Does Training Working Memory or Inhibitory Control Produce Far-Transfer Improvements in Set Shifting for Children with ADHD? A Randomized Controlled Trial

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Abstract

Children with ADHD show impairments in set shifting task performance. However, the limited available evidence suggests that directly training shifting may not improve shifting performance in this population. We hypothesized that this incongruence may be because the impairments exhibited by children with ADHD during shifting tasks are due to deficits in other executive functions, as shifting tasks also engage children's working memory and/or inhibitory control abilities. Therefore, this randomized controlled trial examined the extent to which neurocognitive training of working memory vs. inhibitory control can produce downstream (far-transfer) improvements in set shifting task performance for children with ADHD. Children with ADHD ages 8–12 (M=10.41, SD=1.46; 12 girls; 74% White/Non-Hispanic) were randomized to 10 weeks of training using either central executive training (CET; n=25) or inhibitory control training (ICT; n=29), two next-generation digital therapeutics previously shown to improve their intended neurocognitive targets. Two criterion set shifting tests were administered at pre- and post-treatment. Results indicated that ICT was superior to CET for improving shifting accuracy (treatment × time: p=.03, BF_{10}=3.01, η^2=.09, d=0.63). ICT was also superior to CET for improving shifting speed, albeit on only one of the two outcome tasks (p=.02, BF_{10}=4.53, η^2=.08, d=0.59). CET did not produce improvements in shifting speed or shifting accuracy on either task (p>.52, BF_{01}>2.62), but showed evidence for more general (non-shifting-specific) improvement in response times on one of the two outcome tasks (shift trials, d=0.70; non-shift trials, d=0.68). Taken together, these findings confirm that inhibitory control abilities are important for successful performance on set shifting tests, and suggest that training inhibitory control may reflect a method for improving set shifting difficulties in children with ADHD.

Keywords

ADHD; set shifting; inhibitory control; working memory; randomized controlled trial

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Conflict of Interest:
Michael Kofler/Florida State University (FSU) was awarded U.S. Patent 11,210,967 for the neurocognitive interventions described in the present study. Central Executive Training was recently licensed to Sky Therapeutics, with whom Michael Kofler is in negotiations to serve as Chief Science Officer and consultant. There are no other financial or other conflicts to report.

Set shifting, or cognitive flexibility, is one of three core executive functions (Miyake et al., 2000) and refers to the ability to quickly and efficiently switch between mental sets via activation of the frontoparietal network, including prefrontal and posterior parietal cortices (Bhandari & Badre, 2020; Miyake et al., 2000; Pa et al., 2010). While pediatric attention-deficit/hyperactivity disorder (ADHD) is associated with impaired performance on traditional neuropsychological tests of set shifting (Frazier, et al., 2004; Willcutt et al., 2005), the extent to which set shifting abilities are impaired in ADHD remains unclear as described below (e.g., Snyder et al., 2015). Similarly, questions remain regarding the malleability of set shifting in children and the extent to which set shifting deficits in ADHD – if they exist – can be ameliorated via targeted training (Kray et al., 2012; Rapport et al., 2013). As detailed below, the current secondary outcome study of the Kofler et al. (2020) randomized controlled trial was developed based on the hypotheses that (a) the impaired performance of children with ADHD on set shifting tasks is due to deficits in other executive functions – namely working memory and/or inhibitory control – rather than to deficits in set shifting specifically; and therefore (b) improving working memory and/or inhibitory control via targeted training may improve set shifting task performance in children with ADHD. That is, we examined potential far-transfer effects of training working memory or inhibitory control on set shifting, a distinct neurocognitive outcome that was not directly trained by the interventions.

Is Set Shifting Impaired in Children with ADHD?

Set shifting in the pediatric ADHD literature has been measured primarily via subtests from traditional neuropsychological batteries, with meta-analytic estimates of medium magnitude impairments (d = 0.46–0.64; Frazier, Demaree, & Youngstrom, 2004; Willcutt et al., 2005) resulting from an approximately equal number of studies finding and not finding that children with ADHD perform more slowly and/or less accurately than their peers on these tests (for review see Irwin et al., 2019). Interestingly, children's performance on these neuropsychological tests of set shifting is moderately to strongly related to functional impairments including academic functioning (Bull & Scerif, 2001; Epsy et al., 2004; Hooper et al., 2002; Roberts et al., 2017; Yeniad et al., 2013), problem-solving (Senn et al., 2004), and social competence (Bierman et al., 2008) – all of which are domains in which children with ADHD have documented difficulties (Aduen et al., 2018; DuPaul et al., 2013; Huang-Pollock et al., 2009; Kofler et al., 2015; Sarver et al., 2012). Performance has also been linked to ADHD symptomology with correlational studies suggesting that set shifting test performance is moderately related to ADHD symptoms (r = .17–.61, Chhabildas, Pennington, & Willcutt, 2001; Willcutt et al., 2001), although children with ADHD who have versus do not have set shifting deficits do not appear to differ in ADHD symptom severity (Kofler, Irwin et al., 2018).

Taken together, extant evidence positions set shifting as a potential underlying mechanism that is significantly related to ADHD behavioral symptoms. However, this conclusion merits scrutiny because, to our knowledge, the tests used to measure set shifting in these studies have been uniformly criticized for poor specificity and were developed to assess gross neuropsychological dysfunction rather than set shifting specifically (for review, see Snyder et al., 2015). In contrast, cognitively-informed tests of set shifting abilities such as the

Global-Local task (Irwin et al., 2019; Miyake et al., 2000) typically require children to flexibly switch back and forth between two simple-decision tasks (Bialystok, 2010). This switching generates a measurable temporal cost termed *shift cost*, which refers to the difference between children's slower response times to correct trials that require a rule switch (i.e., shift trials) and their faster response times to correct trials where no such shift is required (i.e., non-shift trials that require the same simple decision process as the previous trial; Miyake et al., 2000; Rubinstein, Meyer, & Evans, 2001). An *accuracy cost* is often computed as well and refers to the difference between children's error rates that occur on shift trials relative to non-shift trials (Irwin et al., 2019). *Shift costs* from correct trials are considered the primary metric of set shifting, whereas *accuracy costs* are thought to reflect children's ability to successfully maintain inactive rule sets in working memory, inhibit the current active rule set, and cognitively shift (Arbuthnott & Frank, 2000; Baddeley et al., 1998; Irwin et al., 2019; Miyake et al., 2000).

