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Abstract

Objective: The aim of this study was to (a) test the usefulness of visuospatial working memory (VSWM) as an endophenotype for ADHD and (b) study the developmental trajectory of VSWM in ADHD. **Method:** A total of 110 ADHD patients, 60 unaffected siblings, and 109 controls, aged 8 to 29 years, were assessed on VSWM functioning. Multilevel analyses were carried out to account for the correlation between measurements within families. **Results:** ADHD patients showed impaired VSWM performance compared with unaffected siblings and controls, with comparable performance between unaffected siblings and controls. Impaired VSWM in ADHD patients was not more pronounced on higher memory loads, signifying executive rather than storage deficits as an underlying mechanism. ADHD patients, unaffected siblings, and controls showed parallel developmental trajectories of VSWM. **Conclusion:** Current findings question the usefulness of VSWM as a neurocognitive endophenotype for ADHD and provide unique insights into the developmental trajectory of VSWM in ADHD. *(J. of Att. Dis. 2014; 18(4) 369-378)*

Keywords

ADHD, visuospatial working memory, WM, development, endophenotype, unaffected siblings, multilevel analysis

Introduction

Neurocognitive deficits have been hypothesized to play a major role in the mechanisms underlying Attention Deficit/Hyperactivity Disorder (ADHD), with some theories suggesting that the behavioral symptoms of the disorder may largely be caused by deficits in executive functions (e.g., Barkley, 1997; Castellanos & Tannock, 2002). Deficits in visuospatial working memory (VSWM) are one of the most consistently found impaired executive functions in patients with ADHD (Gau & Shang, 2010; Kasper, Alderson, & Hudec, 2012; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). However, the exact mechanism underlying these VSWM deficits remains unclear. In Baddeley's model of working memory (see Baddeley, 2007; Baddeley, 2012; Baddeley & Hitch, 1974), three components are identified. The central executive (CE) acts as an attentional controller, coordinating tasks and activities of its two subsystems: the phonological loop (PL) and the visuospatial sketchpad (VS), both storing modality-specific information. A deficiency of these different components translates into different performance deficits on cognitive tasks: Limitations in storage capacity of the VS and PL components are typically characterized by a decline in task performance with increasing memory load or task difficulty (Baddeley, 2003; Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991). CE dysfunctioning translates into a more general performance deficit, stable over different task difficulties. Applying this model to ADHD research, the Group × Task difficulty interaction found in some studies (i.e., the fact that ADHD patients suffer more from an increase in task difficulty than controls; for example, Gau & Shang, 2010; Goldberg et al., 2005) would be indicative of limited VS storage capacity in ADHD. However, other studies that specifically investigated the separate components of Baddeley's model reported that VSWM deficits in ADHD

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are better explained by impaired CE functioning (Karatekin, 2004; Rapport et al., 2008).

While the exact mechanism underlying VSWM deficits in ADHD patients remains unclear, VSWM has been put forward as one of the three most promising neurocognitive candidate endophenotypes for ADHD, together with reward-related and temporal processing deficits (Castellanos & Tannock, 2002; Rommelse, 2008). Endophenotypes can be useful in uncovering the etiology of a disorder, since they are considered to be more closely linked to the genetic and neurobiological underpinnings of a disorder than the (more heterogeneous) behavioral manifestation (Gottesman & Gould, 2003; Rommelse, 2008). Unaffected siblings are uniquely valuable in endophenotype research, since they share 50% of their genes (on average) with their affected siblings, yet they do not show any behavioral symptoms of the disorder. If these unaffected siblings were found to suffer from a VSWM deficit, this would indicate that VSWM deficits are not a result of ADHD symptoms (as unaffected siblings do not display these symptoms), but rather a neurocognitive impairment *underlying* the disorder. Hence, VSWM deficits in unaffected siblings must be a result of their genetic overlap with their affected siblings, which would indicate that VSWM is a useful endophenotype in ADHD (also see Leboyer et al., 1998). In turn, normal VSWM performance in unaffected siblings would be more consistent with the idea that VSWM deficits are a co-occurring problem in ADHD, rather than a cause of the behavioral symptoms.

