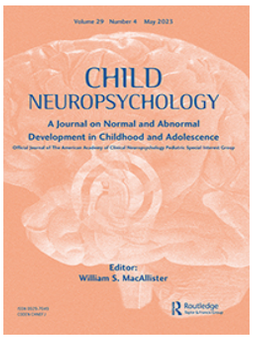

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Working and short-term memory in children with ADHD: an examination of prefrontal cortical functioning using functional Near-Infrared Spectroscopy (fNIRS)

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ABSTRACT

Working memory impairments are an oft-reported deficit among children with ADHD, and complementary neuroimaging studies implicate reductions in prefrontal cortex (PFC) structure and function as a neurobiological explanation. Most imaging studies, however, rely on costly, movement-intolerant, and/or invasive methods to examine cortical differences. This is the first study to use a newer neuroimaging tool that overcomes these limitations, functional Near Infrared Spectroscopy (fNIRS), to investigate hypothesized prefrontal differences. Children (aged 8–12) with ADHD ($N = 22$) and typically developing ($N = 18$) children completed phonological working memory (PHWM) and short-term memory (PHSTM) tasks. Children with ADHD evinced poorer performance on both tasks, with greater differences observed in PHWM (Hedges' $g = 0.67$) relative to PHSTM ($g = 0.39$). fNIRS revealed reduced hemodynamic response among children with ADHD in the dorsolateral PFC while completing the PHWM task, but not within the anterior or posterior PFC. No between-group fNIRS differences were observed during the PHSTM task. Findings suggest that children with ADHD exhibit an inadequate hemodynamic response in a region of the brain that underlies PHWM abilities. The study also highlights the use of fNIRS as a cost-effective, noninvasive neuroimaging technique to localize/quantify neural activation patterns associated with executive functions.

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most common mental health disorders of childhood, affecting approximately 7.2% of children worldwide (Thomas et al., 2015). It is a chronic condition with core features of developmentally inappropriate levels of inattention and/or hyperactivity/impulsivity. Although theories explicating the etiological origins have shifted dramatically over the past century since the condition was first described (cf. Barkley, 2015, for a review), most modern conceptualizations, including within the DSM-5, implicate executive dysfunction as central

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processes underlying the disorder (Barkley, 1997; Rapport et al., 2008; Willcutt et al., 2005). Executive functions (EFs) are a collection of top-down processes that make it possible to pay attention and stay focused, reason and problem-solve, and exercise self-control (Diamond, 2020). Evidence supporting EF-based neurocognitive theories of ADHD origins abound.

Executive dysfunction is continually linked to ADHD core symptoms (Kofler et al., 2010; Orban et al., 2018; Raiker et al., 2012) and functional impairments, such as learning-related (Calub et al., 2019; Eckrich et al., 2019; L. M. Friedman et al., 2018) and social (Kofler et al., 2011) difficulties, and findings are corroborated by extensive neuroimaging evidence documenting hypoactivity (cf. Dickstein et al., 2006; McCarthy et al., 2014, for meta-analytic reviews) and structural and connectivity abnormalities (Carmona et al., 2005; Shaw & Polanczyk, 2017; Shaw et al., 2007, 2012; Wang et al., 2018) in crucial cortical and subcortical areas implicated in executive functioning.

Among the executive functions identified within the extant literature (N. P. Friedman & Miyake, 2017; Miyake et al., 2000), working memory has emerged as the most potent contributor to ADHD sequelae (cf. Friedman, Fabrikant-Abzug, et al., 2022, for a review). Working memory (WM) is a limited capacity system responsible for the temporary storage and processing of internally held information. Nearly all contemporary models of WM include a higher-order, attentional supervisory system that interacts with short- and long-term memory (e.g., A. Baddeley, 2007; Cowan, 1999; Engel et al., 1999; Gray et al., 2017). Baddeley's WM model (A. Baddeley, 2012) is one of the most widely used due to its utility for exploring a range of WM-related mechanisms and frequent adoption in child psychopathology research (Alderson et al., 2010; Dekkers et al., 2021; Rapport et al., 2008). The model views WM as a multicomponent system responsible for temporarily storing, rehearsing, maintaining, processing, updating, and manipulating information (A. Baddeley, 2007; A. D. Baddeley, 2017). The domain general *working* component consists of a central executive (CE) supervisory system that controls attentional focus, reacts to multi-task demands, and oversees/coordinates two modality specific, anatomically distinct memory subsystems. These include phonological and visuospatial short-term memory (STM), which are responsible for temporarily storing and maintaining verbal and non-verbal information, respectively.[1]

Extensive information exists regarding the extent to which upper-level CE (i.e., the *working* part of WM) relative to lower level STM (storage/maintenance capacity) processes are uniquely impaired in children with ADHD. Meta-analytic reviews and experimental investigations consistently report larger magnitude CE process reductions (ES = 2.01 to 2.15; Kasper et al., 2012) relative to phonological storage reductions (ES = 0.55 to 0.89; Rapport et al., 2008). Complementary investigations corroborate the importance of the CE in elucidating ADHD sequelae and consistently document the mediational influence of executive abilities in inattention (Orban et al., 2018) and impulsivity (Raiker et al., 2012), as well as reading (L. M. Friedman et al., 2017), math (L. M. Friedman et al., 2018), social (Kofler et al., 2011), and family (Kofler et al., 2017) functioning. In contrast, nominal or non-significant relations are evident between

[1]A fourth WM component has also been proposed in recent years. The episodic buffer is purported to bind visuospatial and phonological information prior to central executive processing. However, evidence for its validity and purpose is mixed (A. D. Baddeley & Hitch, 2019) and is particularly weak among school-aged children (Gray et al., 2017).

phonological storage abilities and these behavioral and ecologically valid outcomes (cf. Friedman, Fabrikant-Abzug, et al., 2022, for a review).

