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Preschool Executive Function Predicts Childhood Resting-State Functional Connectivity and Attention-Deficit/Hyperactivity Disorder and Depression

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ABSTRACT

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 subjects, but less work has examined relationships to depression or brain network organization. This study examined whether early childhood EF predicted 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 included 247 children who were enrolled at 3 to 6 years of age from a prospective study of emotion development. The Behavior Rating Inventory of Executive Function Global Executive Composite score was used as the measure of EF in early childhood to predict ADHD and depression diagnoses and symptoms across school age. Resting-state functional magnetic resonance imaging network analyses examined global efficiency in the frontoparietal, cingulo-opercular, salience, and default mode networks and six "hub" seed regions selected to examine between-network connectivity.

RESULTS: Early childhood EF predicted new onset and worsening of ADHD and depression symptoms across school age. Greater EF deficits in preschool predicted increased global efficiency in the salience network and altered connectivity with four regions for the dorsal anterior cingulate cortex hub and one region with the insula hub at school age. 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 specific EF deficits are implicated in the development of both disorders.

Keywords: Attention-deficit/hyperactivity disorder, Behavior Rating Inventory of Executive Function, Depression, Executive function, fMRI, Resting-state functional connectivity

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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 to engage in goal-directed behavior, especially in novel situations where more automatized responses are not feasible (1). The assessment of childhood EF deficits often relies heavily on parent-reported behavioral measures. Despite the known limitations of these methods, 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) (2). 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 (3,4) and has been shown to differentiate ADHD subtypes (5). 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. Research examining cognitive and neuroimaging correlates across ADHD and MDD is even more scarce, despite high rates of comorbidity (6–8). Some previous research has shown higher rates of comorbidity between ADHD and depression in preschool compared with other common internalizing disorders, such as anxiety (9), but such findings have varied across studies (10). Nevertheless, the early role of EF deficits in childhood depression remains an understudied area and further examination of comorbidity is warranted (11). Thus, the goal of the current study was to

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examine whether parent-rated EF deficits in early childhood predicted ADHD and/or MDD at later developmental time points and to examine functional brain connectivity correlates of early childhood EF deficits.

EF begins to develop in toddlerhood with important advances in early childhood (12) and continued skill building through early adulthood. In individuals diagnosed with ADHD, EF has been shown to be developmentally delayed (13–15), with impairments consistently found in the inhibition, working memory, and set-shifting cognitive domains. Such EF impairments may contribute to multiple symptoms of ADHD, including difficulties with self-regulation and the ability to complete goal-directed tasks. Further, while EF deficits occur during the early developmental stages of ADHD for many individuals, to our knowledge no studies 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 (15).

EF deficits are not unique to ADHD and have been observed in internalizing disorders such as depression (11). EF deficits in preschool-aged children, as measured by the BRIEF, have been previously associated with depression and anxiety in later childhood (16). Impairments in attention and concentration are common in depression, particularly in later stages of information processing (17) when EF skills are critical. These deficits likely contribute to challenges disengaging attention to negative emotional salient information and subsequent emotion regulation (18). While some associations between EF and depression have been shown in adults (19–22), relatively little research has explored commonalties across depression and ADHD in early childhood, even though comorbidity is common, occurring in approximately 20% to 30% of child and adolescent cases (6–8,23). Furthermore, children experiencing depression often have symptoms of inattention and increased irritability (24), suggesting that ADHD and depression may share some overlapping diagnostic features in early childhood. As such, shared EF deficits across ADHD and depression deserves further exploration, as they may be a common liability for assessing risk of later development of both disorders (15,21).

