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Research Report

Reduced recruitment of inhibitory control regions in very young children with ADHD during a modified Kiddie Continuous Performance Task: A fMRI study

Mohammadreza Bayat [a], *Melissa Hernandez* [a], *Madeline Curzon* [a], *Dea Garic* [b], *Paulo Graziano* [a] *and Anthony Steven Dick* [a,1,*]

[a] *Department of Psychology and the Center for Children and Families, Florida International University, Miami, FL, USA*

[b] *Carolina Institute for Developmental Disabilities and Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

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ABSTRACT

Attention-Deficit/Hyperactivity Disorder (ADHD) symptom profiles are known to undergo changes throughout development, rendering the neurobiological assessment of ADHD challenging across different developmental stages. Particularly in young children (ages 4- to 7-years), measuring inhibitory control network activity in the brain has been a formidable task due to the lack of child-friendly functional Magnetic Resonance Imaging (fMRI) paradigms. This study aims to address these difficulties by focusing on measuring inhibitory control in very young children within the MRI environment. A total of 56 children diagnosed with ADHD and 78 typically developing (TD) 4-7-year-old children were successfully examined using a modified version of the Kiddie-Continuous Performance Test (K-CPT) during BOLD fMRI to assess inhibitory control. We also evaluated their performance on the standardized K-CPT outside the MRI scanner. Our findings suggest that the modified K-CPT effectively elicited robust and expected brain activity related to inhibitory control in both groups who were successfully scanned. Comparisons between the two groups revealed differences in brain activity, primarily observed in inferior frontal gyrus, anterior insula, dorsal striatum, medial pre-supplementary motor area (pre-SMA), and cingulate cortex ($p < .005$, corrected). Notably, for both groups increased activity in the right anterior insula was associated with improved response time (RT) and reduced RT variability on the K-CPT administered outside the MRI environment, although this did not survive statistical correction for multiple comparisons. The study also revealed continuing challenges for scanning this population—an additional 51 TD children and 78 children with

Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder.

* *Corresponding author*. Department of Psychology and the Center for Children and Families, Florida International University, Miami, FL, 33199, USA.
E-mail address: adick@fiu.edu (A.S. Dick).
[1] Present address: Department of Psychology, Florida International University, Miami, Florida, 33199, United States.

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ADHD were scanned, but failed to provide useable data due to movement. In summary, for a subsample of children, we successfully overcame some of the challenges of measuring inhibitory control in very young children within the MRI environment by using a modified K-CPT during BOLD fMRI, but further challenges remain for scanning in this population. The findings shed light on the neurobiological correlates of inhibitory control in ADHD and TD children, provide valuable insights for understanding ADHD across development, and potentially inform ADHD diagnosis and intervention strategies. The research also highlights remaining challenges with task fMRI in very young clinical samples.

1. Introduction

Externalizing behavior problems, particularly symptoms of attention-deficit/hyperactivity disorder (ADHD) such as inattention, hyperactivity, and impulsivity, are among the most common reasons for early childhood mental health referrals (Keenan & Wakschlag, 2000; Mechler, Banaschewski, Hohmann, & Häge, 2022; Thomas & Guskin, 2001; Wolraich et al., 2019). These symptoms are especially prevalent during the preschool and early elementary years (ages 4–7), a period that presents significant challenges in accurate assessment (Furniss, Beyer, & Guggenmos, 2006). Additionally, the symptom profile of young children with ADHD can evolve considerably as they develop, underscoring the need for assessment tools that remain effective from early childhood through adolescence and into adulthood (Danielson et al., 2018). Despite the availability of some lab-based behavioral measures, there is a notable scarcity of neuroimaging studies focused on young children with ADHD (Booth et al., 2005; Vance et al., 2007; Konrad, Neufang, Fink, & Herpertz-Dahlmann, 2007; Durston et al., 2003; Hawkey, Tillman, Luby, & Barch, 2018; Öztekin et al., 2021; Ball et al., 2019; Öztekin et al., 2022), and we couldn't find any that employ well-designed magnetic resonance imaging (MRI) task paradigms in very young children. The limited number of these studies is largely due to the difficulties in designing tasks that can be effectively administered within an MRI environment, particularly for very young children who must remain still and attentive for extended periods. This gap in research contributes to inconsistent measurements of ADHD-related behaviors, thereby impeding a comprehensive understanding of the disorder. While neuroimaging isn't a replacement for traditional behavioral and clinical measures, it can offer complementary insights at different levels of analysis, enriching the understanding of ADHD across development.

Consistent measurement in ADHD research is crucial for several reasons. First, the diversity of symptom profiles among affected children makes defining ADHD particularly challenging, as these children experience impairments across various domains. For example, while *inhibitory control* is often impaired in children with ADHD (Pauli-Pott & Becker, 2011), up to 25 percent of diagnosed children do not exhibit this deficit (Nigg, 1999). Moreover, most studies on this topic focus on older children, even though the disorder's profile can change significantly as children mature. Therefore, it is essential to track ADHD heterogeneity throughout development. Additionally, improving the measurement of ADHD's neurobiological profile during early childhood is important for defining the disorder across multiple levels of analysis. Although there is consensus that certain brain regions involved in inhibitory control—such as regions of the frontal and parietal cortex, basal ganglia, and cerebellum—are affected in ADHD, a comprehensive neurobiological definition of the disorder remains elusive. These regions are also linked to other cognitive and affective processes often impaired in children with ADHD, such as emotion regulation and other domains of executive function (Öztekin et al., 2022), which raises questions of the specificity of regional differences in ADHD as it relates to behavioral performance on inhibitory control tasks. Addressing these definitional challenges at multiple levels is necessary for understanding the etiology of ADHD, especially in very young children. However, current methods are inadequate for this purpose. As we noted above, there are few well-established functional imaging tasks designed for young children. Researchers often rely on electroencephalography and functional near-infrared spectroscopy (fNIRS) (Inoue et al., 2012; Jonkman, 2006; Mehnert et al., 2013; Monden et al., 2015; Zhou et al., 2022; Zinchenko, Chen, & Zhou, 2019) to investigate these questions, but these techniques lack the spatial resolution of fMRI, limiting their utility for addressing some specific questions that only functional MRI could answer.

2. Developing inhibitory control in ADHD

This study aims to address the challenges of measuring inhibitory control within an MRI environment, focusing specifically on very young children aged 4- to 7-years. Inhibitory control, as defined by Aron and colleagues (Aron, Robbins, & Poldrack, 2014), involves the ability to suppress inappropriate responses, stimulus-response mappings, or task sets when the context changes, as well as the suppression of interfering memories during retrieval. In adults, this is typically measured using tasks that require the suppression of a prepotent response established by the task's rules. For example, in stop-signal paradigms (Verbruggen & Logan, 2009), participants must respond to a target (usually via a button press) but withhold their response when a stop signal appears, thereby requiring inhibitory control. A similar paradigm, the Go/NoGo task (Chambers, Garavan, & Bellgrove,

2009; Chikazoe, 2010; Forstmann et al., 2008; Hodgson et al., 2007; Neubert, Mars, Buch, Olivier, & Rushworth, 2010; Wiecki & Frank, 2013), involves participants pressing a button when presented with "Go" stimuli, but refraining from responding to "NoGo" stimuli.

Variations of this paradigm are often referred to as "Continuous Performance Tasks" (CPT) due to the need to maintain attention throughout the stimulus presentation (Huang-Pollock, Karalunas, Tam, & Moore, 2012). Children with ADHD often perform poorly on CPT tasks compared to typically developing (TD) children. A well-established measure of attention maintenance and inhibitory control in very young children is the Kiddie Continuous Performance Task (K-CPT) (Conners, 2006), widely used in both laboratory and clinical settings. Unlike some CPT paradigms that involve responding to rare signals, the K-CPT more closely resembles inhibitory control tasks. In this task, children first establish a prepotent response (e.g., pressing a button upon seeing a picture), and then must inhibit this response when presented with a "NoGo" signal (e.g., a picture of a soccer ball).