Castellanos and Tannock (2002) presented VSWM as a promising endophenotype mostly based on theoretical considerations, due to the strong association between VSWM impairment and deficits found using functional brain imaging and neurochemical measures. However, studies that empirically address VSWM as an endophenotype are limited and have yielded inconclusive results. While some studies found decreased VSWM performance for unaffected siblings compared with controls (Bidwell, Willcutt, Defries, & Pennington, 2007; Gau & Shang, 2010; Rommelse, Altink, Oosterlaan, et al., 2008), which could be interpreted as evidence for VSWM being an endophenotype for ADHD, others did not find any impairment in unaffected siblings (Seidman, Biederman, Monuteaux, Weber, & Faraone, 2000). The positive results reported by Bidwell et al. (2007) are complicated by the fact that unaffected siblings showed elevated levels of ADHD symptoms compared with controls. After controlling for ADHD symptoms, the VSWM impairment in unaffected siblings no longer remained significant. Gau and Shang (2010) did not describe or control for the level of ADHD symptoms in all groups. Consequently, in two of the three studies reporting positive findings, impaired performance by unaffected siblings might be explained by elevated levels of ADHD. The latter would suggest that VSWM deficits are co-occurring with ADHD symptoms, rather than VSWM being an endophenotype for the disorder or an underlying cause of its symptoms. Evidently, more research into the usefulness of VSWM as an endophenotype for ADHD is warranted.

The developmental trajectory of VSWM deficits in ADHD is of importance to determine whether impairment in ADHD patients may normalize at a certain age, or whether VSWM deficits are pervasive or may even worsen into adulthood. This issue is still relatively underexplored. A recent neurodevelopmental model of ADHD proposed by Halperin and Schulz (2006) implicates that neurocognitive dysfunctions in ADHD are relatively pervasive. The authors propose that in most cases, ADHD is caused by a persistent lifelong subcortical dysfunction. Although the model states that prefrontal dysfunction is not the primary cause of ADHD, many patients might experience dysfunctioning of neurocognitive functions mediated by the prefrontal cortex, as a result of neural reorganization and compensation. The recovery of ADHD symptoms experienced by some patients ("remitters") would be associated with development of the prefrontal cortex (and the corresponding development of top–down control) and is hypothesized to parallel improvement in executive functions. Based on this model, it would be expected that adolescents and adults with persisting ADHD ("persisters") show similar VSWM deficits as do younger children with ADHD, while ADHD remitters show improved VSWM compared with the persistent group. Reported findings of a strong association between VSWM functioning and symptoms of inattention in adolescents (Tillman, Eninger, Forssman, & Bohlin, 2011), and studies showing impaired VSWM functioning in adults with (persisting) ADHD (Dowson et al., 2004), fit nicely into this theoretical framework. However, research into the developmental trajectory of VSWM in ADHD is limited. To our knowledge, no studies have studied VSWM in ADHD in a longitudinal sample or in a cross-sectional sample with a broad age range (including children, adolescents and adults) and have reported on the developmental trajectory of VSWM deficits beyond childhood years. Hence, no conclusions can currently be drawn regarding the effect of age on VSWM development in ADHD.

Taken together, current literature is sparse and inconsistent regarding VSWM as a neurocognitive endophenotype for ADHD, and caveats exist concerning the developmental trajectory of VSWM deficits in ADHD. Hence, the first aim of the present study is to assess VSWM in ADHD patients, unaffected siblings, and controls, to investigate the usefulness of VSWM as an endophenotype for ADHD. If VSWM can be considered a useful endophenotype, we expect to find that not only ADHD patients are impaired on VSWM compared with controls, but also their unaffected siblings (although to a lesser degree). The second aim of the current study is to explore the effect of age on VSWM in all groups, to shed more light on the developmental trajectory of

VSWM impairment in ADHD. Based on the model proposed by Halperin and Schulz (2006), we expect to find that VSWM impairment in ADHD continues into young adulthood in our sample of "persisting" ADHD patients. A large number of participants were included in a uniquely broad age range, and all participants were rigorously assessed using strict diagnostic criteria, to be able to draw robust conclusions and provide more insight into these issues.