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 (25–27) using a graph theory approach. Graph theory quantifies complex networks of information and generates metrics that can be used to describe the functional connections between brain regions (28). Of particular interest were the cingulo-opercular network (CON) and frontoparietal network (FPN), which are thought to be involved in top-down control processes that support goal-directed behavior (29). Normative developmental maturation of brain networks has been shown to be disrupted in ADHD, particularly in the organization of the FPN and CON (30,31). We were also interested in the default mode network (DMN), which shows suppression in activation during novel and demanding tasks (32,33). In depression, work has consistently implicated alterations in connectivity in the DMN, salience network (SAL), and central executive network (34), although variability across studies is common. Less work has focused on early childhood, although atypical DMN connectivity has been shown in children with preschool onset depression (35). Lastly, we were interested in the SAL, which is thought to be important for mediating responses to important internal or external signals, and switching between the DMN and FPN (36). Previous work found that integration of a cingulo-opercular/salience network (CON/SAL) predicted performance on a task thought to measure aspects of childhood EF (27), suggesting an important role in early EF. We also 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 (37,38). Previous work has shown the importance of flexible hubs for EF and adaptive task control (39,40), and disruptions of hub connectivity have been associated with cognitive dysfunction, including EF deficits (41). 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 ADHD and MDD symptoms across development and would be more likely to meet diagnostic criteria at school age. We expected that early childhood EF deficits would show some specificity to later ADHD and MDD and would not robustly 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. We expected early childhood EF to be associated with reduced global network efficiency in the FPN, CON, and SAL, increased global efficiency in the DMN, and altered functional connectivity patterns with hub regions in the CON/SAL and FPN. Lastly, we predicted that the altered connectivity associated with early childhood EF would also be associated with ADHD and/or MDD symptoms.

METHODS AND MATERIALS

Study Sample

The full sample included 247 children who were 3 to 6 years of age at the time of recruitment from a longitudinal study of emotion development enriched for preschool depression. Families were recruited through community child care sites and clinics using a caregiver-completed screening checklist, the Preschool Feelings Checklist (42). Detailed recruitment methods, exclusion criteria, and participant details have been described previously (24). Children and primary caregivers participated in one to seven waves of behavioral assessments. A subset of these children participated in a longitudinal imaging component. Only the first scan was included in this study because this was the most proximal scan to the early childhood BRIEF. This imaging sample included 83 children who were 6 to 12 years of age at the time of their first scan (Table 1).

Table 1. Participant Characteristics

Participants	Time of BRIEF (T3) (*n* = 247)	Scan 1 (*n* = 83)
Age, Years, Mean (SD)	5.4 (0.8)	10.1 (1.3)
Sex, Female/Male, %	48/52	48/52
Ethnicity, Caucasian/African American/Other, %	59/28/13	59/29/12
IQ Estimate, Mean (SD)	105 (14.8)	106 (14.9)
BRIEF-GEC *t* Score, Mean (SD)	54.5 (14.4)	N/A
Diagnosed With ADHD, *n* (%)	29 (11.7)	13 (15.6)
ADHD Symptoms, Mean, *n* (SD)	3.1 (3.4)	2.8 (3.3)
Patients Diagnosed With MDD, *n* (%)	36 (14.6)	14 (16.9)
MDD Symptoms, Mean, *n* (SD)	2.3 (1.3)	2.4 (1.3)

ADHD, attention-deficit/hyperactivity disorder; BRIEF-GEC, Behavior Rating Inventory of Executive Function Global Executive Composite; MDD, major depressive disorder.

Measures

The BRIEF, an 86-item, well-validated rating scale (α = .98), was completed by the primary caregiver as a measure of childhood EF (2). The BRIEF includes subscales that form an overall score, the Global Executive Composite (GEC) *t* score, where higher scores indicate more clinically significant EF impairments. In this sample, the BREIF subscales were highly intercorrelated (r = .55 to .96, all $p < .01$). Therefore, the BRIEF-GEC was used as an overall marker of early EF. Additional information about the BRIEF and individual subscales analyses are described in the Supplement. The BRIEF was first collected at the second wave of behavioral assessments, when the children were between 4 and 7 years of age, herein referred to as the early childhood BRIEF visit. A combination of the BRIEF (n = 67) and the preschool version of the BRIEF (n = 180) (43) was used based on the child's age. Symptom counts of ADHD and MDD were collected at each annual visit 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 (T5–T14) was generated as the outcome variable in categorical analyses (44,45) (see Figure 1 for assessment timeline).

Data Analysis for Clinical Variables

We conducted a series of multivariate linear regressions using R Studio software (version 0.99.465) to initially examine whether early EF deficits predicted increased MDD and ADHD symptoms averaged across subsequent study visits, over and above symptom levels assessed in preschool (Supplement). In addition, longitudinal multilevel models were then conducted using the PROC MIXED function in SAS software (version 9.3; SAS Inc., Cary, NC) to examine growth trajectories across childhood. These models included random slopes and intercepts, with unstructured covariance matrices, and time was coded as annual study visit. Predictors were centered and age, sex, IQ, and socioeconomic status were used as control variables. Binomial logistic regression was used to examine whether early EF deficits predicted a later diagnosis of MDD or ADHD to assess new onsets in undiagnosed preschoolers (Table 1). Age, sex, and socioeconomic status were used as control variables. Specificity analyses were completed using the same methods for anxiety, conduct disorder, and oppositional defiant disorder to determine whether the BRIEF was a nonspecific predictor of broader psychopathology. Further, since ADHD and MDD symptoms are frequently 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 models of the other disorder to test whether comorbidity accounted for the variance explained.

