these networks because the BRIEF-GEC provides more a global index from a parent perspective. Alternatively, examination of these networks across later developmental time points may reveal increased evidence for relationships.

Analyses of seed regions shown to be "hubs" in previous work were conducted to examine connectivity across networks. We found that EF deficits predicted stronger positive connectivity between the dACC and bilateral anterior insula, and stronger negative connectivity between the dACC and DLPFC, and the posterior precuneus. The dACC is thought to be

12

important for both the CON and SAL networks. The stronger connectivity of the dACC with the insula may be related to increased activity in these regions when people experience conflict and errors, which is thought to help signal the need for increased cognitive control (45, 46). If children with greater EF deficits are more likely to make errors and experience conflict in cognitive processing, it is possible that this could lead to greater activation and integration of these regions over time. Additionally, we found reduced connectivity between the dACC and both the DLPFC and the precuneus in children with greater EF deficits. As noted above, one hypothesis is that greater activity in the dACC is thought to signal the need for greater cognitive control, which is thought to be supported by the DLPFC and the FPN network. As such, the reduced connectivity between the dACC and DLPFC in children with greater EF deficits may indicate a disruption in the ability to communicate between networks in a way that can effectively enhance EF. Further, the reduced connectivity of the dACC to the precuneus, a part of the DMN, might be related to difficulty balancing between task positive and task negative networks, a role that has been attributed to the description of the dACC in the context of the SAL network (47).

ADHD and MDD symptoms were also significantly correlated with most hub metrics predicted by the early childhood BRIEF, although ADHD symptoms were more robustly correlated and remained significant when controlling for depression. This supported previous research which showed that altered connectivity within highly connected hub regions is associated with psychopathology (48). Additional work has shown that hubs are integration zones of the human brain that are metabolically costly and particularly vulnerable to disease (34, 36), potentially making altered connectivity in these regions particularly important in individuals at greater risk for developing psychopathology.

Several limitations should be noted when considering the results of the current study. Children were oversampled for symptoms of depression during initial recruitment, which may make this sample less generalizable. Despite this, it is notable that findings remained significant when controlling for depressive symptoms in analyses. In addition, we did not have scan data at the time of early childhood BRIEF, nor did we have BRIEF scores at the time of the first two scans. This raises a temporal limitation of our imaging analyses. Future work should examine the links between EF, hub connectivity and network efficiency utilizing longitudinal designs to help clarify the temporal evolution of EF and brain network integration. Finally, since we did not have direct performance based measures of EF, future studies should examine the relationship between performance-based measures and parent-rated EF to help clarify the role specific cognitive processes play in the onset of ADHD and/or MDD symptoms.

The current findings highlight the importance of early EF in the developmental trajectory of both ADHD and MDD. Early childhood EF deficits, as indexed by the BRIEF-GEC, predicted the emergence and worsening of both ADHD and depression symptoms, and were associated with altered functional connectivity in key regions known to be associated with cognitive control. These results suggest that the BRIEF could serve as a behaviorally relevant index of EF that is relatively easy to collect in clinical settings. Critically, research has shown that EF interventions are effective (49), making the early identification of EF deficits essential for the development and course of these disorders throughout childhood.

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Tables and Figures

Table 1. Participant Characteristics

Participants	Time of BRIEF	Scan 1
N	247	83
Age (mean/SD)	5.42 (0.8)	10.08 (1.3)
Gender (female/male)	119/128	40/43
Ethnicity (%Caucasian/African American)	59%/28%	59%/29%
IQ estimate (mean/SD)	105 (14.8)	106 (14.9)

Table 2. Correlations of Connectivity Metrics and ADHD and MDD Symptoms

		BRIEF-GEC[a]	Average ADHD Symptoms	Average MDD Symptoms
dacc seed to insula (R)	Correlation	.46**	.24*	.26**
(+39, +14, -1)	Sig.	0.000	0.015	0.009
dacc seed to dlpfc	Correlation	-.43**	-.22*	-.30**
(-39, +0, +29)	Sig.	0.000	0.026	0.004
dacc seed to insula (L)	Correlation	.42**	0.17	.27**
(-41, +15, +3)	Sig.	0.000	0.064	0.008
dacc seed to precuneus	Correlation	-.44**	-.27**	-.32**
(-28, -64, +40)	Sig.	0.000	0.007	0.002
insula seed to sup. parietal	Correlation	-.53**	-.35**	-.41**
(-28, -63, +44)	Sig.	0.000	0.001	0.000
Salience Network	Correlation	.35**	0.05	0.13
Global Efficiency: K1to5	Sig.	0.001	0.334	0.124
BRIEF-GEC	Correlation	1.000**	.48**	.56**
	Sig.	0.000	0.000	0.000