To our knowledge, only two studies have evaluated set shifting in children with ADHD using these criterion tasks and metrics. One experimental study found that children with ADHD have difficulty maintaining/inhibiting competing rule sets prior to shifting (i.e., deficits in accuracy costs; $d = 0.54$), but that children with ADHD shift just as quickly as their non-ADHD peers (i.e., no deficits in shift costs; $d = 0.009$; Irwin et al., 2019). Similarly, a study of executive functioning heterogeneity in ADHD reported medium magnitude deficits in accuracy costs for children with ADHD based on multiple criterion set shifting tasks ($d = 0.46$), although conclusions are somewhat limited because that study did not directly examine shift costs (Kofler, Irwin et al., 2018). In terms of links between criterion estimates of set shifting and ADHD symptoms/impairments, experimental evidence suggests a potential causal link between set shifting and increased gross motor activity in children, as inducing shifting demands produces systematic increases in objectively assessed motor activity (Irwin et al., 2020).

Can Set Shifting Abilities Be Improved Via Targeted Training in Children with ADHD?

The evidence base at this time indicates that children with ADHD exhibit significant difficulty with set shifting tasks due to difficulty maintaining inactive rule sets in working memory and/or inhibiting the currently active rule set prior to set shifting (i.e., greater accuracy costs), but are able to shift just as quickly as their peers when these prerequisites are met (i.e., unimpaired shift costs; Irwin et al., 2019). In particular, the finding that experimentally manipulating set shifting can produce reliable increases in hyperactive behavior provides a compelling empirical basis for hypothesizing that set shifting tasks may be capturing aspects of neurocognition that reflect underlying mechanisms that produce, at least in part, ADHD behavioral symptoms (Irwin et al., 2020). By extension, if set shifting tasks are tapping a causal mechanism in ADHD, then it stands to reason that training children with ADHD using set shifting protocols may have the potential to produce corresponding reductions in their ADHD symptoms (for review of the conceptual basis for cognitive training in ADHD, see Rapport et al., 2013).

Accordingly, several set shifting training protocols have been developed and tested in neurotypical and clinical pediatric samples. One study revealed small-to-medium set shifting

speed improvements in a neurotypical sample (d=0.41; Karbach & Kray, 2009), but this effect either (a) failed to replicate (Zinke et al., 2012), (b) or only partially replicated due to similarities between the training and outcome tasks rather than improvements in underlying set shifting abilities (Pereg et al., 2013). To our knowledge, only one study has examined set shifting training in children with ADHD (Kray et al., 2012), and showed a similar pattern of results indicating that set shifting training failed to produce superior improvements in set shifting speed or accuracy relative to an active control condition on untrained tasks.[i] In sum, current evidence suggests that set shifting training either fails to produce significant improvements in set shifting speed or produces improvements only on shifting tasks that are nearly identical to the trained tasks (e.g., Pereg et al., 2013). The reason for this lack of strong evidence is unclear; however, at least two possibilities merit scrutiny. First, it is possible that set shifting cannot be improved via targeted training. In this case, we would expect to replicate previous findings (i.e., no significant improvements in set shifting speed following either of the cognitive training protocols described below). Alternatively, to our knowledge only one study has examined set shifting training in pediatric ADHD, and the lack of significant training-specific improvements in set shifting may be due to attempting to train a cognitive ability that is not impaired in this population (Irwin et al., 2019).

Our hypothesis that ADHD-related impairments on set shifting tasks are not due to actual set shifting deficits is based on converging findings from experimental and factor analytic investigations (e.g., Karr et al., 2018; Pereg et al., 2013). In particular, experimental evidence indicates that (a) set shifting tasks contain unique working memory and/or inhibitory control demands (Irwin et al., 2019; Pereg et al., 2013); and (b) impairments on set shifting tasks for children with ADHD appear to be attributable to difficulties maintaining competing rule sets in working memory and/or inhibiting currently active rule sets prior to shifting, rather than to slowed shifting specifically (Irwin et al., 2019). These findings are consistent with emerging factor analytic evidence indicating that set shifting may not be a unique executive function in school-aged children (Karr et al., 2018; Lee et al., 2013; St. Clair-Thompson & Gathercole, 2006; van der Ven et al., 2013). Thus, while the evidence for the structure and hierarchy of executive functions in children continues to emerge, what is evident is that children's performance on set shifting tasks appears to require significant working memory and/or inhibitory control resources (Irwin et al., 2019; Pereg et al., 2013).

Current Study

Taken together, the evidence base at this time indicates that children with ADHD tend to show impairments in shifting accuracy, but not shifting speed, on set shifting tasks (Irwin

[i]Set shifting training has also been studied in college students with ADHD, but its efficacy is uncertain because the authors did not report whether set shifting improved following training (White & Shah, 2006). Instead, the study focused on changes in *mixing costs* (performance on shifting tasks that alternate between two simple decision tasks relative to performance when completing each of the two simple decision tasks separately), which have been shown to reflect other higher-order cognitive processes rather than set shifting per se (e.g., Pereg et al., 2013). Notably, the college ADHD study found that set shifting training produced significantly greater reductions in mixing cost speed for the set shifting training relative to a no-contact control group (White & Shah, 2006). Kray et al. (2009) and Pereg et al. (2013) also reported significantly reduced mixing costs for shifting training relative to active control conditions in neurotypical samples, but this effect failed to reach significance for children with ADHD (Kray et al., 2012). As argued below, the finding that set shifting training produces improvements in mixing costs but not set shifting (shift costs) is generally consistent with the hypothesis that children with ADHD's difficulties on set shifting tasks may be artifacts of difficulties in other higher-order cognitive functions rather than reflective of true deficits in set shifting (e.g., Irwin et al., 2019).

et al., 2019; Kofler, Irwin et al., 2018). However, the limited evidence to date suggests that directly training set shifting may not improve set shifting in children with ADHD or other populations (Kray et al., 2012; Pereg et al., 2013; Zinke et al., 2012). Emerging theoretical and empirical evidence suggests that these disappointing findings may occur because the impairments exhibited by children with ADHD during set shifting tasks are due to deficits in working memory and/or inhibitory control, rather than deficits in set shifting per se (Irwin et al., 2019, Pereg et al., 2013). Given this evidence, a compelling implication is that targeting working memory and/or inhibitory control may lead to improvements on set shifting tasks for children with ADHD. The current study tested this hypothesis by randomly assigning children with ADHD to working memory or inhibitory control training protocols and examining the extent to which these trainings produced improvements in set shifting abilities in children with ADHD.