Imaging Methods

A subset of children was scanned on a Siemens 3T Tim Trio (Siemens, Erlangen, Germany) and completed up to three annual waves. The scanning protocol included two T1 structural scans and two resting-state functional magnetic resonance imaging scans (~6.8 minutes, repetition time = 2.5, 4 mm^3 voxels, 164 frames). Standard preprocessing methods, including global signal regression, were used to reduce motion artifact and other confounds (Supplement). Children who completed scan 1 were included in this study if there were at least 110 frames remaining after motion scrubbing (framewise displacement [FD] 0.2 mm). To further control for potential confounds, each subject's average prescrub FD and time elapsed between the early childhood BRIEF visit and scan 1, which varied somewhat across individuals, were included as covariates in imaging analyses.

Network Analyses

To examine the strength of the connections among regions in particular networks, we used the graph theory metric global

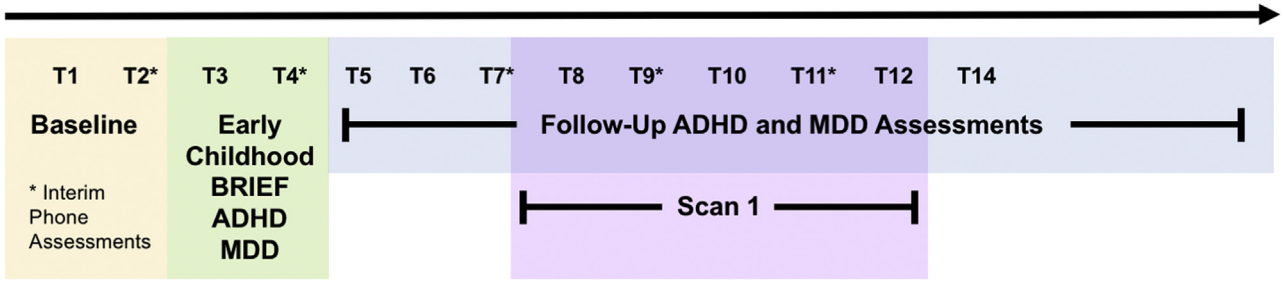

Figure 1. Study timeline for current analyses. The Behavior Rating Inventory of Executive Function (BRIEF) was first collected when children were 3 to 6 years of age and was used to predict later functional connectivity and attention-deficit/hyperactivity disorder/major depressive disorder (ADHD/MDD). The imaging component was funded later and the BRIEF was not collected at every assessment time point.

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% to 10% tie density thresholds, preserving the strongest 1% to 10% of correlations in 1% increments. Although there is no "correct" threshold (25), we tested an average of the top 1% to 5% and 6% to 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 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 EF from the list of nodes in the Power 264 set (25). Three seeds were selected in the CON/SAL in the right and left insula and the dorsal anterior cingulate cortex (dACC). 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 (coordinates shown in Supplemental Table S5). These seeds were used to create functional connectivity seed maps for each child of the correlations between each seed and all the other voxels in the CON/SAL and FPN. 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 other voxels in the CON or FPN. To reduce the search space, a mask was applied for only these two networks, both thought to be involved in top-down control (26). Spherical regions of interest were drawn around coordinates published by Power *et al.* (25) for the CON and FPN to create this mask. Significance thresholds were set using the 3dclustsim function of the Analysis of Functional Neuroimages (version 16.2.09) at p = .005, z = 2.83, and 27 contiguous voxels for a maskwise false positive rate of 0.05. Follow-up exploratory analyses were conducted without this mask examining correlations for the whole brain (Supplement).

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. Mediation analyses were not feasible for this study owing to the alignment of diagnostic and scan visits. Thus, our analyses provide information about the relationships between connectivity and the psychopathology outcomes but cannot formally test mediation.