Method

Participants

A total of 279 participants contributed data to the current study. Participants were divided into three groups: ADHD patients ($n = 110$, of whom 62 met criteria for the combined subtype, 38 for the inattentive subtype, and 10 for the hyperactive-impulsive subtype); unaffected siblings of ADHD patients (unaffected siblings, $n = 60$); and controls ($n = 109$).

Most of the participants originally took part in the Dutch part of the International Multicenter ADHD Genetics (IMAGE) study (as described previously in Müller et al., 2011; Rommelse, Altink, Martin, et al., 2008). Recruitment for IMAGE was done between 2003 and 2006, and concerned families with at least one child with combined subtype ADHD and at least one biological sibling (regardless of ADHD diagnosis). Control families were recruited in which children and their first-degree relatives had no formal or suspected ADHD diagnosis. All participants were reinvited for extensive follow-up assessment between 2009 and 2012, as part of the current NeuroIMAGE study. All family members were invited for follow-up, regardless of their participation in IMAGE. To balance out gender and age differences between groups, additional girls with ADHD (any subtype) and control boys were recruited and included in the study. Inclusion criteria were the same for all participants and largely consistent with IMAGE: Participants had to be between 8 and 30 years, of European Caucasian descent, have an IQ ≥ 70, and have no diagnosis of autism, epilepsy, general learning difficulties, brain disorders, and known genetic disorders (such as Fragile X syndrome or Down syndrome). Since the task used in the current study was administered as part of a larger magnetic resonance imaging (MRI) protocol, participants were excluded if they had any contraindication to MRI scanning (e.g., implanted metal or medical devices, possible pregnancy).

Diagnostic Assessment

Diagnostic assessment of all participants at follow-up included comprehensive assessment of the symptoms of ADHD and comorbid disorders. To determine ADHD diagnoses, a combination of Conners' ADHD questionnaires and a semistructured diagnostic interview was used. Each participant was assessed with a parent-rated questionnaire (Conners' Parent Rating Scale–Revised: Long version [CPRS-R:L]; Conners, Sitarenios, Parker, & Epstein, 1998b) combined with either a teacher-rating (Conners' Teacher Rating Scale–Revised: Long version [CTRS-R:L]; Conners, Sitarenios, Parker, & Epstein, 1998a; applied for participants <18 years) or a self-report (Conners' Adult ADHD Rating Scales–Self-Report: Long Version [CAARS-S:L]; Conners, Erhardt, & Sparrow, 1999; applied for participants ≥18 years). All participants were administered the ADHD section of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS; Kaufman et al., 1997), containing developmentally appropriate questions to assess each of the 18 ADHD symptoms, carried out by trained professionals. Parents, reporting on their children, as well as participants themselves, if ≥12 years old, were interviewed separately. Final scores on each item of the K-SADS were determined by weighing all available information. Initially, all participants were administered the K-SADS ADHD screening interview. Participants with elevated scores on any of the screen items were administered the full ADHD supplement. For participants using medication, ratings of participants' functioning off medication were gathered. Using a diagnostic algorithm, a *combined symptom count* was calculated by adding symptom counts on the K-SADS and CTRS-R:L (for participants <18) or CAARS-S:L (for participants ≥18), both providing operational definitions of each of the 18 behavioral symptoms defined by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association [APA], 2000). Symptoms of the Conners' questionnaires were only added to the combined symptom count if at least two symptoms were reported, to avoid the Conners' score to put too much weight on the diagnosis. Of the Conners' ADHD questionnaires, the following scales were used: *DSM* Inattentive behavior (Scale L of the CPRS-R:L/CTRS-R:L; Scale E of the CAARS-S:L), *DSM* Hyperactive/Impulsive behavior (Scale M of the CPRS-R:L/CTRS-R:L; Scale F of the CAARS-S:L), and *DSM* Total (Scale N of the CPRS-R:L/CTRS-R:L; Scale G of the CAARS-S:L). Participants with a combined symptom count of ≥ six symptoms of hyperactive/impulsive behavior and/or inattentive behavior were diagnosed with ADHD, provided they (a) met the *DSM-IV* criteria for pervasiveness and impact of the disorder (measures derived from the K-SADS), (b) showed an age of onset before 12 (following the proposed changes for the *DSM-V*; see Polanczyk et al., 2010; derived from the K-SADS), (c) received a $T \geq 63$ on at least one of three scales on at least one of the Conners' ADHD questionnaires (pertaining to a period without medication). Participants with a combined symptom count of ≥ six symptoms who did not meet one or