Based on the evidence reviewed above, we hypothesized that working memory and inhibitory control training would both produce far-transfer improvements in children's shifting accuracy (accuracy costs), but not shifting speed (shift costs), during set shifting tasks. The hypothesized benefits of working memory and/or inhibitory control training for set shifting *accuracy* were expected given that (a) children with ADHD exhibit deficits in set shifting accuracy, despite correctly shifting just as quickly as non-ADHD children (Irwin et al., 2019); and (b) set shifting accuracy has been linked with working memory and inhibitory control both experimentally and factor analytically (Irwin et al., 2019; Karr et al., 2018; Pereg et al., 2013). In contrast, the expected null finding for set shifting *speed* was based on the limited available evidence suggesting that (a) set shifting speed of children with ADHD does not significantly improve relative to an active control condition on untrained set shifting tasks (Kray et al., 2012); and (b) children with ADHD do not differ from their neurotypical peers with regards to set shifting speed (i.e., there does not appear to be a deficit in need of remediation; Irwin et al., 2019). No strong predictions were offered regarding whether working memory or inhibitory control training would produce superior improvements in set shifting accuracy due to mixed evidence indicating that (a) set shifting shows similar magnitude correlations with both working memory and inhibitory control (Miyake et al., 2000); and (b) set shifting tasks tend to cross-load onto working memory and inhibitory control factors at similar rates across studies (Karr et al., 2018).

Method

Study Timeline, Randomization, Unpredictable Allocation Concealment, Masking, and Open Science Disclosure Statement

The sample reflects consecutive referrals from March 2017 to March 2019 who were included in the Kofler et al. (2020) randomized controlled trial. Intervention effects on the study's primary outcomes (working memory, inhibitory control, ADHD symptoms) are reported in Kofler et al. (2020); academic outcomes are reported in Singh et al (2022). Randomization was conducted by the study methodologist using unpredictable allocation stratified by medication status according to CONSORT guidelines. Study evaluators were masked to treatment group. Data screening, cleaning, and analyses were conducted masked

to treatment group/target. We report how we determined our sample size, all data exclusions, all manipulations, and all measures in the study.

Treatments

As described in Kofler et al. (2020) and our preregistration website [LINK], our group created two translational, evidence-based, digital therapeutic treatments that include gaming elements. These treatments incrementally increase demands on their target processes (i.e., working memory or inhibitory control) dependent on the training target.

Active, credible, and adaptive control.—As reviewed by Simons et al. (2016), randomized control trials examining treatment effects between groups requires measurement of expectancies and randomization to an ideal control condition that is as identical as possible to the treatment condition in all respects except for the critical, 'active' ingredient of the treatment. CET and ICT were developed specifically and from the outset as active, credible, and adaptive controls for each other. Each intervention targets a model-driven, theoretically important neurocognitive process (Barkley, 1997; Rapport et al., 2001) that is impaired in a large proportion of children with ADHD (Sonuga-Barke et al. 2010) and considered a core executive function in children (Karr et al., 2019). Further, CET and ICT include equivalent contact with the research team and feature the same number of distinct training games (nine) to create protocols that are as identical as possible except for the intervention target (working memory vs. inhibitory control). Specifically, each matched pair of ICT/ CET training games is identical in terms of website address, name, art, animations, storylines, layouts, interfaces, and use of adaptive training algorithms to maximize internal/ construct validity.

Please see Kofler et al. (2020), Singh et al. (2022), and the study's preregistration website for a more detailed description and rationale of the treatments' active control, adaptive training, and methods for maximizing dosage. Both interventions have been shown to have high feasibility and acceptability in terms of high parent satisfaction, high child-reported ease of use, and total child training time Kofler et al. (2018, 2020).

Central Executive Training (CET).—Working memory refers to the active, top-down manipulation of information held in short-term memory (Baddeley, 2007). The computerized CET protocol focused on improving the 'working' components of children's working memory (dual-processing, continuous updating, serial/temporal reordering), that is, their capacity to mentally manipulate/update items rather than merely improving the number of items children can hold in short-term memory (Fosco et al., 2019). This training used algorithms to dynamically adjust multiple parameters to incrementally increase demands on children's central executive processes such as increasing target density, categories:stimuli ratio, target:nontarget stimuli ratio, visual discriminability, and search space size. For example, increasing the search space size produces greater visual saccades, which in turn increase central executive demands during spatial working memory tasks because these saccades interrupt children's spatial rehearsal of stimuli (Awh et al., 2001; Postle et al., 2004). CET also emphasized children's ability to recall instead of just recognize stimuli based on compelling evidence that recognition-based tasks share minimal variance (r=.20)

with criterion working memory recall tasks (Redick & Lindsey, 2013). In each CET training game a unique combination of children's CE process (dual-processing, continuous updating, serial reordering) and stimulus modality (phonological, visual, spatial) were targeted. CET has been shown to be superior to both behavioral parent training (BPT) and ICT for improving working memory (d = 0.96–1.25 across studies), with mechanism of change analyses linking CET-related working memory improvements with CET-related ADHD symptom reductions (Kofler et al., 2018, 2020). In terms of primary clinical outcomes (ADHD symptoms), CET demonstrated superiority to both BPT and ICT for reducing objectively-assessed hyperactivity during clinic-based testing (Kofler et al., 2018, 2020). Similarly, CET was superior to ICT for reducing parent- and masked teacher- reported ADHD symptoms (Kofler et al., 2020).

Inhibitory Control Training (ICT).—Inhibitory control refers to a set of interrelated cognitive processes that underlie the ability to withhold (action restraint) or stop (action cancellation) an on-going response (Alderson et al., 2007; Verbruggen et al., 2013). The computerized ICT protocol focused on improving the 'action restraint' and 'action cancellation' components of inhibitory control by dynamically *adapting* on go:stop target ratio, presentation rate, response speed (e.g., timers), and number of stimuli (Alderson et al., 2007). In this training children were asked to inhibit responses to various stimuli within training games that adapted several parameters including stretching the target density (i.e., increasing the proportion of 'go' trials) making it more difficult to inhibit during infrequently-occurring 'stop' trials (Engle & Kane, 2003). Similarly, the trainings dynamically changed targets from 'go' to 'no go' to engage children's action preparation processes to maximize targeting of the action cancellation component of inhibitory control. ICT has been shown to be superior to CET for improving stop-signal inhibitory control (d = 1.12), despite not improving go/no-go inhibition (Kofler et al., 2020). Despite the mixed findings for ICT in the primary outcomes paper (Kofler et al., 2020), ICT produced somewhat more promising—albeit still mixed—results for improvements in academic functioning (Singh et al., 2022).