Previous studies have shown that the K-CPT, when administered in a laboratory or clinical setting, is highly sensitive in distinguishing children with ADHD from TD children (Barnard et al., 2018; Boucher et al., 2017; Chen et al., 2021; Munkvold, Manger, & Lundervold, 2014). For instance, Breaux and colleagues (Breaux, Griffith, & Harvey, 2016) found that among various neuropsychological measures, the K-CPT was the most effective in predicting whether young children with high externalizing behaviors at age 3 would later be diagnosed with ADHD at age 6. Beyond behavioral assessments, researchers have also explored the neural underpinnings of inhibitory control during the K-CPT using electroencephalography (EEG) (Baijot et al., 2017; Ryoo & Son, 2015).

Despite the K-CPT's effectiveness in distinguishing ADHD from typically developing (TD) children, no studies have yet investigated the specific brain regions differentially engaged in young children with ADHD compared to TD children, as fMRI paradigms for the K-CPT in this age group have not been established. In fact, few studies have assessed inhibitory control in children with ADHD, and those that have typically used different paradigms, focusing on children older than 7 years (Bhaijiwala, Chevrier, & Schachar, 2014; Cao et al., 2008; Godinez et al., 2015; Hart et al., 2014; Kobel et al., 2010; Mulder et al., 2008; Spinelli et al., 2011a; Spinelli et al., 2011b; Wang et al., 2013). Nevertheless, there are well-founded expectations about the neural networks involved in inhibitory control during CPT tasks, derived largely from studies conducted in adults (Corkum & Siegel, 1993; Edwards et al., 2007; Epstein et al., 2003; McGee, Clark, & Symons, 2000). Various models have been proposed to explain the neurobiology of inhibitory control, including Wiecki and Frank's computational model (Wiecki & Frank, 2013) and Aron and colleagues' anatomical model of stopping (Aron, Herz, Brown, Forstmann, & Zaghloul, 2016). These models suggest that inhibitory control in CPT paradigms relies on a specific network of cortico-basal ganglia regions, which includes the right hemisphere's inferior frontal gyrus (IFG), neighboring anterior insula, the pre-supplementary motor area (pre-SMA), the dorsal striatum, the subthalamic nucleus (STN), and other basal ganglia regions.

Within this network, specific brain regions contribute in different ways. The subthalamic nucleus, emphasized by Aron and colleagues (Aron et al., 2016), plays a crucial role in outright action stopping and collaborates with the IFG/anterior insula and pre-SMA, which may trigger STN activity via a hyperdirect pathway (Aron et al., 2016). It may be the case that these regions function differently in children with ADHD compared to TD children, and the K-CPT administered during fMRI may reveal functional activation differences in these particular brain areas. However, research using these paradigms in children aged 4–7 years is almost nonexistent, with our expectations having to be inferred from studies on older children (Booth et al., 2003; Bunge et al., 2002; Chaarani et al., 2021; Durston et al., 2006; Fiske and Holmboe, 2019) or those using fNIRS (Eng et al., 2022).

For example, studies on older TD children (aged 8-years through early adolescence) show that continuous performance and inhibitory control paradigms engage several regions within this proposed network (Booth et al., 2003; Bunge et al., 2002; Durston et al., 2006; Grandjean da Costa et al., 2022; Reveillon et al., 2016). Durston and colleagues (Durston et al., 2006), in a longitudinal study of children aged 9–11 years performing a task similar to the K-CPT, observed age-related reductions in activation across several bilateral regions, including the middle frontal gyrus and anterior cingulate gyrus. Interestingly, only the right IFG showed increased activation with age, correlating with accuracy on non-target trials. However, Bunge and colleagues (Bunge et al., 2002) did not replicate this finding, reporting instead that children did not recruit the right IFG, whereas adults did.

There are only a couple of task fMRI studies of executive function on children in the proposed age range. For example, in one study of 28 6- and 9-year-olds, Poirel and colleagues (Poirel et al., 2012) found an association between Stroop task response time and successful performance on a Piagetian conservation task inside the MRI magnet. Again, this association was specifically found in right IFG/anterior insula. In another study of 10 6-year-old TD children and 10 children born preterm, in an event-related Go/NoGo paradigm, Rèveillon and colleagues (Réveillon et al., 2013) found Go vs NoGo activation differences in right anterior insula. We could find no other studies using task-based fMRI Go/NoGo or comparable executive function paradigms in younger children. There are, however, fNIRS studies of TD children, and these studies generally support the patterns found in task fMRI paradigms (Eng et al., 2022; Mehnert et al., 2013; Smith et al., 2017). For example, Smith and colleagues (Smith et al., 2017) reported that right frontal activation during a Go/NoGo task emerged with age in children aged 4–10 years. Similarly, findings for 4-6-year-olds compared to adults showed increased activation in right frontal regions (Mehnert et al., 2013).

Studies using fNIRS on children with ADHD have consistently shown reduced hemodynamic responses in the prefrontal cortex during Go/NoGo tasks. For instance, Inoue and colleagues (Inoue et al., 2012) observed this reduction in a study comparing 20 9-year-olds with ADHD to 20 typically developing (TD) children, though the averaging of signals across four detector regions limited the spatial specificity of these findings. In another study involving 60 children aged

6–15 years, half of whom had ADHD, TD children recruited the inferior frontal gyrus (IFG) and middle frontal gyrus (MFG) regions to a greater extent during a Go/NoGo paradigm compared to their ADHD counterparts. Conversely, in a smaller study of 6-9-year-olds (15 TD children and 14 children with ADHD), Miao and colleagues (Miao et al., 2017) localized a similar contrast to the left prefrontal cortex. A much larger study involving children as young as 8-years (140 TD and 67 children with ADHD) further indicated a larger hemodynamic response during executive function tasks in both the left and right prefrontal cortex for TD children compared to those with ADHD (Yasumura et al., 2019). However, localizing activity to a high degree of spatial precision is not possible with fNIRS. fNIRS cannot image many of the regions of the proposed network (e.g., anterior insula, dorsal striatum, pre-SMA/SMA, anterior cingulate) which is why paradigms using task-based fMRI are necessary.

In summary, this study has three main objectives. First, we aim to evaluate the suitability of the K-CPT paradigm in identifying the neural network involved in inhibitory control among very young children (ages 4–7 years) with and without ADHD. The key regions within this network, highlighted in Fig. 1, will be a focal point of our investigation. Second, we seek to explore how this network is differentially recruited in young children with ADHD compared to typically developing (TD) children. Finally, we intend to establish connections between performance on the K-CPT and the activation profiles within the inhibitory control/executive function network, analyzing how these profiles differ between the two groups.

Our predictions are as follows: First, we expect both groups to engage a broad cortical and subcortical network involved in inhibitory control, as depicted in Fig. 1, to perform well on the K-CPT. Second, we anticipate that children with ADHD will show reduced activation in the identified inhibitory control regions, especially frontal regions indicated in studies using fNIRS paradigms. Thus, we expect a main effect of group and reduced network recruitment for the ADHD group. Lastly, we predict that task performance will correlate with increased activation in these inhibitory control regions, but given the differential recruitment of children with ADHD, we expected that this association will differ between the two groups, suggesting an interaction between group status and brain activity in predicting performance.