more of these criteria were evaluated by a team of trained experts, to derive a consensus decision on their diagnosis. All unaffected participants were required to receive a $T < 63$ on each of the aforementioned scales of each of the Conners' ADHD questionnaires, and have a combined symptom count ≤ three symptoms. For young adults (≥18 years), criteria were slightly adapted, such that a combined symptom count of five instead of six symptoms was sufficient for a diagnosis (in line with Kooij et al., 2005; Murphy & Barkley, 1996), and they required ≤ two symptoms on the combined symptom count for an "unaffected" status.

The presence of oppositional defiant disorder (ODD) and conduct disorder (CD) was evaluated in all participants using two additional K-SADS sections. The procedures were similar to the ADHD interview: All participants were administered the ODD and CD screening interviews, and participants with elevated scores on one or more items were administered the full supplement. Parents, reporting on their children, as well as participants themselves, if ≥12 years old, were interviewed separately, and the final diagnosis (disorder "present" or "absent") was based on *DSM-IV* criteria for the disorder.

Procedure

The current study was part of a comprehensive assessment protocol encompassing phenotypic, neurocognitive, and MRI assessments. Full-scale IQ was estimated by the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for Children–III (WISC-III) or Wechsler Adult Intelligence Scale–III (WAIS-III; for participants ≥17 years). The visuospatial memory task used in the current study was performed during a functional MRI scan. Testing was carried out either at the VU University Amsterdam and VU University Medical Centre in Amsterdam, or at the Radboud University Nijmegen Medical Centre and Donders Institute for Brain, Cognition and Behaviour in Nijmegen. Use of psychostimulants was discontinued for at least 48 hr before measurement to allow complete washout. Other medication to suppress ADHD symptoms (such as atomoxetine) was tapered off gradually in line with standard procedures, to achieve sufficient washout. During the testing day, participants were motivated with short breaks and were rewarded with €50 and a copy of their MRI scan afterward. Informed consent was signed by all participants (parents signed informed consent for participants under 12 years of age), and the study was approved by the national ethical committee.