Participants

As shown in Table 1, the treated sample comprised 54 children with ADHD aged 8–12 years (M = 10.41, SD = 1.46; 12 girls) from the Southeastern U.S., consecutively referred to a university-based research clinic through community resources. Psychoeducational evaluation reports were provided to caregivers. IRB approval was obtained/maintained; all parents/children gave informed consent/assent. Child race/ethnicity was 74% White/Non-Hispanic, 11% Hispanic, 9% Black, and 6% mixed race/ethnicity. Children randomized to ICT (n=29) versus CET (n=25) did not differ from each other on any of the pre-treatment characteristics shown in Table 1 except for a marginally significant difference in pre-treatment parent-rated hyperactivity on the BASC-3 but not ADHD-5. As reported in Kofler et al. (2020), they also did not differ in terms of comorbidities (e.g., anxiety, ASD, ODD) overall or within each diagnostic category, specific learning disabilities in reading or math, number of children prescribed psychostimulants, medication changes during the study, or training duration.

Inclusion/Exclusion Criteria

All families completed a comprehensive evaluation that included detailed semi-structured clinical interviewing (K-SADS; Kaufman et al., 1997) and age/sex norm-referenced parent and teacher ADHD ratings (ADHD-RS-5 and BASC-3; DuPaul et al., 2016; Reynolds & Kamphaus, 2014). Study eligibility required: (1) DSM-5 diagnosis of ADHD (any presentation) by the directing clinical psychologist and multidisciplinary treatment team based on K-SADS (2013 update for DSM-5) and differential diagnosis considering all available clinical information indicating onset, course, duration, and severity of ADHD symptoms consistent with the ADHD neurodevelopmental syndrome; (2) clinical/borderline elevations on at least one parent and one teacher ADHD rating scale (i.e., >90th percentile), or previous psychoeducational evaluation documenting cross-informant symptoms (e.g., for children prescribed medication that reduces ADHD symptoms at school); and (3) current impairment per K-SADS. Additional details regarding the psychoeducational evaluation and differential diagnosis process can be found on our preregistration website (linked above).

A total of 62 children with ADHD were evaluated; n=6 were eligible but declined participation, and 2 were excluded due to average range or higher on all pretreatment working memory tests; no inhibitory control or set shifting thresholds were set as specified in our NIMH grant.[ii] Treated versus untreated children with ADHD did not differ on age, sex, SES, race/ethnicity, IQ, medication status, ADHD presentation, comorbidities, parent- and teacher-reported ADHD symptom severity, pretreatment working memory abilities, or pretreatment inhibitory control abilities (Kofler et al., 2020). Untreated children were not followed past the pre-treatment evaluation.

Children were excluded from the larger study for gross neurological, sensory, or motor impairment; seizure disorder, psychosis, or intellectual disability; or non-stimulant medications that could not be withheld for testing.

Procedures

Pre-treatment testing occurred during a larger battery of two, 3-hour sessions. Post-testing occurred during a single, 3-hour session following treatment week 10. All tests were counterbalanced within/across sessions and children received preset breaks every 2–3 tasks to minimize order/fatigue effects. Families were not required to withhold psychostimulants prior to child treatment visits. Psychostimulants were withheld ≥24-hours prior to all child pre-, mid-, and post-testing sessions.

As detailed in Kofler et al. (2020), identical procedures were used for both treatment groups. Both CET and ICT are 10-week digital therapeutic treatments accessed via computer or mobile device. Once a week, children were monitored by study staff for a 1-hour session while they completed their training exercises in-office according to identical, manualized procedures. Additional weekly training sessions were parent-supervised, in-home training (goal: 15-min/day, 2–3 days/week). Weekly in-office check-ins were also included. These check-ins were intended to promote adherence and troubleshoot difficulties with the at-home

[ii]An additional 19 children were evaluated by our research clinic during this time-period (i.e., March 2017-March 2019), but were not eligible as they did not meet criteria for a diagnosis of ADHD.

training (e.g., demonstrating login procedures, brainstorming feasible days/times for the child to complete training). No active treatment components are included in the parent check-ins, which were identical across groups and conducted by staff masked to treatment allocation.

Distal Far-Transfer Intervention Target (Set Shifting)

Please see Irwin et al. (2019) and Kofler, Irwin et al. (2018) for detailed descriptions and psychometric support for each of the study's set shifting outcome tests.

Global-Local Task.—The Global-Local test and administration instructions were identical to those described in Irwin et al. (2019). Psychometric support includes excellent internal consistency reliability (α =.86–.90), convergent validity with other set shifting tasks (Kofler, Irwin et al., 2018), and experimental evidence that this task imposes large increases in shift costs and accuracy costs relative to control conditions (ω^2 = .12, .14, both $p < .001$; Irwin et al., 2019). This computerized task uses Navon (1977) figures, which feature a "global" shape (e.g., a circle) constructed using smaller, "local" figures (e.g., triangles). Children were required to shift their response between global and local features. *Shift trials* were trials that switched to a different rule than the previous trial while *non-shift trials* were trials that did not require shifting because they featured the same rule as the previous trial. To reduce memory demands, on-screen rule cues were positioned next to each quadrant. One hundred and twenty trials were administered following three blocks of 6 to 8 practice trials (100% correct required). Children responded via mouse click.

Number-Color Task.—The Number-Color set shifting test and administration instructions were identical to those described in Kofler et al. (2019). Psychometric evidence includes high internal consistency (a = .87–.95) as well as convergent validity with other set shifting measures (Kofler et al., 2019). A pair of single-digit numbers appeared on the screen, and children were instructed to click either the larger or smaller value depending on the font color (blue = bigger, yellow = smaller; colors selected for maximal discrimination across individuals with all types of color vision). Both digits were the same color on any given trial. Trials were presented in a semi-random sequence to require shifting every other trial, with an equal number of bigger-smaller and smaller-bigger shifts (120 total trials). To reduce memory demands, on-screen instructions remained visible throughout the task. Children responded via mouse click.

Dependent Variables

Performance data were recorded for 'shift' and 'non-shift' trials separately for both tasks. Reaction time (RT) and number of errors were collected to examine children's speed and accuracy during set shifting tasks. Reaction time (RT) data was processed following the steps outlined in Irwin et al. (2019) that winsorized the most extreme 2% of reaction times. Following Irwin et al. (2019), speed shift costs were calculated separately for each task for each child (speed shift cost = $RT_{shift} - RT_{non\text{-}shift}$ for correct trials). Accuracy shift costs were also calculated (accuracy shift cost = $Errors_{shift} - Errors_{non\text{-}shift}$). Higher scores indicate worse performance for both speed shift costs (slower shifting) and accuracy shift costs (more shifting errors) at each time point.