The overwhelming majority of investigations elucidating brain-based regions underlying WM difficulties in children with ADHD utilize conventional techniques such as functional magnetic resonance imaging (fMRI) to measure oxygen consumption (hemodynamic response) while performing WM tasks. Extant findings indicate that the dorsolateral prefrontal cortex (PFC) plays an integral role when engaged in tasks that rely on CE abilities, such as updating, manipulating, interference control (Cortese et al., 2012; Curtis & D'Esposito, 2003; Goldman-Rakic, 1995; Wager & Smith, 2003) and particularly serial reordering (e.g., Amiez & Petrides, 2007; Van Hecke et al., 2010). Complementary experimental and meta-analytic reviews document considerable cortical maturational delay (Ha et al., 2020; Shaw et al., 2007), reduced prefrontal volume (Lukito et al., 2020; Mostofsky et al., 2002), and neurofunctional reductions within the dorsolateral PFC among children with ADHD. Meta-analyses of fMRI studies have also indicated reduced activation in other frontal brain regions among individuals with ADHD that are critical for executing aspects of WM tasks, such as the orbitofrontal and supplementary motor cortex (Hart et al., 2013). Specifically, in healthy individuals, the anterior PFC is implicated in maintenance or rehearsal of stored information and inhibitory control (Goldman-Rakic, 1996; Hung et al., 2018; Veltman et al., 2003). Posterior prefrontal/frontal areas, including the frontal eye field and supplementary motor cortex, are critical for coordinating movements to maintain attention and physical orientation to a task (N. P. Friedman & Robbins, 2022; Haber et al., 2022). Recent fNIRS studies of children with ADHD have also identified abnormalities in aspects of anterior and posterior portions of the PFC while completing working memory tasks (Gu et al., 2018), implicating additional cortical regions as contributors to ADHD-related working memory difficulties.

Interpretation of extant results are constrained, however, due to the wide range of cognitive abilities that require movement responses and high sensitivity to movement artifacts associated with traditional functional neuroimaging techniques (Friston et al., 1996; Power et al., 2015)—a phenomenon exacerbated in studies involving children with ADHD (Durston, 2003; Epstein et al., 2007) who move excessively when engaged in cognitively demanding tasks (Orban et al., 2018; Rapport et al., 2008) and may perform better cognitively when movement is permitted (Dekkers et al., 2021; Sarver et al., 2015).[2] The use of functional near-infrared spectroscopy (fNIRS) circumvents the primary methodological constraints of examining WM performance in children with ADHD. It accommodates a wide range of psychometrically validated WM tasks that require movement-related responses, and despite its lower spatial resolution relative to traditional functional neuroimaging approaches, fNIRS is a well-validated technique that compares favorably with fMRI (Cui et al., 2011; Huppert et al., 2006; Strangman et al., 2002). Additional advantages of fNIRS include its low cost, portability, relative comfort, brief set-up time, and potential for widespread availability (Buss et al., 2014; Cutini & Brigadoi, 2014; Ehlis et al., 2014; Tak & Ye, 2014; Xu et al., 2015).

[2]Although sophisticated methods for reducing movement artifacts exist, these statistical correction techniques can improve the signal to noise ratio for small-scale movements emitted within an fMRI scanner but cannot address the larger-scale movements associated with improved performance among children with ADHD (Lloyd-Fox et al., 2010).

Consistent with the fMRI literature, previous studies using fNIRS reveal a general pattern of hypoactivation in the dorsolateral PFC for children with ADHD relative to typically developing children (cf. Mauri et al., 2018, for a review). However, the utility of these collective findings is hindered due to an overly exclusive focus on tasks requiring response inhibition (Inoue et al., 2012; Jourdan-Moser et al., 2009; Miao et al., 2017; Monden et al., 2015; Nagashima et al., 2014; Negoro et al., 2010; Xiao et al., 2012). Because accumulating evidence suggests that behavioral inhibition (a) fails to make mediational contributions to ADHD symptoms (Alderson et al., 2012; Raiker et al., 2012) and (b) is likely downstream of and secondary to WM insufficiency (Alderson et al., 2010; Tarle et al., 2019) or basic attentional processes (Burgess et al., 2010), examining cortical activation during WM tasks is critical.

To date, only a handful of studies have examined WM functional activation using fNIRS. Studies measuring visuospatial WM have been reported; however, results show non-significant (Schecklmann et al., 2010) or weak (Grazioli et al., 2019) correlations between task-related activation and ADHD symptoms or warrant caution given the inclusion of children on an active psychostimulant regimen (Tsujimoto et al., 2013). Even fewer studies have examined phonological WM performance, and all examine WM updating using n-back tasks. These studies have produced mixed results - one study reported reduced recruitment of oxygenated hemoglobin (HbO2) in the right and left ventrolateral prefrontal cortex (Ehlis et al., 2008), whereas a second study using a nearly identical task found between group differences in the right dorsolateral PFC but not the ventrolateral, medial, posterior PFC (Gu et al., 2017). A third study found that reduced activity in the dorsolateral, anterior, and posterior PFC correctly discriminated children with ADHD from typically developing children with 86% accuracy (Gu et al., 2018). However, the exclusive reliance on updating tasks does not allow for measurement of cortical correlates of WM capacity, as they require minimal (1-back) or no (0-back) storage and maintenance of information. In addition, none of these studies examined WM subprocesses or how distinct cortical regions may differentially contribute to executive/storage functioning.

The present investigation is the first to examine the extent to which domain general CE (Phonological WM; PHWM) and specific (Phonological STM; PHSTM) challenges in children with ADHD relative to typically developing (TD) children reflect underlying neurofunctional differences in the dorsolateral, anterior, and posterior PFC – areas implicated in working memory processes. Evidence concerning this phenomenon may be valuable for establishing potential biomarkers and/or areas for targeted treatment. Additionally, the present study is the first to directly measure PHWM and PHSTM components using neuroimaging technology that allows for motor movement.