**. Correlation is significant at the 0.01 level (1-tailed).
*. Correlation is significant at the 0.05 level (1-tailed).
a. All N=81

Figure 1. Dimensional Symptom Regressions

A AVG ADHD Symptoms (at any future time point)

	Model 1			Model 2			Model 3		
	B	CI	p	B	CI	p	B	CI	p
(Intercept)	0.04	-0.06 – 0.15	.409	-0.39	-0.50 – -0.28	<.001	0.17	-0.99 – 1.33	.772
BRIEF-GEC	0.53	0.42 – 0.63	<.001	0.20	0.09 – 0.30	<.001	0.18	0.06 – 0.30	.003
ADHD_S_T3				0.14	0.12 – 0.16	<.001	0.13	0.11 – 0.16	<.001
sex							-0.23	-0.42 – -0.03	.021
agemonths_T3							-0.00	-0.01 – 0.01	.892
SES							0.03	-0.07 – 0.13	.572
IQ							-0.00	-0.01 – 0.01	.613
N	236			230			173		
R^2 / adj. R^2	.297 / .294			.587 / .584			.596 / .581		

ADHD

B AVG MDD Symptoms (at any future time point)

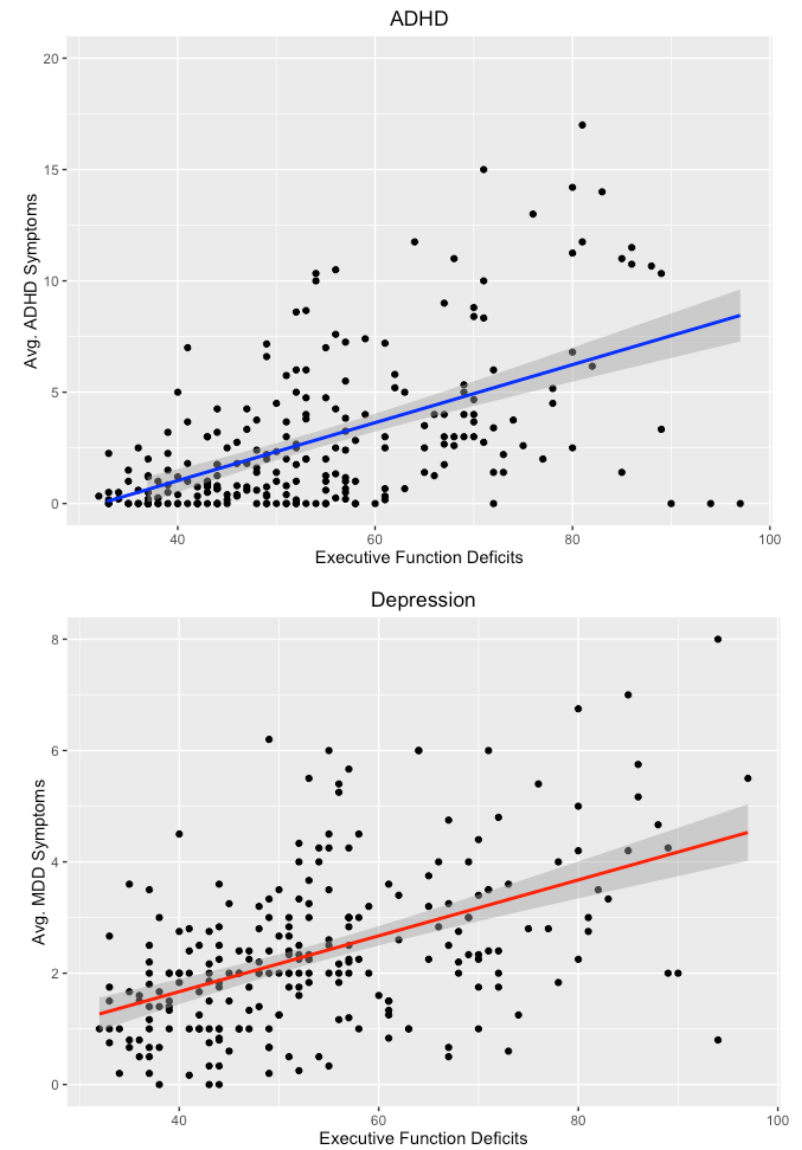|	Model 1			Model 2			Model 3		
	B	CI	p	B	CI	p	B	CI	p
(Intercept)	-1.73	-2.13 – -1.33	<.001	-1.70	-2.08 – -1.32	<.001	-1.60	-3.01 – -0.19	.026
BRIEF-GEC	0.03	0.02 – 0.04	<.001	0.02	0.02 – 0.03	<.001	0.02	0.01 – 0.03	<.001
MDD_S_T3				0.18	0.11 – 0.25	<.001	0.17	0.09 – 0.24	<.001
sex							-0.18	-0.40 – 0.04	.108
agemonths_T3							0.02	0.01 – 0.03	.001
SES							0.01	-0.11 – 0.13	.890
IQ							-0.01	-0.02 – 0.00	.146
N	241			237			174		
R^2 / adj. R^2	.245 / .241			.343 / .338			.377 / .355		