Intellectual Functioning (IQ) and Socioeconomic Status (SES) at Pre-Treatment

IQ was estimated using the WISC-V Verbal Comprehension Index (Wechsler, 2014). Hollingshead (1975) SES was estimated based on caregiver(s)' education and occupation.

Bayesian Analyses

Traditional null hypothesis significance tests (*p*-values) were supplemented with Bayes Factors as recommended (Redick, 2015) as they allow stronger conclusions by estimating the magnitude of support for both the alternative and null hypotheses (Rouder & Morey, 2012). BF_{10} is the Bayes Factor (BF) indicating how much more likely the alternative hypothesis (H_1) is relative to the null hypothesis (H_0). Values ≥3.0 are considered moderate support for the alternative hypothesis (Wagenmakers et al., 2016). BF_{01} is the inverse of BF_{10} (i.e., $BF_{01}=1/BF_{10}$), and is reported when the evidence favors the null hypothesis (Rouder & Morey, 2012). BF_{01} is interpreted identically to BF_{10} (≥3=moderate, >10=strong, >100=decisive evidence that ICT and CET produce equivalent changes in an outcome). We refer to findings of $BF_{10} \geq 3$ as significant evidence *for* an effect (i.e., support for the alternative hypothesis of an effect at/above pre-specified evidentiary thresholds), and findings of $BF_{01} \geq 3$ as significant evidence *against* an effect (i.e., support for the null hypothesis of no effect at/above pre-specified evidentiary thresholds). We refer to effects as 'marginally significant' when results indicate $p<.05$ but $BF_{10} < 3.0$ (i.e., when the effect is supported by null hypothesis testing but the Bayes Factor suggests evidentiary value below our prespecified threshold).

Data Analysis Overview and Preregistration

Trial outcomes and detailed data analytic plans for the central executive training (CET) versus inhibitory control training (ICT) randomized control trial were preregistered at [LINK]. Primary outcomes (effects on working memory, inhibitory control, and ADHD symptoms) are reported in Kofler et al. (2020). Data analyses for the current study were conducted with default prior scales using JASP 0.15 (JASP Team, 2021). The current study used the preregistered set shifting outcome tests and followed the preregistered analytic plan for the primary outcomes with one exception: Our *a priori* analytic plan involved a series of 2 (between-subjects factor group: CET/ICT) × 2 (within-subjects factor task: global-local/number-color) × 3 (within-subjects factor timepoint: pre/mid/post) repeated-measures/mixed-model ANOVAs for speed shift costs and accuracy shift costs, with post hoc comparisons following significant interactions and *a priori* planned contrasts to characterize the pattern of change over time separately for each treatment group. However, due to an administrative error, the Number-Color task was not administered at mid-treatment. To maintain consistency across analyses and allow our primary analyses to include multiple tasks per construct to follow our preregistered analytic plan as closely as possible and control for task-specific (non-construct) error as recommended (e.g., Kofler et al., 2018), we elected to drop the Global-Local mid-treatment data point and analyze changes between pre- and post-treatment across tasks. This decision was made prior to accessing the data and without knowledge of the effects on study results. Exploratory analyses using all three timepoints for the Global-Local task are reported in the Sensitivity Analyses section

for transparency. All data processing and analyses were conducted masked to treatment allocation.

Speed and accuracy shift costs are presented as the primary outcomes given that they are the gold standard metrics for assessing performance during set shifting tasks (e.g., Irwin et al., 2019; Miyake et al., 2000). In addition, our *a priori* plan also called for probing potential improvements in overall task speed and accuracy (i.e., task performance not specifically related to set shifting). This involved repeating the primary models, this time with raw speed and accuracy scores instead of speed/accuracy shift costs, and inclusion of a within-subjects factor for trial type ('shift'/'non-shift'). Finally, we probed for potential speed-accuracy tradeoffs using inverse efficiency scores (IES; Townsend & Ashby, 1978). Inverse efficiency scores are a ratio of RTs to Error Rate and were calculated using shift cost RTs and Error Rates ($IES = RT_{shiftcost}/Error\ Rate_{shiftcost}$). The inverse efficiency score is a summary statistic of children's overall response style during the task and indicate the time (in milliseconds) spent on correct responses. Thus, lower scores indicate quicker correct responses (i.e., better task performance; Statsenko et al., 2020).

Power Analysis

The sample size for the primary outcomes trial was determined by a preregistered stopping rule, which was in turn determined by best practice recommendations for cognitive training studies (Simons et al., 2016). Power analysis using G*Power 3.1 (Faul et al., 2007) indicated that for α=.05 and β=.80, our N=54 is powered to detect within-subject effects of time at $d \geq 0.34$, treatment × time interactions of $d \geq 0.34$, and between-group effects of $d \geq 0.64$. Effects of these magnitudes were considered reasonable given evidence that (a) the associations between set shifting and both working memory (r = .74) and inhibitory control (r = .62; Karr et al., 2018) are large; (b) CET produces large improvements in working memory (d=0.96–1.20; Kofler, Sarver et al., 2018; Kofler et al., 2002); and (c) ICT produces large improvements in stop-signal inhibitory control (d=1.12; Kofler et al., 2020). Thus, the study is sufficiently powered to address its primary aims.

Results

Preliminary Analyses

Outliers beyond 3.00 *SD* were winsorized relative to the within-group distribution, separately for shift and non-shift trials. This process affected less than 2% of data points for each task. Global-Local and Number-Color pre-treatment data for a subset of the current sample were included in the aggregate estimate of set shifting abilities reported in Irwin et al. (2019). Treatment outcome data for these tasks have not been reported previously for any children in the current sample.

Primary Analyses: Set Shifting Speed and Accuracy (Shift Costs)

Set Shifting Speed.—Results of the 2 (between-subjects factor group: CET/ICT) × 2 (within-subject factor task: Number-Color/Global-Local) × 2 (within-subject factor timepoint: pre/post) ANOVA for speed shift costs indicated significant main effects of time (p = .04, BF_{10} = 2.13, η^2 = .08, d = 0.59; faster shifting speed at post-treatment) and task

($p < .001$, $BF_{10} = 2.60 \times 10^{11}$, $\eta^2 = .48$; faster shifting speed on the Number-Color task). In contrast, the main effect of treatment, the time × treatment interaction, and all other 2- and 3-way interactions were not significant (all $p > .20$, $BF_{01} \geq 1.75$, $\eta^2 < .04$). Planned contrasts indicated that the ICT group demonstrated significant pre-post improvements in set shifting speed on the Global-Local ($p = .02$, $BF_{10} = 4.53$, $\eta^2 = .08$, $d = 0.59$; Figure 1a) but not Number-Color task, whereas the CET group did not improve significantly on either task (all $p \geq .52$, $BF_{01} \geq 2.62$, $\eta^2 < .01$; Figure 1b).