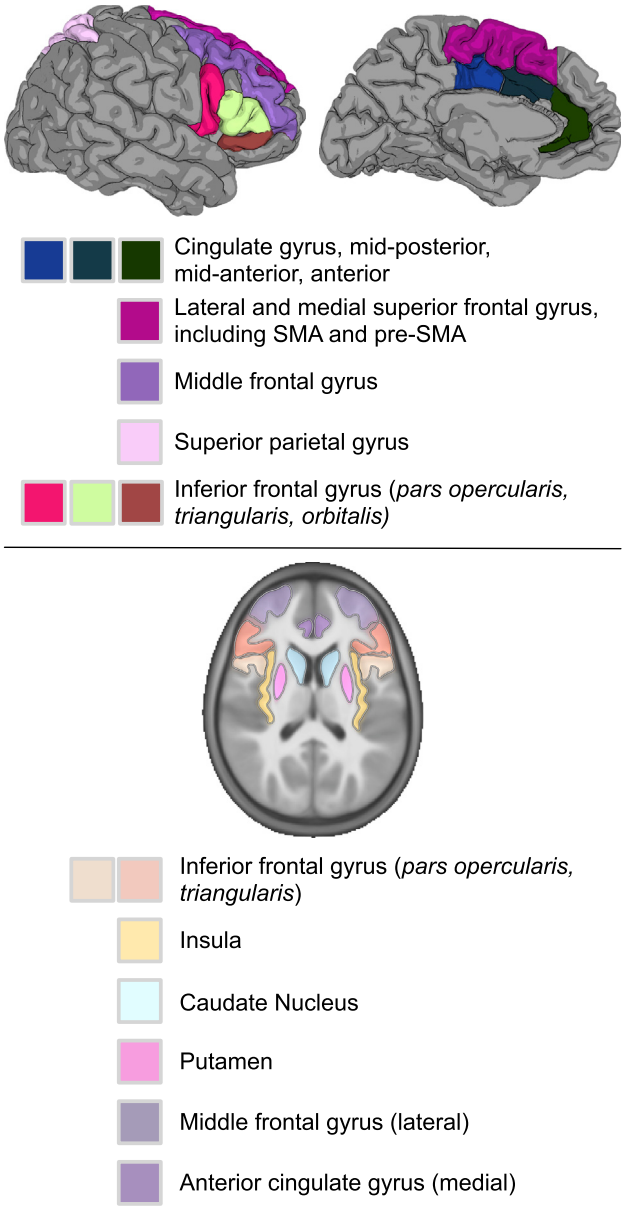

Fig. 1 – *Regions comprising the inhibitory control network.* Top: Cortical surface representation shows regions of lateral inferior frontal gyrus, superior parietal gyrus, and lateral middle and superior frontal gyri (i.e., dorsolateral prefrontal cortex), and medial superior frontal (including SMA and pre-SMA), and middle and anterior cingulate gyrus regions. Bottom: ABCD atlas representation in axial view also shows subcortical regions including caudate and putamen of the dorsal striatum, and the anterior insula neighboring inferior frontal gyrus (not visible from lateral view).

3. Materials and method

3.1. *Participants*

The proposed final sample included 56 children diagnosed with ADHD and 78 typically developing (TD) children. An additional 193 children were recruited as part of a broader study on ADHD, but 31 of them failed to complete either the T1-weighted scan and/or the experimental task EPI scan, 129 exhibited excessive movement during the T1-weighted MRI or task EPI, exceeding pre-determined thresholds (see Movement below), and 33 (15 children with ADHD, 18 TD children) were identified as left-handed according to the Edinburgh Handedness inventory.

To ensure consistent activation profiles across children, we restricted the analysis to right-handed participants as the task required a button press using the right hand, which would recruit consistent left-motor cortical network across all participants for the button press. Additionally, we chose to exclude left-handed participants because hand dominance affects cortical response profiles and response time (Diwadkar

et al., 2018; Kutas & Donchin, 1977), is associated with performance differences on executive function tasks (Beratis et al., 2010), and because prior fMRI and fNIRS studies of executive function in young children apply the same exclusion criteria for the same reason (Durston et al., 2002; Miao et al., 2017; Poirel et al., 2012).

Prior to participation, each child provided verbal assent and each parent provided written informed consent, following the guidelines of the Institutional Review Board for the Division of Social and Behavioral Sciences of Florida International University, which approved the study.

3.2. Recruitment and exclusion criteria

Participants and their caregivers were recruited through brochures, open houses, and parent workshops at local schools and mental health agencies. For the ADHD sample, parents were invited to participate in an assessment to determine study eligibility if they endorsed clinically significant levels of ADHD symptoms (six or more symptoms of either Inattention or Hyperactivity/Impulsivity according to DSM-5 or a previous diagnosis of ADHD), indicated that the child is currently displaying clinically significant academic, behavioral, or social impairments (score of 3 or higher on a seven-point impairment rating scale), and the child was not taking any psychotropic medication.

For the typically developing sample, parents and children were invited to participate in an assessment to determine study eligibility if they endorsed fewer than 4 ADHD symptoms (across either Inattention or Hyperactivity/Impulsivity according to DSM-5), fewer than 4 Oppositional Defiant Disorder (ODD) symptoms, and indicated no clinically significant impairment (score below 3 on the impairment rating scale).

Participants were also required to have been enrolled in school during the previous year, have an estimated IQ of 70 or higher (as assessed by the Wechsler Preschool and Primary Scale of Intelligence 4th edition; WPPSI-IV (Wechsler, 2012)), have no confirmed history of an Autism Spectrum Disorder, and for the ADHD group only, be able to attend an 8-week summer treatment program prior to the start of the next school year. The summer treatment program occurred after all baseline visits as part of a larger study. Due to the young age of the sample, only disruptive behavior disorders were extensively examined for diagnostic purposes.

The diagnosis of ADHD was determined using a comprehensive approach that included a structured parent interview (C-DISC) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), along with parent and teacher ratings of symptoms and impairment using the Disruptive Behavior Disorders (DBD) Rating Scale. This process involved collecting reports on symptoms from both parents and teachers and assessing impairment through the Impairment Rating Scales (Fabiano et al., 2006). The DBD rating scales and the diagnostic interview were integrated using an "or rule," meaning that a symptom was considered present if endorsed by either informant. Clinically significant problems at home and school were defined by a score of at least "3" on a "0 to 6" impairment rating scale (Bird, Gould, & Staghezza, 1992; Sibley et al., 2016). A final diagnosis was confirmed through a review by two PhD.-level clinicians. The demographics of the final sample are presented in Table 1.

Table 1 – Table of demographics by diagnostic group.

	TD	ADHD	p-value
Sex assigned at birth (female)	39.7%	33.9%	.45
Age	5.45 yrs	5.71 yrs	.07
Parental education	4.92	4.53	.11
T1 quality	3.71	3.71	.98
Movement	12.08	14.71	.10

Note. Parental education and T1 quality were measured on 6- and 7-point ordinal scales, respectively. T1-quality had a maximum value of 4, with anchors at 1 "Unusable", 2 "Significant Motion Artifact", 3 "Some Motion Artifact", and 4 "No Motion Artifact", allowing for "in between" ratings (1, 1.5, 2, 2.5, 3, 3.5, 4). Movement was measured as the number of censored TRs in the fMRI scan (out of 254 TRs).

3.3. Image acquisition

All imaging was performed using a research-dedicated 3 Tesla Siemens MAGNETOM Prisma MRI scanner (V11C) with a 32-channel coil located on the university campus. Children first completed a preparatory phase using a realistic mock scanner in the room across the hall from the magnet. They were trained to stay still, and were also acclimated to the enclosed space of the magnet, to the back projection visual presentation system, and to the scanner noises (in this case, presented with headphones). Children were also trained on the fMRI tasks for the scanner, including the K-CPT (described below). Two other short fMRI tasks, and a diffusion-weighted imaging scan, were also acquired but are not analyzed here. When they were properly trained and acclimated, they were moved to the magnet.

Structural MRI scans were acquired using a 3D T1-weighted inversion-prepared RF-spoiled gradient echo sequence with $1 \times 1 \times 1$ mm resolution, lasting 7 min and 14 s with prospective motion correction (Tisdall et al., 2012), according to the Adolescent Brain Cognitive Development (ABCD) protocol (Hagler et al., 2019). The T2*-weighted echo-planar images optimized for blood oxygenation level-dependent (BOLD) effects were obtained with 2.5 mm isotropic resolution and 56 axial slices, using a repetition time (TR) of 1000 ms and an echo time (TE) of 30 ms, with an acceleration factor of 4. The total scan time was under 30 min.