Consistent with extant literature, we hypothesize that children with ADHD will perform significantly worse on PHWM and PHSTM tasks relative to typically developing peers, with greater differences evident in working memory performance relative to short-term memory performance. Additionally, we hypothesize an interaction between children's diagnostic status (ADHD, TD) and cortical prefrontal region (dorsolateral PFC, anterior PFC, and posterior PFC) for the PHWM task based on converging evidence linking these areas to (a) working memory performance (Amiez & Petrides, 2007; Curtis & D'Esposito, 2003; Wager & Smith, 2003) and (b) regional ADHD activation reductions (Fassbender et al., 2011; Gu et al., 2017, 2018). A between-group directional hypothesis for fNIRS activation while completing the PH STM task was not formulated given the

limited number and diverse array of tasks used in previous neuroimaging studies involving children with ADHD.

Method

Participants

Forty children between the ages of 8 and 12 were recruited from the southeast United States via referrals from primary care physicians, community mental health clinics, public and homeschool systems, and self-referral. The age range (8–12) was selected to capture both the onset and overlap of STM and WM abilities (Tillman et al., 2011). Two groups of children participated in the study: 22 children with ADHD and 18 typically developing (TD) children without a psychological disorder. Prior functional imaging studies find several cortical and subcortical differences depending upon the ADHD presentation considered, including within the prefrontal areas under investigation in the present study (Ghaderi et al., 2017; Saad et al., 2020; Solanto et al., 2009). Therefore, only those with the combined presentation were considered for inclusion. Boys ($n = 30$) and girls ($n = 10$) from all racial and ethnic groups participated in the study and mirrored the demographics of the region's population. The gender composition of our ADHD sample (18 males:4 females) was consistent with the known gender ratio in ADHD (i.e., 3.5:1 male:female; Willcutt, 2012). Sample composition was 70.0% White, 7.5% Black or African American, and 22.5% indicated multiple or other races. Of the above categories, 20.0% identified themselves as being Hispanic or Latino/a/x.

Children in the ADHD group met the following inclusion criteria: (1) an independent diagnosis by the directing clinical psychologist using DSM-5 criteria for ADHD-Combined Presentation based on the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS:PL; Kaufman & Schweder, 2004) semi-structured interview with parent and child; (2) parent ratings exceeding the 80th percentile on the Attention-Deficit /Hyperactivity Problems DSM-Oriented scale of the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) or meeting the clinical cut off on the Child Symptom Inventory (CSI; Gadow and Sprafkin, 2004); (3) teacher ratings exceeding the 80th percentile on the Attention-Deficit/Hyperactivity Problems DSM-Oriented scale of the Teacher Report Form (TRF; Achenbach & Rescorla, 2001) or meeting the clinical cut off on the Child Symptom Inventory (CSI; Gadow and Sprafkin, 2004); and (4) full scale intelligence (FSIQ) scores (WISC-V; Wechsler, 2014) between 1 *SD* below (SS ≥ 85) and 1.5 *SD*s above average (SS ≤ 122). Children on a psychostimulant regimen ($n = 5$) were required to undergo a 24-h washout period prior to each testing session (Cortese et al., 2017).

Children meeting the following criteria were included in the typically developing group: (1) no evidence of any clinical disorder based on parent and child K-SADS interview; (2) normal developmental history by parental report; (3) ratings within 1.5 *SD*s of the mean on all CBCL and TRF scales; (4) parent and teacher ratings within the non-clinical range on all CSI subscales; and (5) intelligence scores within 1 *SD* below (SS ≥ 85) and 1.5 *SD*s above (SS ≤ 122) average. All parents and children provided their informed written consent/assent to participate in the study, and the university's Institutional Review Board approved the study prior to data collection. All procedures proposed for the study were in accordance with the ethical standards of the institutional

and/or national research committee and with the 1964 Helsinki declaration and its later amendments and comparable ethical standards.

Procedures

The two tasks described below (PHWM, PHSTM) were programmed using SuperLab Pro 5.0 (Cedrus Corporation, 2014) and administered as part of a larger study to understand neurocognitive performance in children with ADHD. Task administration was counterbalanced across assessment sessions scheduled one week apart to control for order effects. Each child's head was measured and fitted with a lightweight fNIRS cap at the beginning of each session. Placement was determined by measuring from the nasion to the inion and centered on the vertex in accordance with the international 10–20 electrode system for functional brain mapping measurements (Jasper, 1958; Okamoto et al., 2004). Children watched an age-appropriate video of their choosing during the cap set-up and adjustments were made to ensure the comfort and fit of the cap. Light saturation (e.g., concentration change of oxygen bound to hemoglobin [HbO2]) of each fNIRS channel was measured to determine task-related changes in signal strength. If needed, adjustments were made to sensors/detectors to ensure quality of signal strength ($<1.5 \times 10^{-3}$ mmol/L [HbO2/Hb] change) before testing began.

Training trials (approximately 3 min) for each task were completed immediately following the cap set-up to ensure a clear understanding of the task requirements – a minimum of 80% correct on training trials was required prior to administering regular task trials and collecting fNIRS data. Each task consisted of 10, alternating 20-s blocks of the baseline task (fixation cross) and 24-s activation blocks containing four items of the PHWM or PHSTM tasks, depending upon the task condition. A set size consisting of four letter/number stimuli was selected based on recent studies demonstrating that it results in largest-magnitude between-group differences ($d = 1.52$) between children with ADHD and TD children relative to set sizes of 3 ($d = .86$), 5 ($d = 1.37$), and 6 ($d = 1.23$) stimuli (Friedman, Rapport, et al., 2022). Participants completed all tasks while sitting approximately 0.66 m from a computer monitor in an assessment room. An examiner was present throughout the duration of the fNIRS assessments.[3]

Phonological working memory (PHWM) task

The PHWM task is similar to the WISC-V (Wechsler, 2014) Letter-Number Sequencing subtest. Children were presented a series of numbers and a capital letter on a computer monitor and instructed to place the numbers in ascending order and the letter last (e.g., the correct ordering of 7, 3, L, 9 would be 3, 7, 9, L). Stimuli were presented visually on a screen, and participants provided verbal responses.[4] All

[3]The examiner remained in the assessment room but out of the child's view to ensure that children did not spin in their chair or engage in other behaviors that could impact optode placement. The experimenter did not interact with the child or provide performance-related feedback during the tasks.