Task description

The task used to assess VSWM is an adapted version of a task developed by Klingberg and colleagues (Klingberg, Forssberg, & Westerberg, 2002; McNab et al., 2008). During the task, participants were presented with a 4 × 4 grid of white lines on a black background. Two trial types (baseline and working memory) and two memory loads (low and high memory load) were implemented in the task. During working memory trials, participants were presented with a series of either three or six yellow cues (a low and high memory load, respectively), which were sequentially presented on the grid (see Figure 1). Subsequently, a probe, consisting of a number between 1 and 3 (low load) or 1 and 6 (high load) with a question mark, was presented in one of the 16 locations. Participants were asked to remember the spatial order of the presentation of cues, and indicate with a "yes" (right button) or "no" (left button) response whether the location of the probe was stimulated before, at the indicated temporal position. After their response, participants were presented with feedback in the form of a green or red bar (representing a correct or incorrect response, respectively) underneath the probe. The setup of baseline trials was similar to the working memory trials. During baseline trials, red circles and the probe were presented sequentially in the four corners of the grid in a predictive manner. The probe always consisted of the number 8 and a question mark, and was also presented in one of the four corners. Participants were required to pay attention but were not required to remember the sequence, and always had to press the "no" button. Accuracy on both conditions was determined in terms of percentage correct responses. In each condition, each circle was displayed for 500 ms with a 500 ms interstimulus interval (empty grid display). The response window during which the probe was shown and participants had to press the response button was 2,000 ms, followed by a 3,000 ms intertrial interval. The task was administered in four blocks with a short break in between blocks to avoid fatigue effects. Each block contained 24 trials presented in a fixed random order, with trial types completely balanced throughout the task and between the four blocks. Total task duration was approximately 16 min. A practice task with standardized instructions was administered to all participants, shortly before administering the real task. The practice task consisted of three working memory trials and three control trials, followed by four randomized trials. At the end of the practice task, participants had to indicate whether they understood the task. If they did not fully understand the task, the instructions and practice task were repeated.

Statistical Analyses

All continuous variables were checked for outliers ($Z \geq 3.29$ or ≤ -3.29). Two participants from the ADHD group with outliers were excluded from the data set due to lack of compliance during assessment. Remaining outliers were transformed to a value one unit smaller than the most extreme nonoutlier ($n = 11$ data points in $n = 9$ participants; Tabachnick & Fidell, 2001).

Differences between groups in gender, age, IQ, and ADHD symptoms were examined using analysis of