Depression

Figure 2. Resting State Functional Connectivity of the dACC Seed Region and Its Relationship to Executive Function

Figure 3. Resting State Functional Connectivity of the Insula Seed Region and Its Relationship to Executive Function

Figure 1. Dimensional Symptom Regressions

A) Linear regression showing early childhood BRIEF-GEC predicted average school age ADHD symptoms (model 1 and scatter plot). Results remained significant when control variables were included. B) Similar results were found with average school age MDD symptoms.

Figure 2. Resting State Functional Connectivity dACC Seed Region and Its Relationship to Executive Function

A) Region in green is the dACC seed region (-1, 25, 30) showing increased positive connectivity between the dACC and bilateral anterior insula regions (orange) and increased negative connectivity between the dACC and DLPFC and posterior precuneus regions (blue). Seed region distributions were graphed as density (B) and scatter (C) plots to visualize the results.
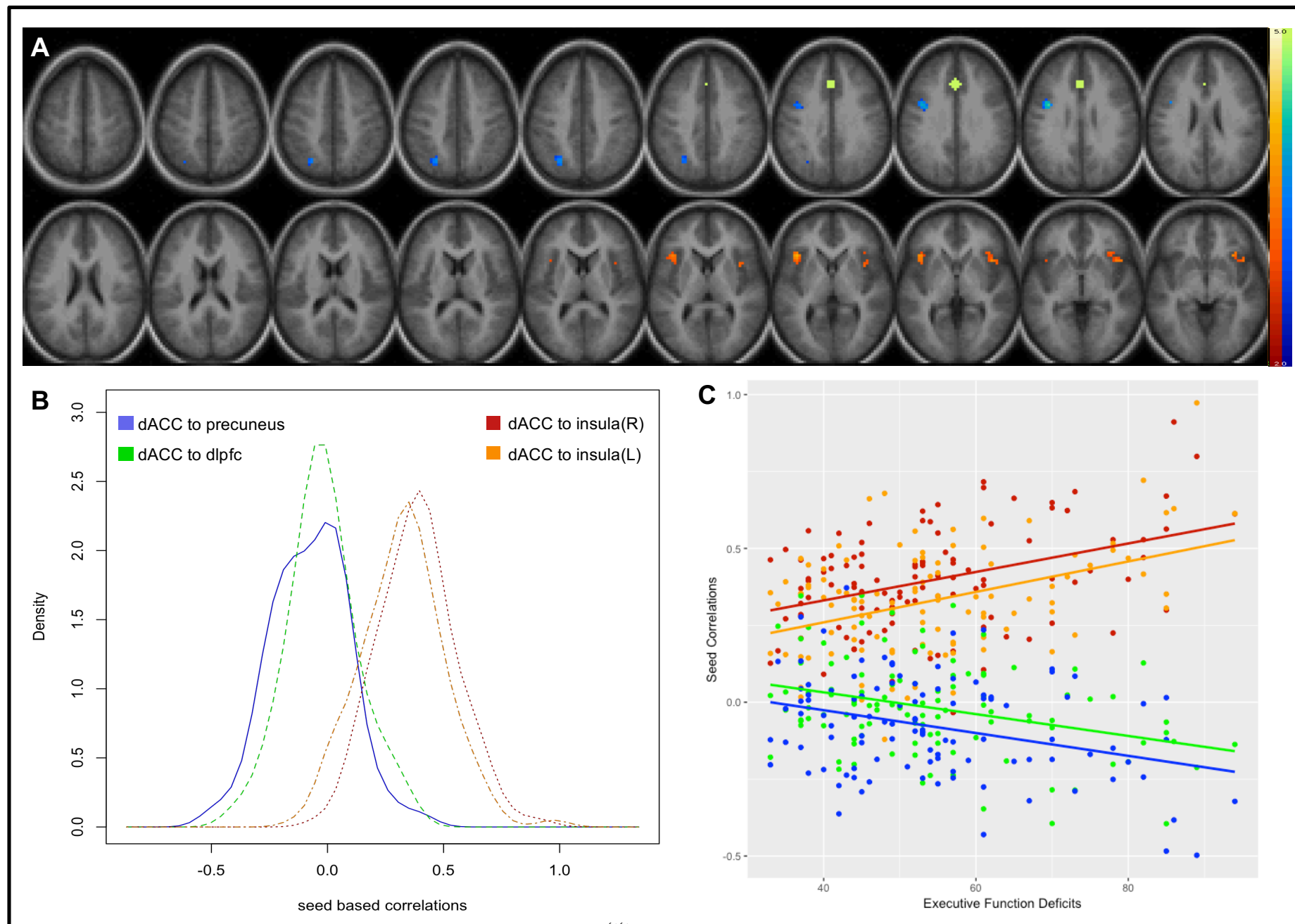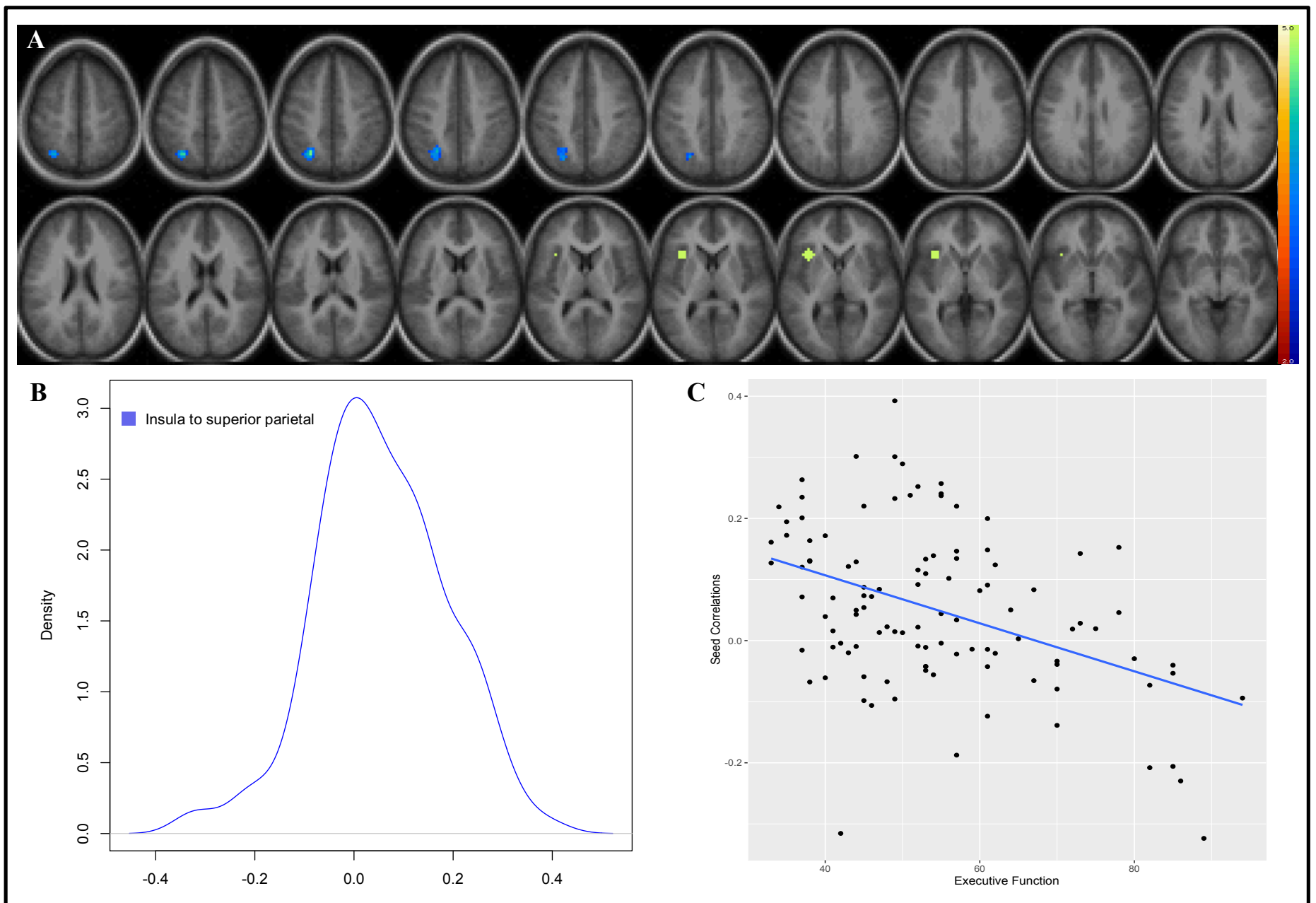
Figure 3. Resting State Functional Connectivity of Insula Seed Region and Its Relationship to Executive Function