[4]Although stimuli were presented visually on a computer screen, the task included herein is still considered a phonological task. Read material, such as the letters and numbers that comprise the stimuli during the present task, is orthographically converted to a phonological code in order to extract meaning from visual stimuli (A. Baddeley, 2007). Once encoded, this newly converted phonological information is stored temporarily in the PHSTM subsystem, whereupon the CE processes held information. Therefore, this task places demands on the domain-specific phonological system, rather than the visuospatial system, and should be considered a PHWM task (see L. M. Friedman et al., 2017 for a review).

children were administered 40 trials of four, to-be-remembered stimuli, with four trials administered per each 24-s active WM block. Verbal responses were recorded by trained independent observers situated outside of the assessment room and wearing headphones. Performance data were collected and scored independently by two trained research assistants. A partial-credit scoring system was implemented in which each digit or letter recalled in the correct sequence was counted (e.g., 7, 3, L, 9 recalled as 3, 5 9, L would be counted at 3 stimuli correct) as recommended (Conway et al., 2005; Tarle et al., 2017). The average number of stimuli correct per trial was used as the outcome measure for task performance. Evidence for reliability and validity for the PHWM tasks includes high internal consistency ($r = 0.82$to 0.97) and inter-rater reliability ($r = 0.96$) (Rapport et al., 2008).

Phonological short-term memory (PHSTM) task

The phonological short-term memory task (PHSTM) is similar to the WISC-V (Wechsler, 2014) Digit Span Forward subtest and assesses verbal short-term memory. Children were presented a series of numbers and a capital letter on a computer monitor and instructed to repeat the series of numbers and the letter in the order they were presented. All participants were administered 40 trials of four to-be-remembered stimuli with four trials administered per each 24-s active PHSTM block.Verbal responses were recorded by trained independent observers situated outside of the assessment room and wearing headphones. Performance data were collected and scored independently by two trained research assistants. A partial-credit scoring system was implemented in which each digit or letter recalled in the correct sequence was counted (e.g., 7, 3, L, 9 recalled as 7, 5, L, 9 would be counted at 3 stimuli correct) as recommended (Conway et al., 2005; Tarle et al., 2017). The average number of stimuli correct per trial was used as the outcome measure for task performance.

Power analysis

A power analysis was conducted to estimate needed sample size based on data from meta-analyses and experimental investigations comparing children with ADHD and TD children on measures of working memory (ES = 2.01 to 2.15; Kasper et al., 2012) and short-term memory (ES = 0.51 to 0.89 Kasper et al., 2012; Rapport et al., 2008; Tiffin-Richards et al., 2008). The effect sizes in the meta-analyses of phonological working memory tasks range from medium to large using Cohen's (1988) criteria. With an alpha =.05, power =.80, and applying the average effect sizes for working and short-term memory tasks ($ES = 1.29$), the projected sample size needed with the average effect size for working memory and storage tasks is approximately $n = 30$ (total sample size) for a between-subject, mixed factor design with one covariate (GPower 3.1.9.2). The adopted sample size of 40 children (TD = 18, ADHD = 22) is sufficient for recommended power guidelines.

Data analytic plan

Functional Near Infrared Spectroscopy (fNIRS). fNIRS measures blood oxygen level dependent (BOLD) responses in the brain by detecting changes in light absorption by

the hemoglobin in blood. Similar to fMRI, which measures BOLD responses via magnetic properties of hemoglobin, fNIRS can be used to analyze changes in metabolic demand while completing a wide array of cognitive tasks. Although fNIRS measurements are limited to cortical layers (approximately 2 cm in depth), they are highly consistent with fMRI measurements across cognitive tasks (Cui et al., 2011). In this study, prefrontal cortex activity was measured using a 20-channel functional near-infrared spectroscopy system from NIRx Medical Technologies, LLC (NIRSport 88 system). Eight sources sent pulses of near-infrared light into the scalp and eight detectors collected the amount of light returning to the surface. Source LEDs emitted near-infrared light at 2 wavelengths: 760 nm and 850 nm. The sampling rate for fNIRS data acquisition was 7.8 Hz per second. Data were collected using NIRx NIRStar acquisition software. fNIRS channels measured task-related concentration changes in HbO2, Hb, and total hemoglobin. Measurement channels recorded bilaterally in approximately the following areas: (a) posterior PFC, including frontal eye fields (Brodmann Area; BA 8), (b) medial dorsolateral PFC (BA 9 and BA 46), and (c) anterior PFC (BA 10).

Optode positions were based on the International 10–20 system used conventionally in EEG data collection. Individual structural differences in neuroanatomy and the absence of overlapping MRI brain scans necessitate approximate determinations of Brodmann areas for this study. Children were permitted to move their arms and legs while seated during the tasks but instructed to resist engaging in excessive head and gross motor movements.

fNIRS data preprocessing

NIRSLab analysis software, a suite of MATLAB tools provided with the NIRx system, was used for data preprocessing. As recommended, spike artifacts and discontinuities were detected and eliminated automatically (Gratzer & Kollias, 2009). A low pass filter was applied to remove signals related to respiration and heart rate. An additional filter was used to reduce artifacts related to excessive movement. fNIRS is relatively resilient to movement artifacts, which is ideal given the propensity of children with ADHD to engage in excessive gross motor activity relative to their same age peers (Dekkers et al., 2021; Ehlis et al., 2014). A change between adjacent data points larger than five standard deviations from the mean for each channel's time course was considered a movement artifact, as recommended (Gramlich et al., 2017). Data were bandpass filtered subsequently to remove slow data drift (low cutoff frequency = 0.01 Hz) and high-frequency noise (high cutoff frequency = 0.2 Hz). After preprocessing, raw optical density values were transformed to produce estimates of oxygenated hemoglobin (HbO2) concentration changes at each sample point using the modified Beer-Lambert Law (MBLL) in nirsLAB v201904 (http://nirx.net/nirslab-1). Hemodynamic state conversion parameters were based on Gratzer and Kollias (2009). Participants with greater than 40% channel oversaturation were eliminated from the analysis due to poor signal quality. A total of four participants (two children in the ADHD group, and two in the TD group) had missing data due to poor signal quality during the PHSTM condition. Inclusion or exclusion of the data did not impact overall trends; therefore, group means for that condition were imputed as replacement.