3.4. Experimental paradigm

3.4.1. Standardized K-CPT

We administered the standardized K-CPT 2nd Edition (Conners, 2006) outside the MRI magnet, which served as our primary behavioral measure of task performance because it is an empirically normed, reliable and valid measure. Our reasons for using this valid and reliable measure outside the magnet rather than in-magnet performance is based on recent recommendations for improving validity of brain-behavior association studies in neuroimaging (Makowski et al., 2024). That is, the in-magnet task, which we describe below, is optimized for detection of the BOLD response in a short scan time. Relative to the outside-the-scanner measure,

the in-magnet measure has fewer trials for reliable measurement of the key outcome variables.

The standardized K-CPT is administered on a computer and scored with accompanying software. On the K-CPT, children are presented with a series of pictures (i.e., bicycle, car, fish, hand, horse, house, sailboat, scissors, telephone, train, and soccer ball). The child is required to press the space bar every time he or she sees a picture that is *not* a soccer ball. They are required to withhold responding every time a soccer ball is presented. The duration of a single K-CPT run is 7.5 min. Each administration of the K-CPT comprises 5 blocks, with each block consisting of a 20-trial sub-block featuring 1500 ms inter-stimulus intervals (ISIs) followed by another 20-trial sub-block with 3000 ms ISIs, resulting in a total of 200 trials. The designated time for presenting stimuli is 500 ms. The task was administered by trained examiners using a standardized script and protocol on the second of three visits. The MRI was acquired at the third visit. The K-CPT 2nd Edition was validated on a sample of four-to seven-year-old children including children diagnosed with ADHD. Based on this validation, the scoring software generates *T*-scores and percentiles for several variables, including commission errors (responding to the non-target soccerball), omission errors (failing to respond to a target stimulus), hit RT (RT response to the target), and hit RT variability.

3.4.2. *Modified K-CPT for MRI*

The standardized K-CPT was modified for the MRI environment. Stimuli were projected onto a screen behind the MRI magnet, visible to the participants via a mirror attached to the imaging head coil. The stimuli were identical to the standardized K-CPT stimulus set (bicycle, car, fish etc.). Each picture was displayed for either 3000 ms or 1500 ms, with a 500 ms interstimulus interval (ISI). During the ISI and between epochs, a red fixation cross was shown on a black screen.

The fMRI task followed a block design with four epochs, using EPrime software (version 2.0.10.356 or later). The presentation was set to start with a trigger pulse from the MRI scanner. The task started with 30 s of fixation (with a 10-s pad for later censoring), followed by 36 s of continuous stimulus presentation. In each epoch, the soccer ball picture was randomly interspersed four times, resulting in a total of 16 soccer ball presentations across all epochs. Each epoch was separated by 20 s of fixation, and the block design concluded with 20 s of fixation, making a total of 254 TRs (254 s). The period of fixation and overall design was determined 1) because increasing the gap between stimuli in block designs increases the accuracy of parameter estimation (Shan et al., 2014), with optimal gaps that allow the BOLD response to return to baseline occurring between 12 and 20 sec (Robinson et al., 2006); 2) power simulations based on the design indicate sufficient power in a short scan time (Parrish et al., 2000a; b).

The children were instructed to press a button as quickly and accurately as possible in response to any picture except the soccer ball, for which they were instructed to withhold their response. Prior to the actual MRI scanning, the children practiced the task in the mock scanner to ensure they understood the instructions. Response compliance was actively monitored during scanning, and omission errors (i.e., failing to hit the key when a target stimulus is presented), commission errors (i.e., hitting a key when the non-target soccer ball is presented), RT, and standard deviation of RT were recorded via the button box. This process took about 30 min.

4. Data analysis

4.1. *T1-weighted post-processing*

T1-weighted images were visually inspected for quality control and rated on a seven-point scale. T1-quality scores had a maximum value of 4, with anchors at 1 "Unusable", 2 "Significant Motion Artifact", 3 "Some Motion Artifact", and 4 "No Motion Artifact", allowing for "in between" ratings (1, 1.5, 2, 2.5, 3, 3.5, 4) The average rating for the T1-weighted images analyzed in this study was 3.712 ($SD = .518$), indicating very good T1 images, on average. After visual inspection, the T1-weighted MRI images underwent post-processing using FreeSurfer v7.0. Any errors detected during the segmentation of grey and white matter or the subcortical segmentation and cortical parcellation were manually edited according to recommended protocols (McCarthy et al., 2015), and the brains were reprocessed until they met the acceptable quality control standards. The edited brains were then used in the BOLD EPI processing stream.

4.2. *Movement*

Excessive movement was defined as a framewise displacement (FD) greater than 0.9 mm between successive TRs, based on (Siegel et al., 2014), with participants excluded if the percentage of TRs that were censored exceeded 15%. Included and excluded groups were statistically different in terms of ADHD symptomology $t(287.75) = -3.52$, $p < .0005$. This resulted in the exclusion of 51 (34%) participants from the TD group and 78 (43%) participants from the ADHD group. After applying this exclusion criteria, the two groups did not significantly differ in terms of FD movement, $t(120.61) = -1.659$, $p = .100$.

4.3. *BOLD EPI post-processing*

We used fMRIprep (Esteban et al., 2019) to post-process the MRI data. T1-weighted structural volumes were corrected for intensity non-uniformity (N4BiasFieldCorrection) (Tustison et al., 2010) and skull-stripped (antsBrainExtraction from Advanced Normalization Tools; ANTS). Functional data were motion-corrected using MCFLIRT (from FSL) (Jenkinson, Bannister, Brady, & Smith, 2002) and slice-time corrected to the middle of each TR using 3dTshift (from AFNI) (Cox, 1996). Functional images were co-registered to corresponding T1-weighted images using boundary-based registration (Greve & Fischl, 2009) with nine degrees of freedom via FreeSurfer. The motion correction transformations, distortion correction warp, functional to anatomical transformation, and anatomical to template warp were all concatenated and applied in a single step using Lanczos interpolation (from ANTs) (Avants et al., 2011).

From this point we employed two pipelines, one in the Adolescent Brain and Cognitive Development (ABCD) Atlas space, and the other in the original participant space. In the individual space, we made use of the individualized

parcellation and segmentation maps generated by FreeSurfer to examine the association between performance on the K-CPT outside the scanner and brain activation during the scanning portion of the study.

We also conducted a voxel-wise analysis in the ABCD Atlas space. This atlas is normed on a large child sample from the ABCD study (Hagler et al., 2019) which avoids warping to an adult template, and allows for examination of subcortical structures important for this study. To do this we warped each brain to the atlas space using nonlinear registration in ANTs. Spatial smoothing in the volume space was applied for the voxel-wise analysis only (AFNI 3dmerge; 4 mm FWHM kernel).

For both pipelines, the following steps were implemented: 1) FD was calculated for each scan, and a censor file was established implementing a 0.9 mm cutoff. The first three TRs of each scan were also censored to allow the MR signal to reach a steady state; 2) prior to the general linear model, percent signal change was calculated on the native time series; 3) the general linear model was employed to model the degree of BOLD activity during the K-CPT task against a resting baseline (fixation) using AFNI 3dDeconvolve. The peak amplitude was set to 1. In addition to the stimulus timing predictor, we included in the model the censor file for movement censoring, polynomial drift predictors, six movement parameters, and signal from CSF and white matter. The output of this last step included, for each voxel, beta values representing percent signal change over resting baseline, and their associated t-statistics.

Second-level group analyses were conducted in the volume space to assess the difference in brain activity during the K-CPT across groups (ADHD vs TD). The group analysis was conducted on the level-1 beta weights using Fast and Efficient Mixed Effects Algorithm (FEMA) (Parekh et al., 2024), which is optimized for the ABCD brain atlas. The design matrix was set up to examine the main effect of Diagnostic Group on voxel-wise beta estimates of activation, and included age, sex assigned at birth, parental education, and movement (in number of censored TRs) as covariates. Statistical parametric maps were thresholded at a single voxel threshold of $p < .005$. Simultaneously, threshold free cluster enhancement (Smith & Nichols, 2009) (using FEMA) was applied to the same maps. This method enhances cluster-like structures without defining clusters in a binary way. Using this method, we identified a mask of enhanced clusters on unthresholded data, and applied that mask to thresholded statistical parametric maps of each respective comparison.