A) Region in green is the insula seed region (-34, 16, 3) showing increased negative connectivity between the insula and a superior parietal region (blue). Seed region distributions were graphed as density (B) and scatter (C) plots to visualize the results

Supplemental Information

Additional Behavioral Analyses

To further examine diagnostic specificity, binomial logistic regression analyses were conducted on the full sample using generalized anxiety disorder, conduct disorder and oppositional defiant disorder as outcomes. Although basic models without the covariates were significant, none remained significant when controlling for current symptom counts of each disorder, age, gender, IQ, and SES at the time of the early childhood BRIEF (see Table S2), indicating that early childhood EF deficits showed some diagnostic specificity to ADHD and MDD and was not just a broad predictor of any later psychopathology.

Imaging Acquisition

Scans were performed using a 3.0 Tesla TIM TRIO Siemens whole-body scanner with a 12-channel head coil. Quality assurance measures included having subjects practice in an MRI simulator, giving real-time feedback on subject head motion during structural scans, and recollection of data if necessary. Structural data were obtained using two 3D T1-weighted scans (TR 2,300 ms, TE 3.16 ms, TI 1,200 ms, flip angle 8°, 160 slices, 256 x 256 matrix, field of view 256 mm, 1.0 mm^3 voxels, 6.18 min per scan) in the sagittal plane using magnetization-prepared rapid gradient echo (MPRAGE) sequence. The two MPRAGE scans were assessed visually, and the best one selected for further processing by blind raters. The selected MPRAGE for each scan wave was processed using the longitudinal stream in FreeSurfer v5.3.[1] Two rsfMRI scans were obtained during the same session using the TRIO scanner with T2*-weighted spin-echo echo-planar sequence (TR 2,500 ms, TE 27 ms, flip angle 90°, 36 slices, field of view 256 mm, 4 mm X 4 mm X 4 mm voxels, approx. 6.8 min per scan, 164 frames) in the axial plane. Subjects were instructed to remain awake and rest with their eyes closed during the resting state scan. To

facilitate registration between structural T1 and functional scans, a T2 image was acquired in the same space as the functional scans (TR 2,500 ms, TE 96 ms, flip angle, 36 slices, field of view 256 mm, 1 x 1 x 3 mm voxels).