Event-related analysis

Event-related analysis is widely used in fNIRS because HbO2 concentration often declines rapidly after reaching its peak (Holtzer et al., 2011; Themelis et al., 2007). Maximum HbO2 values were extracted from the first 10 s following stimulus onset for the 10 trial epochs during both tasks (PHSTM, PHWM). Trial epochs were baseline corrected by subtracting the mean HbO2 value from the 0.2 s preceding each stimulus onset. The corrected trial epochs were averaged, and the maximum HbO2 value was then extracted for each task and channel. These maximum HbO2 values were used in the ensuing statistical analyses to examine the influence of diagnostic group and task modality.

Region of interest

Regions of interest (ROI) that reflected the contributions of approximate cortical regions including the dorsolateral, anterior, and posterior PFC were selected due to extant literature demonstrating region-specific effects on working memory performance broadly (e.g., updating, manipulating, serial reordering; Curtis & D'Esposito, 2003; Goldman-Rakic, 1995) and serial reordering specifically (e.g., Petrides, 1991; Amiez & Petrides, 2007; Wager & Smith, 2003). Neuroimaging studies typically demonstrate hypoactivity in the lateral areas of the prefrontal cortex for children with ADHD relative to TD controls during inhibition tasks (Inoue et al., 2012; Jourdan-Moser et al., 2009; Negoro et al., 2010; Van Hecke et al., 2010). Less is known, however, about the differential cortical activation patterns that may emerge during storage/maintenance of internally held phonological information among children with ADHD and is a purpose of the present study.

Seminal studies demonstrate an increase in HbO2 in more ventrally located portions of the dorsolateral PFC during simple storage tasks and activation in more medial-located areas of dorsolateral PFC during manipulation of phonological information, such as serial reordering (Amiez & Petrides, 2007; Van Hecke et al., 2010; Wager & Smith, 2003). The prefrontal cortex ROIs in this study focused on bilateral changes in HbO2 concentration measured across three areas (a) anterior PFC approximating BA 10 and posterior BA 11 areas (average of channels 4, 11, 13, and 19); (b) the medial dorsolateral PFC approximating mid-dorsal location of BA 9 (average of channels 7 and 14); and (c) posterior PFC approximating BA 8 and anterior BA 6 (average of channels 2, 8, 10, and 17). The average HbO2 concentration in the ROIs were used as the outcome measures for each group (TD, ADHD) across tasks (PHWM, PHSTM).

Proposed analyses

All statistical analyses were performed using SPSS (IBM Corp., 2019). Preliminary analyses involved investigation of missing data and examination of demographic characteristics for potential between group differences (see Table 1). Primary analyses involved mixed factor analyses of variance (ANOVAs) examining within (Region: Dorsolateral PFC, Anterior PFC, Posterior PFC) and between (Diagnostic Status: Typically Developing; ADHD) group effects to identify potential region-specific differences in activation among children with ADHD relative to typically developing children. Separate models were run to examine PHWM and PHSTM activity. Post-hoc analyses examined simple effects. To reduce the likelihood of Type I error, all post-hoc analyses

Table 1. Comparisons by diagnostic status using independent samples *t*-test.

	ADHD		Typically Developing		Comparisons
	Mean	*SD*	Mean	*SD*	*t*
Age	9.87	1.51	10.01	1.29	0.32
FSIQ	101.24	9.85	103.86	10.27	0.76
SES	50.60	9.86	57.10	5.18	2.04
CBCL ADHD Prob.	71.53	5.69	56.25	8.95	5.83**
TRF ADHD Prob.	67.11	6.82	54.63	6.14	4.99**

ADHD = attention-deficit/hyperactivity disorder; CI = Confidence Interval; FSIQ = Full Scale Intelligence Quotient, SES = socioeconomic status; CBCL = Child Behavior Checklist; TRF = Teacher Report Form; *$p \leq .05$, **$p \leq .01$.

were performed using the Benjamini – Hochberg False Discovery Rate (FDR; Benjamini & Hochberg, 1995) applied within domain. The FDR is associated with lower rates of familywise error relative to other approaches (e.g., Bonferroni correction). For all pairwise comparisons, Hedges' *g* effect size metrics are provided (0.2 = small, 0.5 = moderate, 0.8 = large).

Analyses were completed initially without covariates. We then performed exploratory ANCOVAs using the following covariates: participant age, race, and socioeconomic status (Hollingshead, 1975); however, inclusion did not change the pattern or interpretation of results. Therefore, simple models without covariates are presented. We did not include IQ as a covariate, consistent with best practice recommendations (Dennis et al., 2009; Miller & Chapman, 2001). Briefly, working memory shares significant variance with IQ ($r = .68$ to $.79$), and removal of variance attributable to IQ would also remove variance in working memory – the key construct under investigation in the present study. In addition, most etiological conceptualizations of ADHD (Rapport et al., 2008; Willcutt et al., 2005) implicate decreases in neurocognitive functioning as either causal or correlated processes of ADHD, and cognitive differences that contribute to children's IQ scores are (a) inherent to the ADHD phenotype and (b) do not represent systematic error (Calub et al., 2019). Including IQ as a covariate would thus violate the fundamental assumptions of covariance (see Dennis et al., 2009; Miller & Chapman, 2001, for a discussion of this phenomenon).