RESULTS

ADHD and EF

Dimensional. Multivariate linear regression showed that early childhood BRIEF-GEC predicted increased cumulative ADHD symptoms averaged across later study visits over and above current ADHD symptoms (Supplemental Table S1). Individual subscales of the preschool version of the BRIEF also predicted cumulative ADHD symptoms (Supplemental Tables S2 and S3). Longitudinally, the early childhood BRIEF strongly predicted greater levels of ADHD symptoms across childhood, but the interaction with time was not significant (Table 2, Figure 2A). This suggests that children with greater EF deficits overall have increased ADHD symptoms across development but not necessarily a different trajectory than children with normative levels of EF.

Categorical. Using 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% confidence interval 1.020–1.086; p = .001) when controlling for current ADHD symptoms, the aforementioned control variables (p = .02), and MDD symptoms (p = .04).

MDD and EF

Dimensional. Multivariate linear regression showed that early childhood BRIEF-GEC predicted increased cumulative MDD symptoms averaged across later study visits over and above current MDD symptoms (Supplemental Table S1) and that the individual subscales of the preschool BRIEF also predicted cumulative MDD symptoms (Supplement). Longitudinally, a similar pattern was found for MDD showing that the early childhood BRIEF strongly predicted greater levels of

Table 2. Multilevel Model Dependent Variable: ADHD and MDD Symptoms

	Estimate	SE	t	p Value
ADHD Sum Score (n = 173)				
(Intercept)	3.5417	0.3105	11.41	<.0001
Time	−0.2184	0.0497	−4.39	<.0001
Age T3	−0.0016	0.0186	−0.09	.9303
Sex	0.7716	0.3362	2.29	.0230
SES	0.0656	0.1854	0.35	.7240
IQ	−0.0085	0.0143	−0.59	.5555
ADHD sum T3	0.5333	0.0670	7.96	<.0001
BRIEF-GEC T3	0.0754	0.0215	3.50	.0006
ADHD sum (T3) × time	−0.0155	0.0131	−1.19	.2378
BRIEF-GEC (T3) × time	−0.0078	0.0043	−1.82	.0704
MDD Sum Score (n = 174)				
(Intercept)	2.0795	0.1555	13.37	<.0001
Time	0.0401	0.0253	1.59	.1131
Age T3	0.0327	0.0094	3.48	.0006
Sex	0.2898	0.1703	1.70	.0908
SES	0.0248	0.0941	0.26	.7927
IQ	−0.0108	0.0073	−1.48	.1415
MDD sum T3	0.3468	0.0896	3.87	.0001
BRIEF-GEC T3	0.0357	0.0098	3.65	.0003
MDD sum (T3) × time	−0.0199	0.0178	−1.12	.2646
BRIEF-GEC (T3) × time	−0.0021	0.0020	−1.09	.2776

ADHD, attention-deficit/hyperactivity disorder; BRIEF-GEC, Behavior Rating Inventory of Executive Function Global Executive Composite; MDD, major depressive disorder; SES, socioeconomic status.