<u>Functional Connectivity Processing</u>

Processing of the rsfMRI scans involved (1) correcting for slice-dependent time shifts, (2) removing the first five images from each run, allowing for the BOLD signal to reach steady state, (3) eliminating odd/even slice intensity differences due to interpolated acquisition, (4) realignment of data acquired from each subject within and across runs to compensate for rigid body motion, (5) intensity normalization to a whole-brain mode value of 1,000, (6) Registration of the 3D structural volume (T1) to the atlas representative template in the Talairach coordinate system [5] using a 12-parameter affine transform and resampling to a 1mm cubic representation,[6] (7) co-registration of the 3D fMRI volume to the participant's T2 image, and the T2 image to the participant's T1 structural image and (8) transformation of the fMRI image to a 3 mm x 3 mm x 3 mm voxel atlas space using a single affine 12-parameter transform.

Further preprocessing steps were performed using in-house software written in Matlab (Mathworks, Natick, MA). Nuisance variables, including ventricle, whole-brain, and deep white matter signal (defined using FreeSurfer segmentation), as well as six head realignment parameters and their first derivatives, were regressed from the BOLD data. A temporal bandpass filter was applied (0.009 Hz < f < 0.08 Hz), and spatial smoothing was applied using a 6-mm full-width half-maximum Gaussian filter. Average global signal and its derivate were regressed out, based upon evidence that this reduces motion and signal artifacts.[7-10] Frames with excess head motion artifact were censored based on frame-wise displacement (FD),[9] calculated by the sum of the absolute values of the six linear and rotational head displacement values from

realignment parameters. Volumes with frame-wise displacement greater than 0.2 were censored and scan runs with less than 40 frames after censoring and participants with less than 110 frames after censoring were excluded from analyses. Lastly, the initial rs-fcMRI processing was reapplied to the raw data interpolating over the censored frames.[9] Application of these quality assurance approaches results in usable rsfMRI data available for N = 123, 143, and 130 respectively across the three scan waves.

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Supplemental Tables and Figures

Table S1. Details of Selected Hub Regions Used as Seeds in Connectivity Analyses.

Seed	Participation Coefficient	Num. Voxels	Suggested System	x	y	z	Hemi-sphere	Lobe	Gyrus	Brodmann
1	5.93	19	Dorsal attention	26	-9	54	R	Frontal	Middle Frontal	area 6
2	5.79	19	Dorsal attention	20	-66	45	R	Parietal	Precuneus	area 7
3	5.46	19	Salience	-34	16	3	L	Sub-lobar	Insula	area 13
4	5.38	19	Salience	34	17	7	R	Sub-lobar	Insula	area 13
5	4.88	19	Salience	-1	25	30	L	Limbic	Cingulate	area 32
6	4.79	19	Fronto-parietal	37	13	42	R	Frontal	Middle Frontal	area 6

Table S2. Diagnostic Specificity Analyses.

ANXIETY Diagnosis (Categorical at any time point)				
	N	B	SE	p
BRIEF-GEC	247	0.040	0.010	**<0.001**
BRIEF-GEC (T3_INT_SX)	240	0.015	0.011	**0.184**
BRIEF-GEC (T3_INT_SX, sex, age, IQ, SES)	223	0.013	0.012	**0.294**
CONDUCT Diagnosis (Categorical at any time point)				
	N	B	SE	p
BRIEF-GEC	247	0.051	0.011	**<0.001**
BRIEF-GEC (T3_EXT_SX)	240	0.000	0.016	**0.998**
BRIEF-GEC (T3_EXT_SX, sex, age, IQ, SES)	223	-0.008	0.017	**0.624**
ODD Diagnosis (Categorical at any time point)				
	N	B	SE	p
BRIEF-GEC	247	0.065	0.011	**<0.001**
BRIEF-GEC (T3_EXT_SX)	240	0.027	0.014	**0.045**
BRIEF-GEC (T3_EXT_SX, sex, age, IQ, SES)	223	0.034	0.014	**0.02**

Figure Captions

Figure S1. dACC Seed Region Density Plots

Dorsal anterior cingulate (dACC) seed region denisty plots binned by quartiles. A) dACC seed to left anterior insula. B) dACC seed to left anterior insula. C) dACC seed to posterior precuneus. D) dACC to dorsolateral prefrontal cortex.

Figure S1. dACC Seed Region Density Plots