Results

Preliminary analysis

All independent and dependent variables were screened for multivariate outliers using Mahalanobis distance tests ($p < .001$) and univariate outliers as reflected by scores exceeding 3.5 standard deviations from the mean in either direction. No significant outliers were identified. Independent sample *t*-tests were used to compare the means of children with ADHD and TD children on demographic variables. No statistically significant between-group differences in age ($p = .745$), sex ($p = .283$), or FSIQ ($p = .444$) were observed; however, scores on the parent and teacher behavior rating scales were significantly higher for the ADHD group relative to the TD group, as expected (see Table 1).

Task performance

As a first step and manipulation check, between group differences in PHWM and PHSTM task performance were examined in a 2 (Diagnostic Status: TD, ADHD) x 2 (Task: PHWM, PHSTM) mixed factor ANOVA. Means comparisons are shown in Table 2. As expected, a significant main effect of Diagnostic Status was observed, $F(1,38) = 16.05$, $p < .001$, indicating large magnitude ($\eta^2 = .30$) between-group differences in task performance (see Table 2). A significant main effect of Task, $F(1,38) = 18.28$, $p < .001$ and Diagnostic Status X Task interaction, $F(1,38) = 6.26$, $p = .02$, were also observed. Post-hoc analyses using the Benjamini-Hochberg FDR correction revealed that the performance of children with ADHD was significantly poorer during the PHWM ($g = 0.67$, 95% CI =.54 to 1.89) and PHSTM ($g = .39$, 95% CI =.22 to 1.51) task conditions relative to typically developing children (see Figure 1). Inspection of within-group performance effects indicates that children with ADHD experienced a significant decrement in task performance under the PHWM relative to the PHSTM task condition ($g = -0.90$, 95% CI = −1.40 to −0.38), whereas no significant between-task effects were evident for typically developing children ($g = -0.43$, 95% CI = −0.91 to 0.06). Thus, results indicate that children with ADHD evince

Table 2. Phonological working and short-term memory performance.

	PHWM M (*SD*)	PHSTM M (*SD*)	Group F
ADHD	2.85 (.82)	3.49 (.50)	24.88***
TD	3.66 (.36)	3.83 (.18)	1.46
Task F	15.02***	7.64**	
Group Contrasts	TD>ADHD ($g = 0.67$)	TD>ADHD ($g = 0.39$)	

*$p < .05$; **$p < .01$; ***$p < .001$.
g = Hedges' g effect size estimates.
ADHD = Attention-Deficit/Hyperactivity Disorder, PHWM = Phonological Working Memory, PHSTM = Phonological Short-Term Memory; TD = Typically Developing.

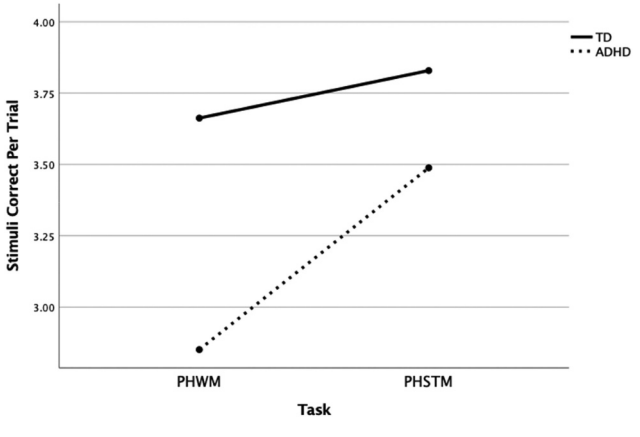

Figure 1. Phonological working memory and phonological short-term memory performance among children with ADHD and typically developing children. ADHD = Attention Deficit/Hyperactivity Disorder; PHWM = Phonological Working Memory; PHSTM = Phonological Short-Term Memory; TD = Typically Developing.

significant, moderate to large magnitude PHWM and PHSTM reduction relative to peers, with greater differences evident on working memory performance relative to short-term memory performance.

Functional Near Infrared Spectroscopy (fNIRS) activation

Phonological working memory (PHWM)

A 2 (Diagnostic Status: TD, ADHD) X 3 (Region: Anterior PFC; Posterior PFC; Dorsolateral PFC) mixed factor ANOVA was conducted to examine potential between-group, region-specific activation differences during the PHWM task, and revealed a significant Diagnostic Status X Region interaction, $F(1,38) = 4.27$, $p = .02$; Figure 2). Means comparisons are shown in Table 3. The main effects for Diagnostic Status $F(1,38) = 0.64$, $p = .43$, and Region $F(2,37) = 0.32$, $p = .73$, were nonsignificant, whereas post-hoc analyses revealed reduced cortical activation in the dorsolateral PFC during the PHWM task for children with ADHD relative to typically developing children ($g = 1.95$, 95% CI = 1.07 to 2.81). No significant between-group differences were evident within the anterior PFC ($g = -0.13$, 95% CI = −0.75 to 0.50) or posterior PFC ($g = -0.35$, 95% CI = −0.97 to

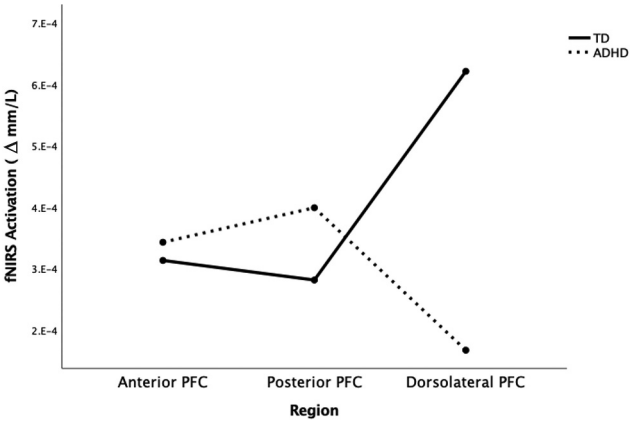

Figure 2. Region-specific fNIRS activation patterns among children with Attention Deficit/Hyperactivity Disorder (ADHD) and typically developing (TD) children; PHWM = Phonological Working Memory; PFC = prefrontal cortex.