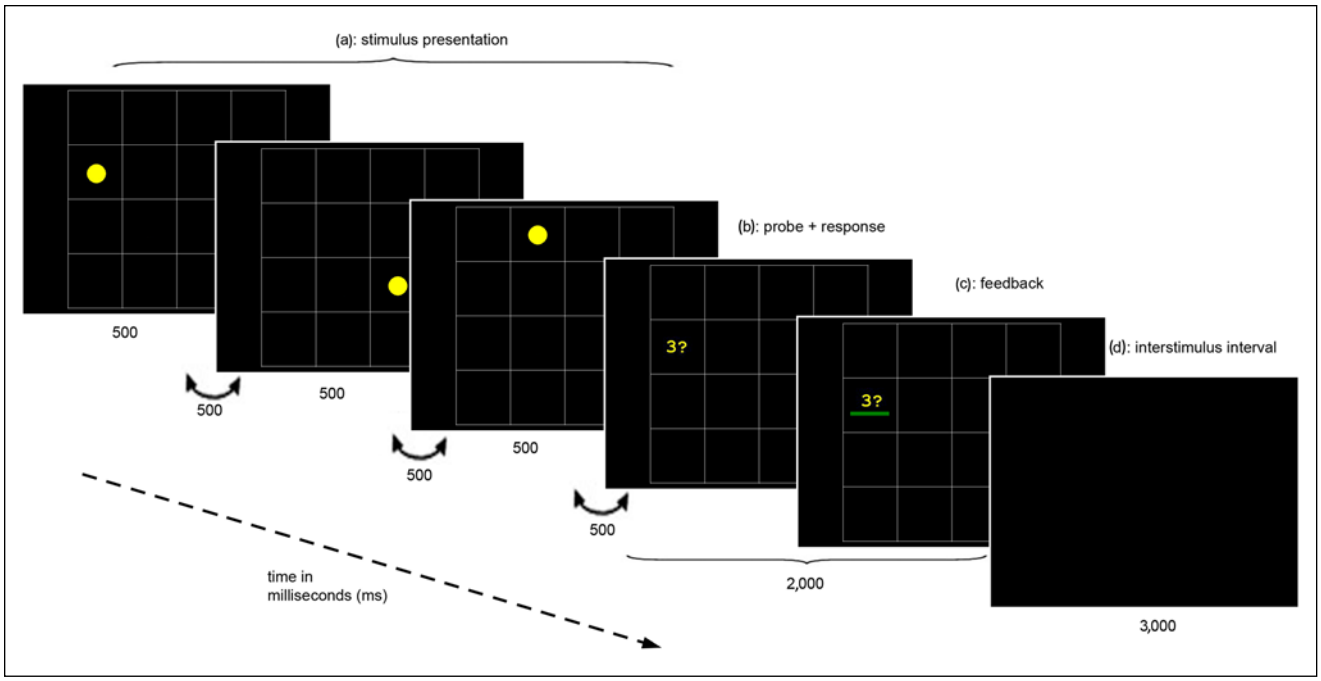

Figure 1. Schematic overview of a working memory trial with low memory load on the VSWM task. Each trial consisted of a sequence of either three or six circles, displayed on a 4 × 4 grid for 500 ms each, with a 500-ms interstimulus interval in between (a). Subsequently, during a 2,000-ms response window, the probe was presented and the participant was required to press a response button (b), after which feedback was presented for the remainder of the response window (c). Each trial was followed by a 3,000-ms intertrial interval, consisting of a black screen (d).
Note: VSWM = visuospatial working memory.

variance and chi-square tests. Analyses investigating the effects of group and age on VSWM performance were done using multilevel analysis, to account for the hierarchical structure of the data, using SPSS Mixed Models (IBM SPSS Statistics Version 19). Multilevel analysis is an extension of General Linear Modeling, taking into account clustering of data at different levels. The model consisted of three levels: a repeated measure comprising a low and a high memory load (Level 1) within each subject (Level 2), with subjects nested within families (Level 3). By using this structure, systematic variation within subjects (i.e., repeated measures within the subject) and within families (i.e., participants belonging to the same family) was incorporated in the model, thereby accounting for the nonindependency of observations within the subject and family level. The data set did not contain any monozygotic twin pairs. Memory load was used as a repeated measure (Level 1), with accuracy on baseline trials as a covariate (to control for basic processing or motivational deficits). At the subject level (Level 2), gender and group (controls, unaffected siblings, and ADHD) were added as predictors. To study the developmental trajectory of VSWM, both age and the quadratic effect of age were added as Level 2 predictors, to test for a linear or nonlinear effect of age on VSWM performance. A random intercept was fitted for each family, allowing families to vary in VSWM performance. Initially, a full factorial model was built. Interactions with $p > .05$ were dropped from the model, as well as nonsignificant main effects that did not positively influence the overall fit of the model, leaving a parsimonious model with optimal fit (i.e., the lowest −2 log likelihood; Raudenbush & Bryk, 2001). If a significant main effect of group was found, post hoc analyses were conducted using Fisher's least significant difference (LSD) to evaluate pairwise group differences. As there is ongoing debate about correcting for IQ (e.g., Dennis et al., 2009), the final model was rerun with IQ as a covariate. The final model was also rerun while correcting for the presence of ODD or CD by adding the presence of either of these disorders as a dichotomous factor (ODD or CD "present" or "absent").

Results

Sample characteristics are summarized in Table 1.

The final random intercept multilevel model revealed significant variation between family intercepts ($p < .05$), indicative of familial influences on VSWM performance. Baseline accuracy and memory load significantly contributed to VSWM performance ($p < .001$), with higher baseline accuracy and lower memory load resulting in better VSWM performance. While adding gender significantly improved the overall fit of the model, the effect of gender was not

Table 1. Sample Characteristics.