5. Region of interest analysis

We were primarily interested in identifying regions that are sensitive to the K-CPT task. Based on prior literature, we expected the anterior insula, IFG, superior parietal lobule, mid and anterior cingulate, and superior frontal gyrus medial wall (SMA and pre-SMA) to be the regions most likely to be involved in this task. We identified these regions (bilaterally) anatomically on individual cortical surfaces based on manual refinement of the automatic FreeSurfer parcellation (Destrieux, Fischl, Dale, & Halgren, 2010), in addition to dosoral and lateral frontal regions implicated in fNIRS studies. The 24 atlas regions (12 each hemisphere) were IFG *pars opercularis, pars triangularis, pars orbitalis*, superior parietal gyrus, mid and anterior cingulate gyrus, superior and middle frontal gyrus, short insular gyrus of anterior insula, anterior segment of circular sulcus of insula, superior segment of circular sulcus of insula, and caudate (see Fig. 1). These were corrected for multiple comparisons using False Discovery Rate correction (FDR; Benjamini & Hochberg, 1995).

To assess the association between K-CPT performance measured outside the scanner, and activity in our defined ROIs, multiple regression analyses were conducted using R (v. 4.1.3; https://cran.r-project.org/). Activity for each ROI was extracted by averaging the hemodynamic response estimates (betas) for each participant for each defined ROI in the volume space (FreeSurfer aparc + aseg using the Destrieux atlas (Destrieux et al., 2010), based on the anatomical conventions of Duvernoy (1999)). Data were missing for all four K-CPT variables measured outside the scanner (27% were missing for commissions, ommissions, and Hit RT; 35% were missing for RT Variability). Missingness occurred due both to the COVID-19 pandemic (for which some in person visits were modified or suspended), or in some cases the scoring program failed to compute the appropriate score due to insufficient useable data. This resulted in slightly higher missingness for the RT variability data. In order to deal with missing data for these outcome measures, we used multiple imputation with Multivariate Imputation by Chained Equations (MICE) in R (package mice). Twenty imputation sets were defined, and the data were pooled during model estimation according to Rubin's rules (Rubin, 1987).

In addition to dealing with missing data, we also down-weighted outlying values using robust regression. Outliers were thus downweighted using a Huber loss function in the regression model (R function *rlm*; Huber & Ronchetti, 1981; Wilcox, 2011; Wright & London, 2009).

6. Results

6.1. *Behavioral compliance and responses to the task inside the magnet*

We examined behavioral responses to the standardized K-CPT outside the magnet, and those recorded by the button box for children completing the task during scanning. These are reported in Table 2. The data suggest children in both groups actively engaged in the task, which, for the MRI task, is also supported by the baseline activation maps reviewed below.

The data on the standardized K-CPT are also comparable to other studies of TD children in this age range (Barnard et al., 2018; Munkvold et al., 2014), although the averages for RT are slightly higher. The data summarized in Table 2 are calculated for the sample of children after the movement cutoff is applied. When we examine group differences for the standardized K-CPT before the movement cutoff is applied, we find the group differences are slightly more pronounced. Thus, before movement exclusion, group differences (controlling for age, sex assigned at birth, parent education, and movement) were found for commissions ($t(277) = -3.31$, $p = .001$, $\beta = -.19$, $B = -3.70$, 95% Confidence Interval $B = -5.90$

Table 2 – Comparison of ADHD and TD groups on K-CPT performance inside and outside the magnet.

Standardized K-CPT (Outside MRI)				
	Omissions t-score *	Commissions t-score	Hit RT t-score	Variability t-score *
ADHD mean (SD)	70.31 (15.43)	52.36 (8.79)	64.64 (9.25)	65.65 (11.53)
TD mean (SD)	59.11 (13.58)	48.30 (9.98)	62.36 (9.73)	57.93 (12.81)
Modified K-CPT (Inside MRI)				
	Omissions raw score	Commissions raw score	RT raw score *	RT raw score SD *
ADHD mean (SD)	9.88 (9.09)	4.19 (4.84)	729.60 (169.73)	290.16 (101.65)
TD mean (SD)	6.87 (4.67)	3.22 (4.15)	708.34 (160.09)	245.65 (95.24)

Note. * indicates a ADHD vs TD group difference of $p < .05$ by independent samples t-test.

to −1.50), omissions ($t(277) = -6.37$, $p < .0001$, $\beta = -.35$, $B = -11.51$, 95% Confidence Interval $B = -15.07$ to -7.95), and RT Variability ($t(277) = -3.68$, $p < .0005$, $\beta = -.23$, $B = -6.10$, 95% Confidence Interval $B = -9.37$ to -2.83), but not for Hit RT ($t(277) = -1.75$, $p = .08$, $\beta = -.10$, $B = -2.05$, 95% Confidence Interval $B = -4.35$ to .24).

6.2. *Whole brain analysis*

Fig. 2 demonstrates that the K-CPT, as implemented, effectively engages the expected inhibitory control network (Swick, Ashley, & Turken, 2011), as discussed in the Introduction. The data, projected onto the average cortical surface representation of the sample, reveals significant activity above the resting baseline in various brain regions ($p < .005$, cluster corrected). These include bilateral visual and left motor cortex, bilateral anterior insula linked to visual attention, right middle/superior frontal cortex and parietal regions associated with working memory, midline cingulate, pre-SMA, and SMA regions involved in motor planning and execution, as well as subcortical thalamic and striatal regions related to motor execution. Remarkably, these network activations are consistently robust across groups, indicating that the participants engaged with the task as expected. They are also consistent with meta-analytic results of Go/NoGo tasks (Swick et al., 2011), as seen in Fig. 2 (bottom).

With the robust activation of the anticipated networks established across groups, our focus shifted to investigating

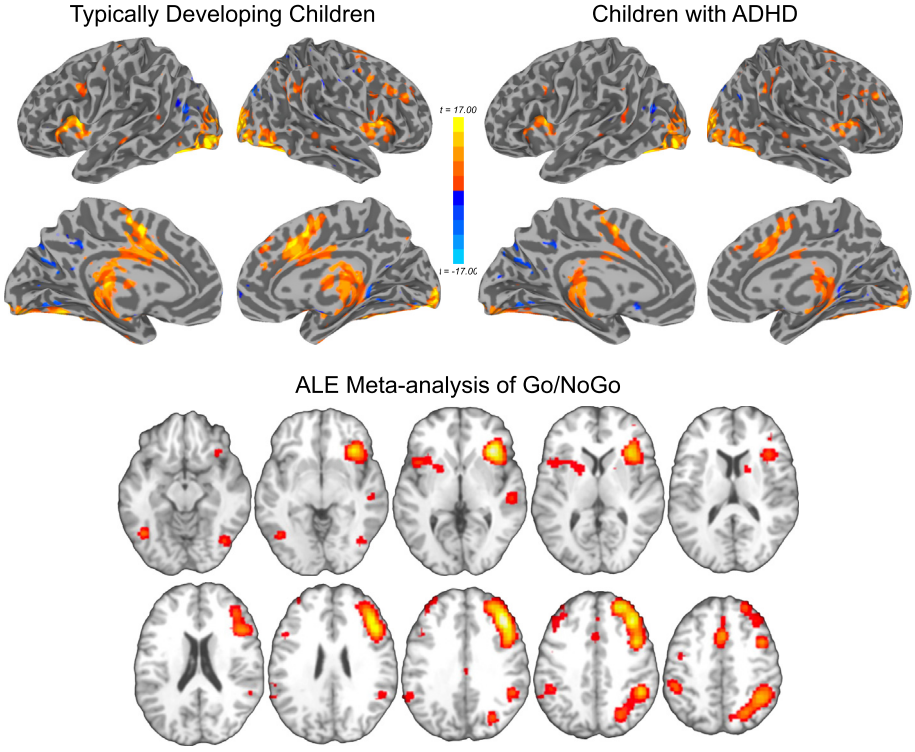

Fig. 2 – Cortical activation maps for inhibitory control. Top: Results of the whole brain analysis for *K-CPT > Resting Baseline* for both Typically Developing Children (left) and Children with ADHD (right). Results are projected to the cortical surface representation of the average sample brain ($p < .005$, cluster corrected). Bottom: For comparison, results from a meta-analysis of Go/NoGo tasks showing comparable activation. Modified from Fig. 1 of Swick, D., Ashley, V., and Turken, A. U., (2011). Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. *NeuroImage*, 56, 1655–1665.