Set Shifting Accuracy,—Results of the 2 (between-subjects factor group: CET/ICT) × 2 (within-subjects factor task: Number-Color/Global-Local) × 2 (within-subjects factor timepoint: pre/post) ANOVA for accuracy shift costs indicated a significant main effect of time ($p = .02$, $BF_{10} = 3.10$, $\eta^2 = .10$, $d = 0.67$; fewer shifting errors at post-treatment) and a significant time × treatment interaction ($p = .03$, $BF_{10} = 3.01$, $\eta^2 = .09$, $d = 0.63$), indicating that ICT was superior to CET for improving set shifting accuracy. In contrast, the main effects of task and treatment were not significant, and no additional 2- or 3-way interactions were significant (all $p > .31$, $BF_{01} \geq 3.23$, $\eta^2 \leq .06$). Planned contrasts indicated that the ICT group demonstrated significant pre-post improvements in set shifting accuracy on the Number-Color task ($p < .01$, $BF_{10} = 29.40$, $\eta^2 = .14$, $d = 0.81$; Figure 1d) and showed similar improvements on the Global-Local task that fell just below our predefined significance threshold ($p = .08$, $BF_{10} = 2.17$, $\eta^2 = .06$, $d = 0.51$; Figure 1c). In contrast, the CET group did not improve shifting accuracy on either task (both $p > .72$, $BF_{01} > 3.63$, $\eta^2 = .01$).

Secondary Analyses: Speed-Accuracy Tradeoffs

An additional set of analyses were added to probe speed-accuracy trade-offs as a potential explanation for the pattern of results reported above. Results for the inverse efficiency scores (IES) indicated main effects of time ($p = .04$, $BF_{10} = 2.06$, $\eta^2 = .08$, $d = 0.59$) and task ($p < .001$, $BF_{01} = 1.83 \times 10^{11}$, $\eta^2 = .48$), indicating that the CET and ICT groups both responded quicker to correct trials at post- relative to pre-treatment. In contrast, there was no evidence to support effects of treatment, the treatment × time interaction, or any other interaction (all $p > .10$, $BF_{01} > 7.80$, $\eta^2 < .05$), suggesting that speed-accuracy trade-offs cannot account for the differential effects of treatment reported above.

Secondary Analyses: Non-Shifting-Specific Task Performance

As noted above, we also probed for treatment-related improvements in non-specific aspects of task performance by repeating the previously reported models using overall task speed and accuracy. Results are detailed in the Supplementary (Online) Materials, were generally consistent with those reported above, and indicated that ICT was superior to CET for improving overall task accuracy ($\eta^2 = .10$, $d = 0.67$; Figure S1d) on the Number-Color task, whereas neither group improved on overall task accuracy for the Global-Local task (Figure S1c). ICT was also the only group to demonstrate improved reaction times specifically during shift trials (i.e., their speed of shifting improved; $\eta^2 = .03$; Figure S1b) on the Number-Color task.

Interestingly, the lack of improvement in set shifting speed for the CET group reported above appears to have occurred because CET produced non-specific improvements in speed on the Number-Color task, such that their response speed improved similarly on both shift (d = 0.70) and non-shift trials (d = 0.68). In other words, this pattern of findings indicated that the ICT group showed differential improvement during shift trials, whereas the CET group showed more general improvement on both Number-Color trial types. Consistent with the accuracy data, neither group improved on overall task speed for the Global-Local task (Figure S1a).

Sensitivity Analyses: Medication Status and Medication Changes During Treatment

Finally, we conducted sensitivity analyses to probe for medication-related explanations for the pattern of results reported above. Although children's set shifting performance was tested off medication at all timepoints (i.e., following a >24 hour washout), and despite the groups not differing in terms of pre-treatment medication status or medication changes during the course of treatment (Table 1), it was possible the significant main effects of time were attributable to one or both of these potential confounds rather than the tested treatments. This hypothesis was unsupported: the pattern, significance, and interpretation of all results were unchanged when medication status or medication changes were added to the models with two minor exceptions: (1) there was a marginally significant main effect of medication status in the shifting accuracy model, indicating children prescribed ADHD medication shifted more accurately than children not prescribed ADHD medication at pre- and post-treatment (p = .01, BF_{10} = 1.70, η^2 = .12); and (2) medication status interacted with time (p = .02; η^2 = .10) in the shifting speed model, with children prescribed ADHD medication showing greater response to treatment (p = .02; η^2 = .10) than children not prescribed ADHD medication (p = .99). However, there were no significant effects of changes in medication status in either model, and neither medication status nor changes in medication status interacted with treatment, task, or the treatment × time interaction (all p > .11, η^2 < .05). Taken together, these sensitivity analyses suggest that the primary results cannot be explained by medication-related confounds, while suggesting ADHD medication status may predict greater improvements in set shifting during treatment.

Discussion

The current study was the first to examine the extent to which training working memory or inhibitory control produced far-transfer improvements in set shifting abilities for children with ADHD. Overall, the most robust finding was that ICT was superior to CET for producing improvements in set shifting accuracy (treatment × time interaction d = 0.63), with ICT producing medium-to-large magnitude improvements across tasks (d = 0.51–0.81) relative to negligible changes from CET (both d = 0.10). Similarly, ICT (d=0.57) but not CET (d = 0.16) was associated with significant improvements in set shifting speed on the Global-Local task, but this finding should be considered tentative given the unsupportive omnibus treatment × time interaction. Interestingly, there was no evidence linking CET with improvements in set shifting accuracy or speed, with one exception: our secondary analyses indicated that the CET group improved significantly and similarly on both shift (d = 0.70) and non-shift trials (d = 0.68) during the Number-Color task, which contrasted the ICT

group's pattern of improving specifically during shift trials (d = 0.38). Taken together, this pattern of results provides evidence to suggest that inhibitory control is associated more specifically with successful and quick shifting in school-aged children with ADHD, whereas working memory may be more important for maintaining overall task goals (thus impacting shift and non-shift trials similarly).