Table 3. Between-group, region-specific activation differences (Δmmol/L) during the PHWM task.

	Anterior PFC M (*SD*)	Posterior PFC M (*SD*)	DL PFC M (*SD*)
ADHD	3.41E–04 (4.96E–04)	3.99E–04 (3.82E–04)	1.67E–04 (2.32E–04)
TD	2.87E–04 (2.94E–04)	2.81E–04 (2.45E–04)	6.21E–04 (8.95E–04)
Group Contrasts	TD=ADHD	TD=ADHD	TD>ADHD* $g = 1.95$

ADHD = Attention-Deficit/Hyperactivity Disorder, DL = Dorsolateral, PFC = Prefrontal Cortex, TD = Typically Developing; *$p < .05$.

Table 4. Between-group, region-specific activation differences (Δmmol/L) during the PHSTM task.

	Anterior PFC M (SD)	Posterior PFC M (SD)	DL PFC M (SD)
ADHD	2.90E–04 (3.37E–04)	3.50E–04 (3.99E–04)	2.62E–04 (3.90E–04)
TD	3.30E–04 (3.27E–04)	2.18E–04 (1.93E–04)	3.57E–04 (6.28E–04)

All between-group contrasts were nonsignificant. ADHD = Attention-Deficit /Hyperactivity Disorder, DL = Dorsolateral, PFC = Prefrontal Cortex, PH STM = phonological short-term memory, TD = Typically Developing.

0.27) regions. Collectively, results reveal large-magnitude cortical activation reduction among children with ADHD relative to typically developing children in the dorsolateral prefrontal cortex while completing the phonological working memory task.

Phonological short-term memory (PHSTM)

Between-group, region-specific activation differences during the PHSTM task were examined subsequently. A 2 (Diagnostic Status: TD, ADHD) X 3 (Region: Anterior PFC; Posterior PFC; Dorsolateral PFC) mixed factor ANOVA revealed a nonsignificant Diagnostic Status X Region interaction, $F(2,37) = 0.64$, $p = .54$, as well as nonsignificant main effects for Diagnostic Status $F(1,38) = 0.01$, $p = .92$, and Region $F(2,37) = 0.31$, $p = .74$. Mean comparisons are shown in Table 4. Collectively, significant differences in regional cortical activation patterns did not emerge between children with ADHD relative to typically developing children while completing the phonological short-term memory task.

Discussion

The present study is the first to use a movement-tolerant neuroimaging tool, functional Near Infrared Spectroscopy (fNIRS), to investigate hypothesized prefrontal hemodynamic functioning (HbO2) differences between children with ADHD and typically developing children while they complete phonological memory tasks differing in cognitive processing demands (i.e., PHWM: working memory, PHSTM: short-term memory). As hypothesized, children with ADHD recalled fewer items correctly relative to typically developing children on both tasks, with larger magnitude between-group performance differences evident on the PHWM task relative to the PHSTM task. Obtained hemodynamic responses revealed reduced HbO2 levels in the dorsolateral PFC among children with ADHD during the PHWM condition, which required both maintenance and higher-order processing of the phonological information held in short-term memory (A. D. Baddeley, 2017; Engel et al., 1999). Between-group differences were nonsignificant in other prefrontal regions during the PHWM task, and in the three regions assessed (anterior, posterior, dorsolateral PFC) during the PHSTM task, which required simple maintenance and minimal executive processing of held information.

The present study contributes uniquely to the growing literature of fNIRS studies involving children with ADHD and is the first to demonstrate decreased prefrontal regional cerebral blood flow (hypoactivity) in children with ADHD relative to neurotypical children while completing serial reordering working memory tasks. Our findings of

hypoactivation in the dorsolateral PFC and corresponding between group decrements in task performance are consistent with those reported in a majority of fNIRS investigations examining behavioral inhibition (Nagashima et al., 2014; Negoro et al., 2010; Yasumura et al., 2014) and set-shifting (Weber et al., 2005; Yasumura, 2015). In contrast, some studies report no changes in hemodynamic response for children with ADHD while engaged in inhibitory control tasks (Araki et al., 2015; Jourdan-Moser et al., 2009; Miao et al., 2017; Xiao et al., 2012), or n-back tasks (Grazioli et al., 2019; Gu et al., 2017); however, the observed changes in hemodynamic response for these latter studies were unaccompanied by between-group performance differences on the tasks, and interpretation of their findings warrant caution.

Our findings that performance and neurovascular deficiencies are present among children with ADHD introduces the possibility that decreased HbO2 levels in the dorsolateral PFC may support a putative neurophysiological explanation for ADHD-related working memory difficulties. This conclusion rests, in part, on past studies demonstrating decreased thickness and volume of the prefrontal cortex of children with ADHD relative to neurotypical children (Shaw et al., 2007, 2012), coupled with significant evidence of functional deficiencies within this region while completing working memory tasks using fMRI (Cortese et al., 2012, for meta-analytic review). Collectively, these findings may imply that the reduced recruitment and expenditure of oxygenated hemoglobin observed in children with ADHD relative to neurotypical children is an expected manifestation of the immature development of this region, and may provide a neurobiological explanation to the well-documented working memory performance differences among children with ADHD (Kasper et al., 2012; Kofler et al., 2020; Orban et al., 2018; Rapport et al., 2008).