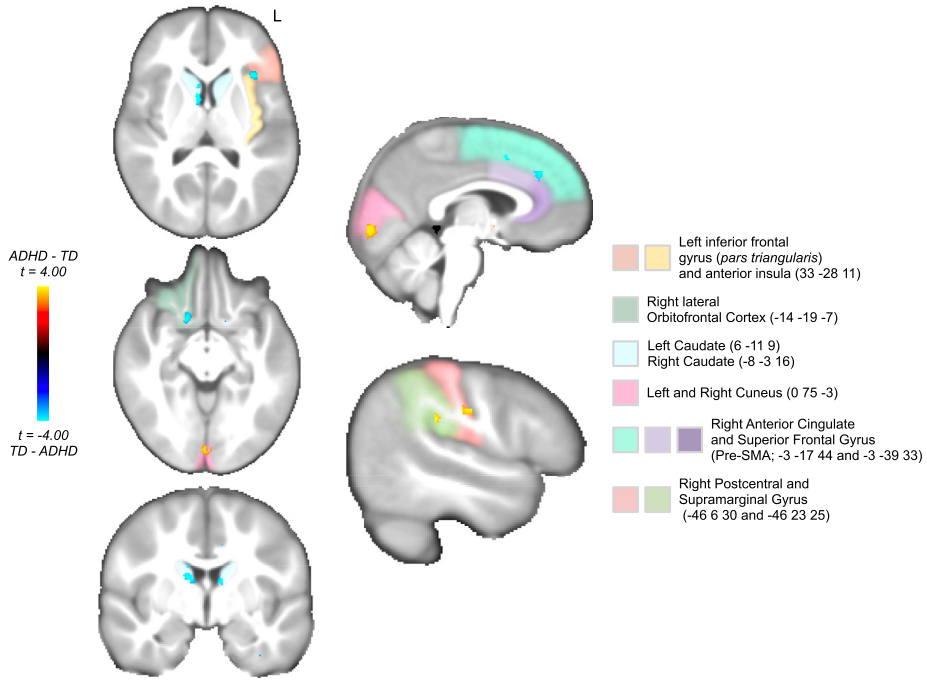

Fig. 3 – Differences in activity between ADHD and TD groups are overlayed on the ABCD group atlas. Activity favoring the TD group (shown in dark-blue-to-light-blue spectrum) was found in some regions of the putative inhibitory control network, including left inferior frontal gyrus and anterior insula, right pre-SMA and anterior cingulate, and bilateral caudate nucleus. One cluster was also found in lateral orbitofrontal cortex, not typically associated with inhibitory control. Activity favoring the ADHD group was also found in regions outside the putative inhibitory control network (shown in red-to-yellow spectrum, in bilateral cuneus, and right postcentral and supramarginal gyrus). All comparisons are $p < .005$, cluster corrected. Coordinates are reported in ABCD atlas space, which is LPS (DICOM).

group differences in these networks. Fig. 3 illustrates the outcomes of the TD vs. ADHD group comparison. Notably, the TD group exhibited greater activation in regions of the inhibitory control network, including the left inferior frontal gyrus and anterior insula, right pre-SMA and anterior cingulate cortex, and bilateral caudate. One cluster was found in the lateral orbitofrontal cortex, which is not typically associated with inhibitory control. On the other hand, the ADHD group demonstrated greater activity than the TD group, although mostly outside the putative inhibitory control network, involving regions such as bilateral cuneus, right postcentral, and supramarginal gyrus. Results were thresholded at $p < .005$, cluster corrected. Data are reported in ABCD LPS atlas coordinates (L = +; P = +; S = +), which are derived from the DICOM coordinate system.

6.3. *ROI analysis*

Next, we examined the association between brain activity in our 24 identified ROIs and behavioral measures of the computerized K-CPT administered outside the MRI scanner. The model included diagnostic group and the group by brain interaction, in addition to sex assigned at birth, age, parent education, and movement in the scanner as covariates of non-interest.

Only one brain region was associated with K-CPT performance outside the magnet. That is, activation in the right short gyrus of the anterior insula was associated with both Hit RT ($t(100.27) = -2.05$, $p = .04$, $\beta = -.28$, $B = -16.70$, 95% Confidence Interval $B = -32.85$ to $-.55$) and RT Variability ($t(96.56) = 3.90$, $p = .014$, $\beta = -.33$, $B = -26.96$, 95% Confidence Interval $B = -6.21$ to $-.05$; see Fig. 4). Although there was a trend ($p = .059$), there was no significant Diagnostic Group by Brain interaction in either region, and neither main effect survived a FDR correction for multiple comparisons across brain regions (across 24 bilateral regions), but we report the effect here to be comprehensive.

7. Discussion

Behavioral continuous performance paradigms have demonstrated good sensitivity in distinguishing very young children (i.e., pre-school, pre-kindergarten, and early school-age) with ADHD from typically developing (TD) children (Breaux et al., 2016). However, their use in understanding the neural circuitry underlying inhibitory control in these very young children is rare. In fact, as we reviewed in the Introduction, fMRI paradigms investigating inhibitory control networks in very young children are scarce overall, despite their significance in mapping functional activation differences between ADHD and TD children. Developing such paradigms presents an opportunity to elucidate the neurobiology of inhibitory control impairments observed in children with ADHD and establish a framework for future investigations into the development of these networks in both TD children and those with ADHD. To

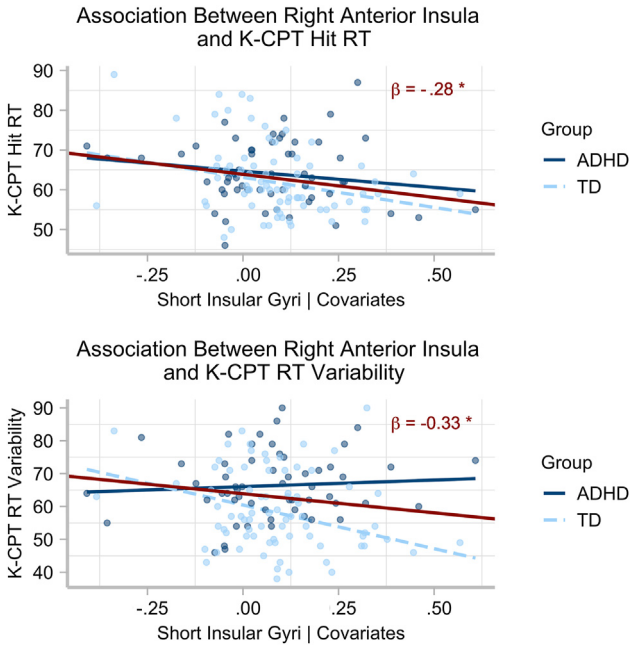

Fig. 4 – Association between right anterior insula activity and Kiddie Continuous Performance Test (K-CPT) scores, controlling for age, sex assigned at birth, family education, and movement in the scanner. Main effects were found for the association between brain activity and Hit RT, and RT Variability. No significant Diagnostic Group by Brain interaction effects were found. We show the main effect in the crimson least squares line, and report the group (ADHD and TD) least squares lines only for illustration. β is the standardized regression slope for the main effect. *$p < .05$, uncorrected for multiple comparisons.

address this objective, we studied a cohort of 56 children diagnosed with ADHD and 78 TD children, all aged 4- to 7-years. We used a modified version of the K-CPT during BOLD fMRI and assessed their performance on the clinically established and standardized K-CPT outside the MRI scanner. Our findings revealed the following: 1) the modified K-CPT effectively elicited robust activity in established inhibitory control networks for both groups; 2) group comparisons yielded small clusters of activity differences, primarily in brain regions known to be involved in inhibitory control (e.g., inferior frontal gyrus, anterior insula, dorsal striatum, medial pre-SMA, and cingulate cortex); and 3) increased activity in the right anterior insula was associated with reduced Hit RT and RT Variability on the K-CPT administered outside the MRI environment. These results highlight three key points: (1) the modified K-CPT was adapted for use in the fMRI setting with very young children, successfully eliciting a robust response in expected regions for both groups. However, the caveat is that this was successful only for a subset of children who could remain still in the MRI environment; (2) the paradigm exhibited modest sensitivity to group differences in inhibitory control network regions; and (3) the paradigm captured activity associated with performance on the standard K-CPT administered outside the fMRI environment, although this effect did not survive statistical correction for multiple comparisons across the number of ROIs. Further detailed discussion of these specific results follows below.