Overall, the current findings were generally consistent with our hypothesis that training the other core executive functions would improve set shifting abilities in children with ADHD, and indicated that inhibitory control training successfully improved children's accuracy, and potentially speed, of set shifting. In contrast, working memory training improved overall task performance rather than shifting-specific performance– albeit on one but not both set shifting tasks, highlighting the task impurity problem and importance of using multiple measures for each cognitive outcome of interest (e.g., Irwin et al., 2019; Kofler et al., 2018). Therefore, these results suggest that set shifting abilities in children with ADHD can be improved on untrained tasks via targeted inhibitory control training, which appears inconsistent with the limited available literature indicating that set shifting training does not produce significant improvements in set shifting performance on untrained tasks (Kray et al., 2012; Pereg et al., 2013). This inconsistent finding may be due to the different approaches in study design. That is, we hypothesized that ADHD-related impairments on set shifting tasks are not due to actual deficits in set shifting abilities (Irwin et al., 2019), but rather deficits in other executive functions that are necessary to perform set shifting tasks (Pereg et al., 2013). Thus, by targeting inhibitory control and focusing on shift costs, we were able to find improvements on untrained set shifting tasks unlike previous trials.

The current findings also have implications for theoretical models of executive functioning in children by providing experimental evidence to support previous correlational/factor analytic conclusions (Karr et al., 2018; St. Clair-Thompson & Gathercole, 2006; van der Ven et al., 2013). In particular, the finding that training inhibitory control produced significant changes in set shifting abilities appears to support the hypothesis that impairments on set shifting tasks in children with ADHD are attributable, at least in part, to difficulties inhibiting currently active rule sets rather than an additional deficit in set shifting (Irwin et al., 2019), and to a lesser extent to difficulties maintaining task goals in working memory (Pereg et al., 2013). Additionally, our finding that inhibitory control training produced improvements on untrained set shifting tasks is generally consistent with two-factor models where set shifting may not be a unique executive function in school-aged children (Irwin et al., 2019; Karr et al., 2018; Lee et al., 2013; St. Clair-Thompson & Gathercole, 2006; van der Ven et al., 2013). The current study extends this line of work by demonstrating the significant inhibitory control and working memory demands required for successful performance on set shifting tasks (Irwin et al., 2019), consistent with prior correlational/factor-analytic evidence showing considerable overlap in variance between set shifting tasks and the other two core executive functions in school-aged children (Karr et al., 2018).

Contrary to our hypotheses, ICT produced significant improvements in set shifting speed on one of the two tasks, whereas there was no evidence for improved set shifting speed following CET. This finding was unexpected given previous evidence suggesting that set shifting speed may be intact in children with ADHD, and thus not a deficit in need of

remediation (Irwin et al., 2019; Kofler, Irwin et al., 2018). A potential explanation for this incongruence may be that children with ADHD improved from average to above average in terms of their set shifting speed, although this hypothesis must be considered speculative given the lack of a normative comparison group in this study. A more likely explanation is that ADHD is a clinically and neurocognitively heterogeneous disorder (Kofler, Irwin et. al., 2018), making it possible that the current sample included a larger proportion of children with set shifting deficits than previous studies (Irwin et al., 2019). This is plausible, as we specifically recruited children with ADHD who exhibited difficulties with working memory, which is in turn moderately correlated with set shifting (Karr et al., 2018). Thus, future studies are needed to compare potential deficits in set shifting speed between cognitively heterogeneous children with ADHD and neurotypical children.

Limitations

The current study was the first to assess potential far-transfer effects of working memory and inhibitory control training protocols on set shifting abilities in a sample of children with ADHD using a preregistered randomized controlled trial, construct-valid outcome measures, and masked evaluators and data processing. Despite these methodological refinements, the following limitations must be considered when interpreting results. Although our use of the CET and ICT training protocols to test for far-transfer effects on set shifting abilities was theoretically driven, and the CET/ICT protocols served as ideal active, credible, and matched controls for each other, adding a set shifting training protocol to the study design would have acted as an additional active control that would assist in delineating the efficacy of ICT and potentially CET compared to directly training set shifting (Kray et al., 2012). Similarly, the findings herein reflect changes at immediate post-treatment; the extent to which training-related gains in set shifting are maintained over time is unknown. Thus, future studies that include direct training of set shifting and longer-term follow up evaluations are needed to further examine the effects of the ICT and CET training protocols.

Despite robust evidence indicating ICT specifically improved children's performance on shifting trials (i.e., sensitivity analyses indicating shifting improved on shift, but not non-shift, trials), it seems reasonable to hypothesize that the overall pattern of results could be suggestive of a non-specific cognitive boost from inhibitory control training rather than an improvement in set shifting specifically. However, this possibility is unlikely given previous evidence that ICT specifically improved the action cancellation component of inhibitory control but did not improve working memory, whereas CET improved working memory (Kofler et al., 2018, 2020) but did not improve set shifting as evidenced in the current study.

Next, despite our recruitment and careful assessment of children with ADHD, recent heterogeneity studies suggest that a smaller proportion of children with ADHD have set shifting deficits than working memory deficits (e.g., 62% exhibit working memory vs. 38% exhibit set shifting vs. 27% exhibit inhibitory control deficits; Kofler, Irwin et al., 2018). In that context, our inclusion criteria did not require children to exhibit below average set shifting or inhibitory control abilities, but did require below average working memory. Although only two cases were excluded based on this criterion, this study design element may have blunted our ability to detect changes in set shifting across tasks because children