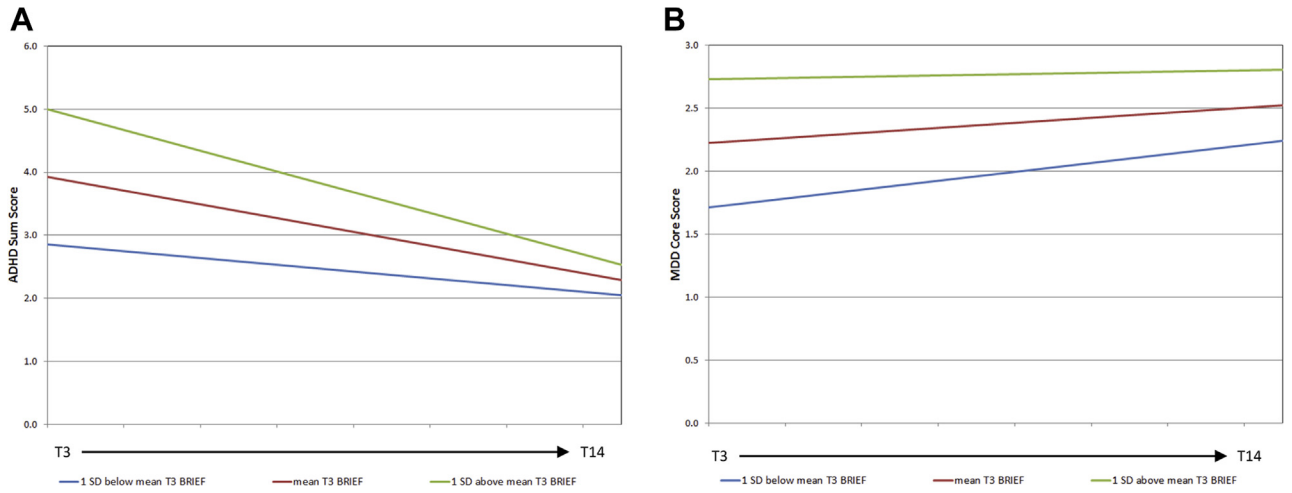

Figure 2. Multilevel models of **(A)** attention-deficit/hyperactivity disorder (ADHD) and **(B)** major depressive disorder (MDD) symptoms. Growth models show that early childhood executive function deficits predicted levels of ADHD and MDD symptoms across childhood but did not interact with time. BRIEF, Behavior Rating Inventory of Executive Function.

MDD symptoms across childhood, but again the interaction with time was not significant (Table 2, Figure 2B).

Categorical. 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 the criteria for MDD (odds ratio = 1.05; 95% confidence interval 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 oppositional defiant disorder, conduct disorder, and anxiety as outcomes. Although some basic models were significant, none remained significant when control variables were added (Supplemental Table S4). In addition, since a few children included in the sample had estimated IQ scores below 80 ($n = 11$) or were taking psychotropic medications during testing visits ($n = 8$), all behavioral analyses were rerun without those subjects and all results remained significant.

Network Analyses

Early childhood EF deficits were associated with increased global efficiency in the SAL at an average threshold of 1% to 5% ($\beta = .003$, $t_{81} = 3.682$, $p < .001$) and 6% to 10% ($\beta = .002$, $t_{81} = 2.609$, $p = .011$). This result opposed our hypothesis and remained significant when controlling for age, sex, average FD at scan 1, time elapsed between the early childhood BRIEF visit and scan 1 ($p = .002$), and when correcting for multiple comparisons using the Bonferroni-adjusted α level of .0125 (.05/4). Global efficiency was not significantly associated with early childhood BRIEF in any other a priori networks selected for this study.

Hub-Based Analyses

When associations were restricted to the FPN/CON, early childhood BRIEF-GEC significantly predicted connectivity with four regions for the left dACC hub seed region (Figure 3). Worse (higher) early childhood BRIEF-GEC scores predicted stronger positive connectivity between the dACC and bilateral anterior insula (Figure 4). Higher BRIEF-GEC scores also predicted stronger negative connectivity between the dACC and a dorsolateral prefrontal cortex (DLPFC) region as well as the posterior precuneus (Figure 4). In addition, higher early childhood BRIEF-GEC scores predicted stronger negative connectivity between the insula hub seed region and a superior parietal region (Figures 5 and 6). All results remained significant when controlling for average FD at scan 1 and time elapsed between the BRIEF visit and scan 1. Seed region distributions were graphed as density and scatter plots to visualize the patterns of positive and negative connectivity (Figures 4 and 6; Supplemental Figure S2). Whole-brain analyses showed significant associations between the selected seed regions of interest and several cortical regions outside the CON and FPN that are also typically associated with cognitive function (Supplement).

Furthermore, global efficiency and hub connectivity metrics predicted by early childhood BRIEF scores were also correlated with ADHD and/or MDD symptoms through school age. Both ADHD and MDD symptoms were significantly correlated with most hub metrics predicted by the early childhood BRIEF but not SAL global efficiency (Table 3). Interestingly, all metrics correlated with ADHD remained significant when controlling for MDD symptoms (p values $< .05$), 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, children with greater EF deficits overall had higher levels of ADHD and MDD symptoms across school age even when controlling for preschool symptoms, age, sex, and socioeconomic status. Children with EF deficits who did not meet baseline diagnostic criteria for ADHD in early childhood were also more likely to be diagnosed with ADHD in later childhood, even when controlling for cumulative MDD