7.1. *The modified K-CPT elicits a robust response in regions of the inhibitory control network for both groups*

The modified K-CPT elicited a robust response in brain regions of the inhibitory control network for both groups. This is consistent with a number of fMRI CPT and inhibitory control studies in adults and adolescents (Chaarani et al., 2021; Ogg et al., 2008; Schneider et al., 2010; Shang, Sheng, Yang, Chou, & Gau, 2018; Tana et al., 2010; Zilverstand et al., 2017). For example, in adults these task paradigms, typically event-related designs, elicit activity in brain regions associated with initiating the response (i.e., "Go" process), such as motor and premotor cortex, dorsal striatum, pallidum, and thalamus. The "Stop" process recruits right inferior frontal cortex, pre-SMA, anterior cingulate, anterior insula, and parts of the basal ganglia, including the subthalamic nucleus. In Aron and colleagues' model of inhibitory control, right inferior frontal cortex and pre-SMA collaborate with basal ganglia circuits to initiate and implement action plans, with the subthalamic nucleus as the terminal target via hyperdirect pathways from both inferior frontal cortex and pre-SMA (Aron et al., 2016). As expected, the baseline response was robust for both groups in these regions. It is particularly striking to note that the activation profiles were largely symmetric bilaterally, with especially robust responses in bilateral anterior insula, middle frontal gyrus, and SMA, pre-SMA, and anterior cingulate cortices. Investigation of the ALE maps from published research (Fig. 2 bottom) shows that this is expected for these regions, based on studies in adults. Establishing that this paradigm elicits robust above–baseline activity is critically important for examining group differences. We can now turn to these group differences.

7.2. *Direct group comparisons yielded activity differences in brain regions putatively involved in inhibitory control, but brain activation associations with performance outside the scanner did not differ across groups*

We turn first to the elicited activity in anterior insula, which often extends into the neighboring inferior frontal gyrus (e.g., see ALE maps in Fig. 2). Robust activity in the anterior insula in response to inhibitory control demands has been a focus of inquiry in recent years. It has been observed that the anterior insula is often the site of peak activation during inhibitory control paradigms in adults (Cai, Ryali, Chen, Li, & Menon, 2014; Swick et al., 2011), and in two studies of younger children (Poirel et al., 2012; Réveillon et al., 2013), right anterior insula activity differences are associated with executive function performance differences, or with the Go/NoGo condition differences. However, it is worth noting that the anterior insula is absent in some prominent models of inhibitory control (Aron et al., 2014; Wiecki & Frank, 2013), although others have shown interest in defining its function more specifically. For instance, Molnar-Szakacs & Uddin (2022) proposed that the anterior insula serves as a "gatekeeper of executive control," citing its anatomical and functional associations with other regions and networks involved in

executive function. This notion is supported by meta-analyses of both SST and Go-NoGo paradigms, which consistently demonstrate bilateral activation of the anterior insula, along with the pre-SMA and SMA (Swick et al., 2011). In fact, Swick and colleagues (Swick et al., 2011) noted "results clearly demonstrate the importance of bilateral anterior insular regions and medial BA 6 (SMA/pre-SMA) for successful performance in response inhibition tasks." Finally, a number of studies report that anterior insula is also differentially recruited in response inhibition tasks by older youth with ADHD (Cubillo et al., 2010; Hwang et al., 2016; Hwang et al., 2019; Peterson et al., 2009; Rubia, Halari, Mohammad, Taylor, & Brammer, 2011), showing it's potential sensitivity to ADHD symptomology.

Typically, inhibitory control paradigms emphasize the importance of the right hemisphere inferior frontal gyrus and anterior insula (Howlett, Park, & Paulus, 2023). But in a direct comparison between the groups, we found that only *left* anterior insula extending into inferior frontal gyrus showed greater activation for the TD group relative to the ADHD group. We do note that at a reduced threshold ($p < .01$), the right insula/inferior frontal gyrus also showed the same activation pattern, but this did not survive the stricter threshold (i.e., $p < .005$). In studies with adults, both left and right anterior insula are associated with inhibitory control (Cai et al., 2019) and error processing (Wessel, Danielmeier, Morton, & Ullsperger, 2012), with stopping efficiency in inhibitory control paradigms and general accuracy in those paradigms (Boehler, Appelbaum, Krebs, Hopf, & Woldorff, 2010), and differences in both left and right insula are found for adults with ADHD (Congdon et al., 2014). Boehler and colleagues (Boehler et al., 2010) interpreted left insula activity in inhibitory control paradigms to indicate general attention modulation, which is consistent with the role for this region ascribed by Molnar-Szakacs & Uddin (2022). It is possible the difference in activity across groups is indicative of this general attention modulation. Some suggestive evidence for this exists. In one study of 8-12-year-old children using a Go/NoGo paradigm with food cues, *left* anterior insula was active specifically during successful inhibition (Grandjean da Costa et al., 2022). In a study of eighty adolescents (49 with ADHD), increasing ADHD symptom severity was associated with decreased recruitment of left anterior insula during a Go/NoGo task (Hwang et al., 2019). They likewise interpreted this association as reflecting the general attentional demands of the task, although it is difficult to tease apart the distinction between attentional load and response control in the present paradigm (Droutman, Bechara, & Read, 2015).

The *right* lateral frontal cortex extending into insula is also an important node in the inhibitory control network, and the regions are often coactivated in many inhibitory control paradigms, making their roles in such tasks difficult to distinguish (Ghahremani, Rastogi, & Lam, 2015). Indeed, in the present study, although the group difference was most notable in left insula/inferior frontal gyrus, the association between activation and K-CPT performance (namely Hit RT and RT Variability) was actually found in the *right* anterior insula (defined at the ROI level). Furthermore, there was no group by brain activation interaction, suggesting that greater activation in right anterior insula was associated with both faster RT, and reduced RT variability, in *both* groups. Despite the fact that the reported association did not survive statistical correction, the effect size, especially for RT variability, was meaningful. In the latter comparison, the β was $-.34$, which is a sizeable association, especially considering it accounts for a number of covariates. However, the lack of significance after correction suggests we should interpret the result with caution. Furthermore, we associated the brain activity with the standardized K-CPT outside the magnet, which is a reliable and valid measure with better psychometric properties than the in-scanner version. The short duration of the scan limited the number of presentations of the NoGo stimulus, and furthermore, the novelty of the scanning environment may interfere with attention in some children. In short, the brain-behavior associations we report should be understood in this context.

In addition to the lateral cortical regions, we also observed group differences in the bilateral caudate and medial frontal cortical regions, including the anterior cingulate and pre-SMA. These regions are crucial nodes in the neural system involved in stopping behaviors, such as the ability to withhold a response in the K-CPT (Aron et al., 2016; Boehler et al., 2010; Cruz et al., 2023; Jahanshahi, Obeso, Rothwell, & Obeso, 2015; Meffert, Hwang, Nolan, Chen, & Blair, 2016; Wessel & Aron, 2017; Wiecki & Frank, 2013). In models of inhibitory control, pre-SMA and striatum (including caudate) play a role in the downstream selection of a competing action among a space of possible action programs. The dorsal striatum is uniquely situated as the interface between cortex and the rest of the basal ganglia, forming part of an indirect cortico-basal ganglia-thalamic loop involved in action selection (Cruz et al., 2023). In an event-related study of adults with ADHD, Sebastian and colleagues (Sebastian et al., 2012) found less activation in right caudate for people with ADHD compared to control participants, which is in line with what we report here.