Contrary to our hypotheses, no hemodynamic differences were observed within the anterior and posterior PFC during the PHWM tasks. Our initial supposition was predicated on evidence that these regions are (a) implicated in complex attentional (N. P. Friedman & Robbins, 2022; Haber et al., 2022) and information maintenance/rehearsal processes among typically developing individuals (Goldman-Rakic, 1996; Hung et al., 2018; Veltman et al., 2003), and (b) show evidence of reduced activation during fNIRS investigations examining n-back performance among participants with ADHD (Gu et al., 2018). Recent evidence, however, suggests that poor information rehearsal fails to explain ADHD-related short-term memory recall difficulties (Rapport et al., 2022), which may account for the lack of between-group activation differences within these regions that support rehearsal processes. Our use of a serial reordering task to measure working memory may also explain discrepant findings with extant literature. The physical orientation demands necessary to complete n-back tasks that require rapid information presentation likely engage brain areas responsible for motor planning and oculomotor orientation (i.e., frontal eye fields and supplementary motor cortex regions) to a greater extent. In contrast, reordering tasks require higher order processing in addition to prolonged information storage and maintenance (Kofler et al., 2020); thus, the type of attentional demand differences between the two working memory tasks may explain different findings.

Interestingly, hemodynamic between-group differences did not occur in any region of interest during the PHSTM task. This finding was largely anticipated based on extant research demonstrating that engaging in tasks requiring PHSTM is usually associated

with increased activation of the temporoparietal lobe (A. Baddeley, 2007; Herman et al., 2013), an area with few or no neuroanatomical differences among children with ADHD relative to TD children (Shaw et al., 2007, 2012). The between-group performance differences on the PHSTM task were marginal and consistent with empirical (Kofler et al., 2020; Rapport et al., 2008; Tiffin-Richards et al., 2008) and meta-analytic findings (Kasper et al., 2012; Martinussen et al., 2005) that report nonsignificant or small magnitude differences on tasks requiring brief maintenance and minimal or no additional processing of information within the PH storage subsystem.

Despite the numerous strengths of the study (e.g., multi-method/multi-informant diagnostic procedures; PHWM and PHSTM tasks with strong psychometric qualities) potential limitations of the study merit discussion. fNIRS resolution has limited spatial localization with a shallow depth of approximately 2 cm and consequently does not measure activity in other cortical and subcortical brain regions (e.g., temporal, parietal, occipital, cerebellum) that may be involved in working and short-term memory performance. There are also individualized neuroanatomical variations in cortical structure that may affect the location of the targeted cortical region. Future studies may benefit from validating fNIRS findings with simultaneous measurement using tools with enhanced spatial resolution such as fMRI. Alternative statistical approaches, such as channel-wide analyses, may also be preferred for detecting broad regional atypicality (e.g., Brodmann areas, laterality, anterior vs. posterior); however, such procedures also increase probability of Type 1 or familywise errors unless exceptionally large samples are recruited. In addition, the present study investigated hemodynamic response across the entire working memory task, yet evidence suggests that encoding, attention, manipulation, and maintenance processes may be differentially impacted among children with ADHD (Raiker et al., 2019; Rapport et al., 2022). Future fNIRS studies may benefit from including cognitive tasks, such as delayed estimation tasks (Zhang & Luck, 2008), that allow for nuanced fractionation of working memory subprocesses. Such tasks have been employed extensively in the EEG literature but have neither been utilized with fNIRS technology nor investigated among children with ADHD. Lastly, this study focused on a relatively small population of participants within the most prevalent subtype of ADHD (ADHD-Combined, Takeda et al., 2010), and therefore the results may not generalize to other presentations (e.g., ADHD-inattentive and ADHD-hyperactive/impulsive). Future studies should seek to increase statistical power and use an intersectional approach to elucidate the impact of symptom severity/distribution and age on clinical diagnosis commensurate with the Research Domain Criteria (RDoC) recommendations.

The primary findings that children with ADHD demonstrate reduced dorsolateral prefrontal cortex activity compared to neurotypical children when engaged in tasks that require phonological WM represents a crucial first step in explicating brain-based processes that underlie core cognitive difficulties in ADHD. Complementary fNIRS investigations are needed to assess hemodynamic responses during other higher-order cognitive processes inherent to working memory (e.g., dual-processing, interference control), and that involve other modalities (e.g., visuospatial). In a related vein, the importance of understanding the complex interplay among gross motor movement, cognitive performance, and associated neurovascular phenomena in children with ADHD relative to neurotypical children warrants scrutiny. Investigations of this type may be particularly informative given the potentially facilitative impact of increased

movement in children with ADHD on cognitive tasks and educationally related activities that involve working memory processes (Dekkers et al., 2021; Hartanto et al., 2016; Sarver et al., 2015).

Our findings may be particularly relevant for identifying a neuroanatomical target and/or biomarker that can be used to corroborate performance-derived improvements in WM associated with cognitive training interventions, pending the replication and extension of the current results using larger samples and a wider range of cognitively demanding WM tasks. Currently, cognitive training programs developed to improve WM and related aspects of cognitive function in children with ADHD have met with mixed and largely disappointing results (cf. Cortese et al., 2015; Rapport et al., 2013, for meta-analytic reviews). Moderate gains are often found for near transfer training effects, such as improvement on similar tasks or exercises as those used during training; however, demonstrating far-transfer training effects on meaningful phenomena, such as academic functioning and foundational learning, have remained elusive. Notwithstanding the foregoing, an accurate target may facilitate the evaluation of natural developmental trajectories of brain activity and assessment of cognitive gains associated with differences between near and far transfer of acquired cognitive skills. Additionally, establishing an accurate neurological target via performance on a WM task may be particularly impactful for children with ADHD given WM's central role in foundational learning (L. M. Friedman et al., 2016, 2018) and fluid intelligence (Calub et al., 2019; Shipstead et al., 2016). Lastly, fNIRS training may serve as a viable neurofeedback treatment in and of itself if children can learn to self-regulate hemodynamic responses known to be associated with cognitive processes involved in attention and higher-order executive functions.

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