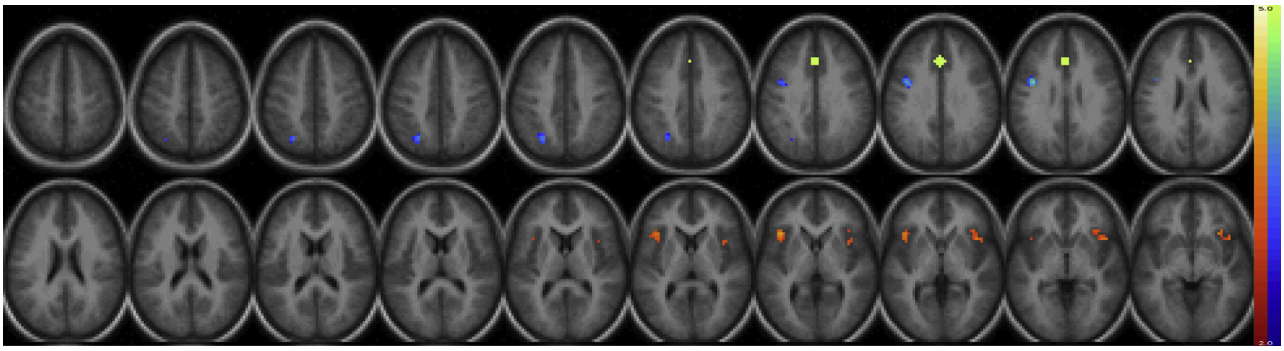

Figure 3. Resting state functional connectivity in the dorsal anterior cingulate cortex (dACC) seed region and its relationship to executive function. The region in green is the dACC seed region (−1, 25, 30) showing increased positive connectivity between the dACC and bilateral anterior insula regions (orange) and increased negative connectivity between the dACC and dorsolateral prefrontal cortex and posterior precuneus regions (blue) as a function of greater executive function deficits in early childhood.

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 oppositional defiant disorder, conduct disorder, or anxiety in this sample, indicating that early EF deficits did not indiscriminately predict later psychopathology.

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 (46), and it is plausible that the distress caused by difficulty implementing goal-directed behavior may be a contributing factor. 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 (19,47). Therefore, early childhood EF deficits could be an important precursor in the development of ADHD and/or depression. 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.

When examining network integration, EF deficits predicted increased global efficiency in the SAL. We had predicted that better EF would be associated with increased global efficiency, since the SAL is thought to be involved in guiding the ability to switch between tasks and regulate attentional fluctuations. Further examination of the integration and segregation of the SAL longitudinally would help clarify this finding. One possible explanation is that the SAL is differentially activated in children with early executive deficits leading to alterations in network integration. The lack of association between EF and global

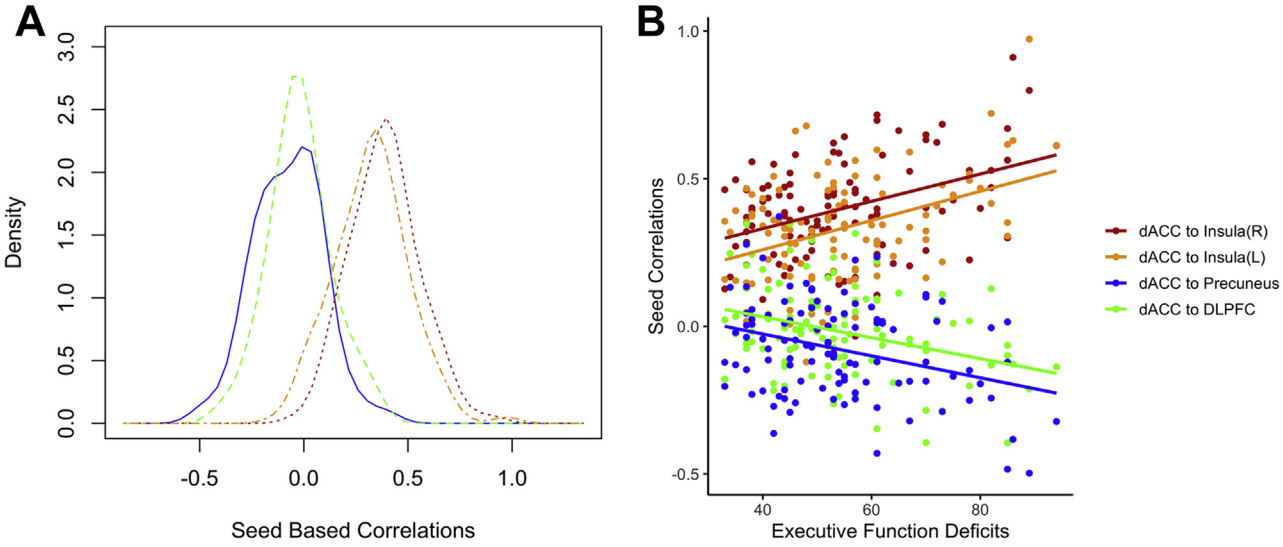

Figure 4. Visualization of the dorsal anterior cingulate cortex (dACC) seed region and its relationship to executive function. dACC seed region (−1, 25, 30) distributions were graphed as density **(A)** and scatter **(B)** plots to visualize the results. DLPFC, dorsolateral prefrontal cortex; L, left; R, right.