with set shifting deficits were not specifically recruited. Thus, future trials may benefit from implementing a personalized medicine approach in which children are assigned to specific training protocols based on their neurocognitive profile. Future studies should focus also on replications with larger samples, diverse age groups, and diverse clinical control populations to assess this pattern of results across development and clinical populations. Taken together, results of the current study indicate that inhibitory control training produced superior far-transfer improvements in children's set shifting accuracy, and potentially speed, compared to working memory training. In contrast, working memory training appears to improve overall task speed rather than shifting speed specifically. However, larger trials are needed to test for the extent to which the ICT-related improvements in set shifting detected herein exert downstream effects on aspects of behavior and functioning known to depend, at least in part, on set shifting abilities (e.g., Harmon et al., 2020; Irwin et al., 2020). That is, future studies should examine the extent to which ICT-related set shifting improvements are associated with even more distal, but clinically relevant outcomes (e.g., task switching in daily living activities).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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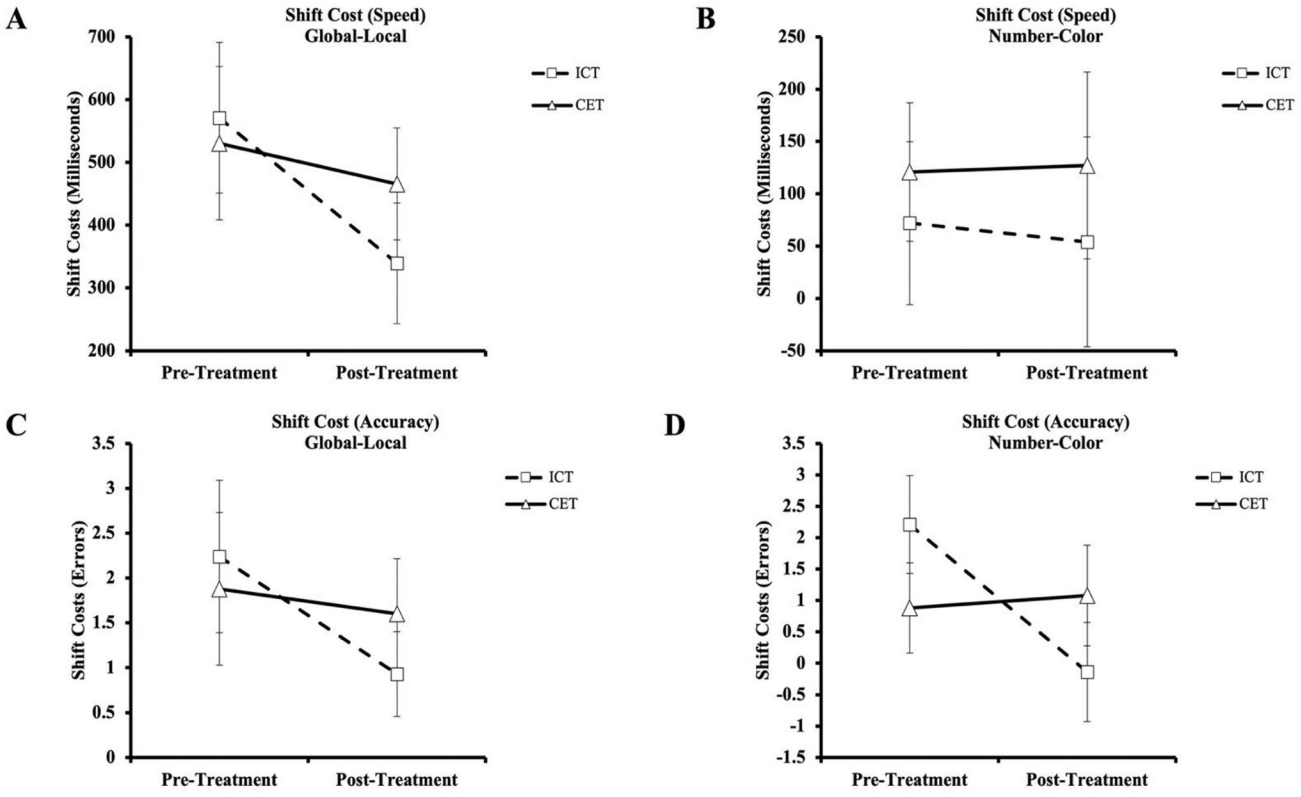

Figure 1.

Graphs depicting pre-post treatment group mean differences in (A) set shifting speed during the Global-Local and (B) Number-Color tasks, and in (C) set shifting accuracy during the Global-Local and (D) Number-Color tasks. Error bars reflect 95% confidence intervals.

Table 1.

Pre-Treatment Sample and Demographic Variables.

Variable	ICT (*n*=29)		CET (*n*=25)		Cohen's *d*	BF_{01}	*p*
	M	*SD*	*M*	*SD*			
Gender (Girls/Boys)	8/21		4/21		--	2.25	.31, *ns*
Age	10.07	1.46	10.23	1.39	−0.10	3.39	.68, *ns*
SES	49.48	9.46	45.08	12.70	0.30	1.79	.20, *ns*
WISC-V VCI	105.93	12.29	103.16	12.42	0.18	2.75	.42, *ns*
Medication (No/Yes)	20/9		15/10		--	2.53	.49, *ns*
Race/ethnicity (W/B/H/M)	20/4/3/2		20/1/3/1		--	13.64	.61, *ns*
ADHD Presentation (I/H/C)	9/1/19		6/1/18		--	11.14	.85, *ns*
Comorbidity (No/Yes)	16/13		11/14		--	9.77	.79, *ns*
BASC-3 Attention Problems (T-score)							
Parent	67.00	7.34	69.60	6.04	−0.32	1.61	.17, *ns*
Teacher	65.52	7.59	63.52	6.18	0.24	2.31	.30, *ns*
BASC-3 Hyperactivity (T-score)							
Parent	66.52	13.01	73.52	10.86	−0.49	0.58	.04 *
Teacher	62.45	11.09	62.84	13.80	−0.02	3.62	.91, *ns*
ADHD-RS-5 (T-Score)							
Attention Problems (Parent)	67.66	5.56	69.00	4.89	−0.20	2.53	.35, *ns*
Hyperactivity/Impulsivity (Parent)	64.55	8.13	67.56	4.25	−0.37	1.17	.10, *ns*
Shift Costs-Speed (ms)							
Global-Local	571.10	449.91	530.31	458.04	0.09	3.48	.74, *ns*
Number-Color	71.90	291.88	120.89	248.12	0.18	3.04	.51, *ns*
Shift Costs-Accuracy (errors)							
Global-Local	2.24	3.19	1.88	3.19	0.11	3.39	.68, *ns*
Number-Color	2.21	2.93	0.88	2.70	0.47	1.09	.09, *ns*

Note. Raw *p*-values are presented (uncorrected for multiple comparisons). BASC-3 = Behavior Assessment System for Children (T-scores); BF = Bayes Factor, BF_{01} is the odds ratio of the evidence favoring the null to the evidence favoring the alternative hypothesis. A value of 1 indicates that the data are equally likely under the null and alternative hypotheses, values >1 favor the null hypothesis that the groups are equivalent, and values ≥3 are considered statistically significant evidence of equivalence. BF_{10} can be computed as the inverse of BF_{01} ($1/BF_{01}$); CET = Central Executive Training; ICT = Inhibitory Control Training; Medication Changes (Stop = Discontinued Medication During Study, No = No Changes Reported, Add = Started Medication During Study); ms = milliseconds; Race/ethnicity (W = White, B = Black, H = Hispanic, M = Mixed); VCI = Verbal Comprehension Index (IQ; standard scores).