Medial frontal cortex, especially SMA and pre-SMA, are projecting nodes as part of a "hyperdirect pathway" to the subthalamic nucleus (STN) (Bingham, Petersen, Parent, & McIntyre, 2023). These hyperdirect projections also include M1 and lateral inferior frontal cortex, and together these regions function to influence STN activity, which via globus pallidus and thalamic activation works to suppress motor output (Aron et al., 2016; Song, Lin, & Liu, 2023; Wessel, Waller, & Greenlee, 2019). Pre-SMA also likely collaborates directly with lateral inferior frontal cortex as part of this loop (Aron et al., 2016; Swann et al., 2012). Given that we found differences in several key nodes of this putative inhibitory control network, we could cautiously interpret the findings to indicate differences in recruitment of the whole network, which may in turn indicate group differences in the efficiency or functional dynamics in response to inhibitory control demands. However, we should also be careful here to not overstep the limits of the BOLD paradigm as it relates to the measurement of network-level dynamics.

Other regions outside the putative inhibitory control network also showed group differences. For example, right supramarginal gyrus and postcentral gyrus, and occipital cortex, showed greater activity for the ADHD group. Right

supramarginal gyrus and occipital cortex were actually identified as reliably active by Boehler and colleagues (Boehler et al., 2010) in a comprehensive conjunction analysis of the stop-signal paradigm, along with regions of the putative inhibitory control network. Activation in these regions was interpreted to indicate sensory processing of the stop stimulus (occipital cortex) and attentional modulation of sensory stimuli, or bottom-up attentional recruitment (supramarginal gyrus). It is possible that less efficient processing in frontal regions of the inhibitory control network elicited greater demand on these regions involved in attentional modulation, leading to recruitment to a greater degree in the ADHD group.

7.3. Limitations

Although this study suggests that the modified K-CPT paradigm can be used in young children and is sensitive to group differences in regions of the inhibitory control network, as well as the association between activation in the right insula and task behavior outside the scanner, there are several significant limitations. First, movement was a substantial issue for a large portion of the sample, which was expected given the young age of the participants (Gaffrey, Barch, Luby, & Petersen, 2021). To address this, we implemented a strict movement cutoff to establish a reliable inhibitory control network against the resting baseline. While this cutoff aligns with optimal analytic protocols for dealing with movement (Siegel et al., 2014), it is more stringent than what is sometimes used in pediatric fMRI studies, which can set cutoffs as large as a voxel or more. Consequently, we excluded a considerable number of both TD and ADHD children (see, e.g., Gaffrey et al., 2021) for comparable attrition in this age range). This almost certainly introduces a selection bias favoring children with less severe ADHD symptoms within the ADHD group. Thus, the observed group differences may not be as pronounced as they would have been with a less strict movement criteria. That is, larger behavioral differences likely translate into larger effect sizes for brain-behavior associations, and reducing those differences will result in reduced statistical power. In addition, the exclusion criteria limits the external validity of the study, as the sample represents children who are able to stay still in a MRI scanner. However, employing a more lenient movement criteria would likely have compromised the reliability of the data, or led to activation differences in regions susceptible to movement artifact (e.g., at the edges of the brain). It is worth noting that movement poses a significant challenge in pediatric fMRI (Frew, Samara, Shearer, Eilbott, & Vanderwal, 2022), as it strongly influences the initial estimation of the BOLD response due to movement-related noise (Friston, Williams, Howard, Frackowiak, & Turner, 1996). While including movement as a regressor in the second-level analysis is important, it does not completely address the issue of movement in the first-level estimation of the BOLD response. One could argue that our arbitrary inclusion cutoff of 15% of the time series is overly conservative, but unfortunately, to our knowledge no established guidelines exist in the literature (Ciric et al., 2017). Therefore, we opted for caution, and based our analysis decisions on more recent recommendations for best practice (Makowski et al., 2019), which are more stringent than past studies.

As a consequence, the reported differences should be interpreted in light of the final analyzed sample. This sample successfully facilitated a meaningful comparison between ADHD and TD children. Notably, all ADHD children met strict diagnostic criteria as determined by two clinicians, and we observed behavioral differences in K-CPT performance, particularly in terms of RT variability, which is the most sensitive K-CPT measure associated with ADHD (Breaux et al., 2016). However, group differences might have been more pronounced if children with more significant ADHD symptomatology had been included in the final sample. There is thus a cost-benefit to conducting such research in very young children. The improved spatial resolution and ability to scan deep neural structures, relative to modalities such as fNIRS and EEG, comes at some cost to generalizability to children with more severe symptomology.

A strength of this study is the investigation of younger participants. This adds to a sparse literature on neurobiological differences, as measured by fMRI, in children with ADHD and TD children. However, this brings up a second limitation, which is the potential limited generalizability of these results to older children. Most investigations of children with ADHD involve older children (typically over 9-years of age) and young adults. Studies of typical children using other paradigms (e.g., verbal fluency or passive tasks like listening to sentences) suggest that functional networks change, sometimes markedly, over development (Holland et al., 2001; Jonkman, 2006; Olulade et al., 2020). For example, in a study of verbal fluency from 7 to 18-years, Holland and colleagues (Holland et al., 2001) reported increased left laterality of activation as a function of age. In other words, the functional network of this standard executive control task shifted substantially as children entered adolescence. Thus, it is possible that the reported differences apply generally to younger children, but may not in fact reflect activation profiles of older children with ADHD. For example, in a small sample of 6-7-year-old children during a Go/No-Go paradigm, left anterior insula was also identified as more active in control children compared to children born preterm (Réveillon et al., 2013). Whether these regions remain the key nodes in older children would be most appropriately addressed in a longitudinal investigation.

7.4. Conclusions

To briefly summarize the findings, our research uncovered the following: 1) the modified K-CPT successfully triggered strong and expected brain activity related to inhibitory control networks in both groups of participants; 2) when comparing the two groups, we observed modest differences in brain activity primarily in regions associated with inhibitory control, including the inferior frontal gyrus, anterior insula, dorsal striatum, medial pre-SMA, and cingulate cortex; 3) heightened activity in the right anterior insula was linked to quicker and more consistent response times on the K-CPT conducted outside the MRI scanner. The findings broadly support the usefulness of this paradigm for very young children who are able to stay still in the MRI environment. However, they also reveal the limitations in studying children with ADHD in this age range within the MRI environment, even with careful procedures to minimize movement. This led to the need for a

large initial sample size to ensure an appropriate investigative sample. Our exclusion criteria, especially for movement, might have resulted in the exclusion of children with more severe ADHD, and could limit the differences between the two groups. Therefore, we should interpret our reported results in the context of these limitations and the young age of the sample.

CRediT authorship contribution statement

Mohammadreza Bayat: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Melissa Hernandez:** Project administration, Data curation. **Madeline Curzon:** Project administration, Data curation. **Dea Garic:** Project administration, Data curation. **Paulo Graziano:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Anthony Steven Dick:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to improve grammar and flow of content originally-drafted by the authors, or to help with R coding. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Scientific transparency statement

DATA: All raw and processed data supporting this research are publicly available: https://nda.nih.gov/edit_collection.html?id=2781

CODE: All analysis code supporting this research is publicly available: https://github.com/anthonystevendick/kcpt.

MATERIALS: No study materials supporting this research are publicly available.

DESIGN: This article reports, for all studies, how the author(s) determined all sample sizes, all data exclusions, all data inclusion and exclusion criteria, and whether inclusion and exclusion criteria were established prior to data analysis.

PRE-REGISTRATION: No part of the study procedures was pre-registered in a time-stamped, institutional registry prior to the research being conducted. No part of the analysis plans was pre-registered in a time-stamped, institutional registry prior to the research being conducted.

For full details, see the Scientific Transparency Report in the supplementary data to the online version of this article.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2024.11.025.

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