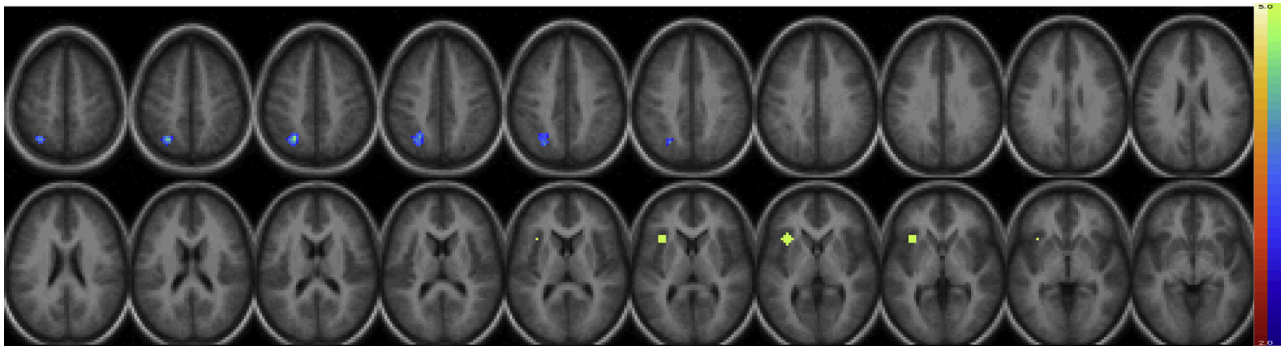

Figure 5. Resting state functional connectivity of the insula seed region and its relationship to executive function. The region in green is the insula seed region (−34, 16, 3) showing increased negative connectivity between the insula and a superior parietal region (blue) as a function of greater executive function deficits in early childhood.

efficiency in the FPN, CON, and DMN may reflect the need to examine more specific aspects of EF in relation to these networks across later developmental time points as EF skills continue to mature.

Analyses of hub seed regions were conducted to examine connectivity of key regions across networks. Early EF deficits predicted stronger positive connectivity between the dACC and bilateral anterior insula, which indicates that increasing correlated activation in these regions is associated with EF deficits. These regions have been shown to be involved in conflict and error processing, which is thought to help signal the need for increased cognitive control (48,49). 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. In addition, we found reduced connectivity between the dACC and both the DLPFC and the precuneus in children with greater EF deficits. The dACC is thought to be important for both the CON and SAL. As noted, one hypothesis is that greater activity in the dACC is thought to signal the need for greater cognitive control, which is supported by the DLPFC and the FPN. 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 in response to the experience of conflict and errors. Further, the reduced connectivity of the dACC to the precuneus, a part of the DMN, which shows suppression during task activation, might be related to difficulty balancing between task-positive and task-negative networks, a role that has been attributed to the anterior ACC in the SAL (50).

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 showing that altered

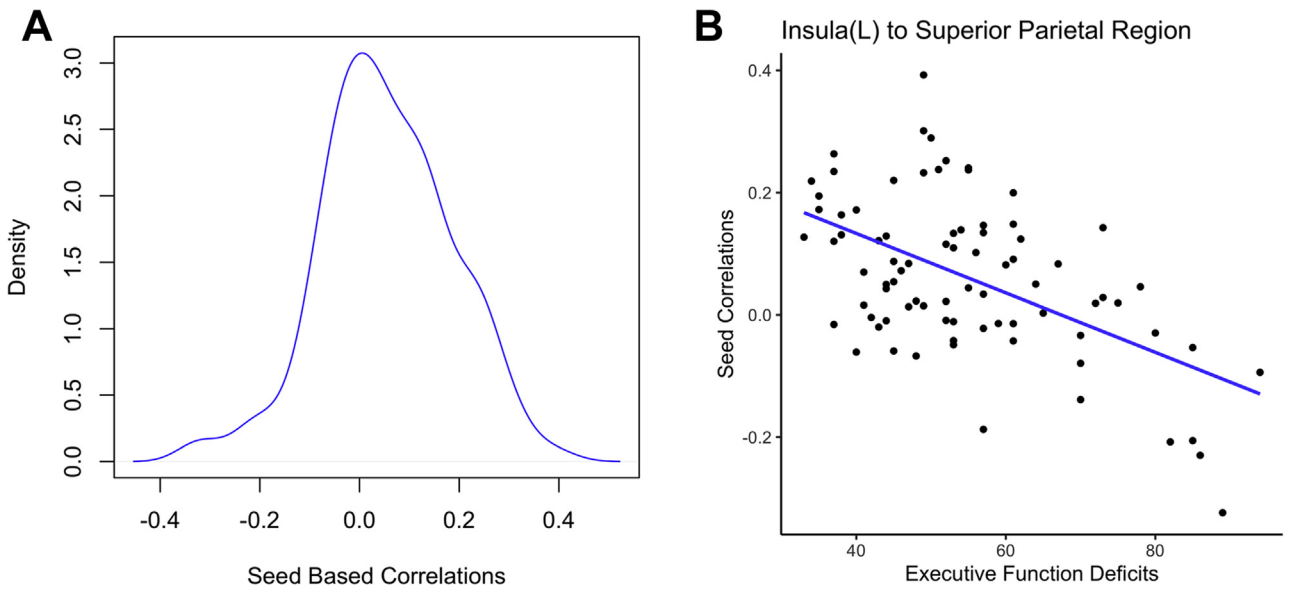

Figure 6. Visualization of the insula seed region and its relationship to executive function. Insula seed region (−34, 16, 3) distributions were graphed as density **(A)** and scatter **(B)** plots to visualize the results. L, left.

Table 3. Correlations of Connectivity Metrics and Attention-Deficit/Hyperactivity Disorder and Major Depressive Disorder Symptoms

Connectivity Metric	BRIEF-GEC (n = 81)	Average ADHD Symptoms	Average MDD Symptoms
dACC Seed to Insula (R) (39, 14, −1)			
Correlation	.464[a]	.241[b]	.261[a]
Significance (2-tailed)	.000	.015	.009
dACC Seed to DLPFC (−39, 0, 29)			
Correlation	−.433[a]	−.217[b]	−.297[a]
Significance (2-tailed)	.000	.026	.004
dACC Seed to Insula (L) (−41, 15, 3)			
Correlation	.424[a]	.170	.266[a]
Significance (2-tailed)	.000	.064	.008
dACC Seed to Precuneus (−28, −64, 40)			
Correlation	−.435[a]	−.270[a]	−.320[a]
Significance (2-tailed)	.000	.007	.002
Insula Seed to Superior Parietal (−28, −63, 44)			
Correlation	−.534[a]	−.353[a]	−.407[a]
Significance (2-tailed)	.000	.001	.000
Salience Global Efficiency K Density 1–5%			
Correlation	.348[a]	.048	.130
Significance (2-tailed)	.001	.334	.124
BRIEF-GEC			
Correlation	1.000[a]	.475[a]	.563[a]
Significance (2-tailed)	.000	.000	.000

ADHD, attention-deficit/hyperactivity disorder; BRIEF-GEC, Behavior Rating Inventory of Executive Function Global Executive Composite; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; L, left; MDD, major depressive disorder; R, right.

[a]Correlation is significant at the 0.01 level (1-tailed).

[b]Correlation is significant at the 0.05 level (1-tailed).

connectivity within highly connected hub regions is associated with psychopathology (51). Additional work has shown that hubs function as integration zones of the human brain that are metabolically costly and particularly vulnerable to disease states (37,41), theoretically 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. This sample was enriched for preschool 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, and variance was similar across the symptom domains. In addition, we did not have scan data at or before the time of early childhood BRIEF. This timing precluded the use of formal mediation analyses in the current study. Nonetheless, our analyses linking the connectivity changes at school age with levels of ADHD and depression symptoms suggest potential biological mechanisms that may contribute to later psychopathology, generating specific hypotheses to be tested in data sets that include imaging assessments much earlier in development (e.g., starting at birth). Finally, future studies should examine the relationship between performance-based measures of EF and parent-rated EF to help clarify the role that 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, which show high rates of comorbidity. 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 (52), making the early identification of EF deficits essential for the development and course of these disorders throughout childhood.

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