	ADHD, *n* = 110	US, *n* = 60	NC, *n* = 109			
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	Test statistic	*p* value	Contrasts[a] (*p* < .05)
Age	17.5 (3.2)	17.2 (4.0)	17.6 (3.7)	$F(2,276) = 0.18$	.838	
Gender (M:F)	76:34	27:33	45:64	$\chi^2(2, N = 279) = 18.98$	<.001	
IQ	97.9 (15.9)	101.6 (13.1)	105.2 (12.9)	$F(2,276) = 7.15$	<.001	ADHD < NC
Parent-rated ADHD symptoms[b]						
Inattentive	66.7 (11.1)	47.5 (7.0)	46.9 (5.9)	$F(2,270) = 183.508$	<.001	ADHD > US = NC
Hyperactive/impulsive	70.0 (14.4)	46.4 (5.5)	47.2 (5.9)	$F(2,270) = 152.826$	<.001	ADHD > US = NC
Total	70.5 (12.7)	46.8 (6.3)	46.5 (5.8)	$F(2,270) = 214.615$	<.001	ADHD > US = NC
Teacher-or self-rated ADHD symptoms[c]						
Inattentive	64.2 (12.5)	49.5 (9.2)	46.9 (8.8)	$F(2,270) = 183.508$	<.001	ADHD > US = NC
Hyperactive/impulsive	60.9 (14.1)	48.4 (11.5)	45.1 (9.0)	$F(2,270) = 152.826$	<.001	ADHD > US = NC
Total	64.8 (13.3)	48.9 (11.6)	45.5 (8.6)	$F(2,270) = 214.615$	<.001	ADHD > US = NC

Note: M = male; F = female; NC = normal controls; US = unaffected siblings.
[a]Group contrasts represent Tukey post hoc results.
[b]ADHD symptoms represent T-scores on Conners' Parent Rating Scale–Revised: Long version.
[c]ADHD symptoms represent T-scores on Conners' Teacher Rating Scale–Revised: Long version (for participants <18 years) or Conners' Adult ADHD Rating Scales–Self-Report: Long Version (for participants ≥18 years).

Table 2. Multilevel Model for VSWM Performance.

	Coefficient	*SE*	Test statistics	*p* value
Fixed effects				
Baseline accuracy	0.700	0.156	$t(407) = 4.48$	<.001
Memory load (high vs. low)	−5.948	0.705	$t(277) = -8.43$	<.001
Gender (F vs. M)	−1.724	1.265	$t(255) = -1.36$	.174
Age	4.106	1.256	$t(261) = 3.27$	.001
Age × Age	−0.088	0.035	$t(261) = -2.52$	.012
Group			$F(2,237) = 5.03$	.007
ADHD versus NC	−4.522	1.553	$t(211) = -2.91$	.004
US versus NC	−0.574	1.743	$t(230) = -0.33$	.742
ADHD versus US	−3.947	1.672	$t(252) = -2.36$	.019
Random effects				
Family	25.237	10.056	Wald Z = 2.51	.012
Deviance	4,239.864			
Deviance empty model	4,364.915			

Note: VSWM = visuospatial working memory; *SE* = standard error; F = female; M = male; US = unaffected siblings; NC = normal controls. Indented group contrasts represent Fisher's least significant difference post hoc results.

significant, suggesting no substantial differences between male and female participants ($p = .174$). A significant main effect was found for group ($p < .01$), but there were no significant interactions between group and any of the other independent variables (all $p > .05$), indicating that groups differed equally on both low and high memory loads, and the effect of gender and baseline accuracy was similar for all groups. Post hoc analysis showed that the ADHD group performed less accurate than the controls ($p < .01$) and unaffected siblings ($p < .05$), with similar performance between unaffected siblings and controls ($p = .742$).

For the developmental trajectory of VSWM, the model revealed that an inverse quadratic effect best described the effect of age on VSWM performance ($p < .05$). The absence of a significant interaction between age and group ($p = .352$) indicated that this effect did not differ between groups. Results are summarized in Table 2, Figure 2, and Figure 3. Adding ODD/CD comorbidity to the final model did not change the significance of any of the predictors, and ODD/CD did not have a significant effect on VSWM performance. When IQ was added to the final model, the main group effect just escaped conventional levels of

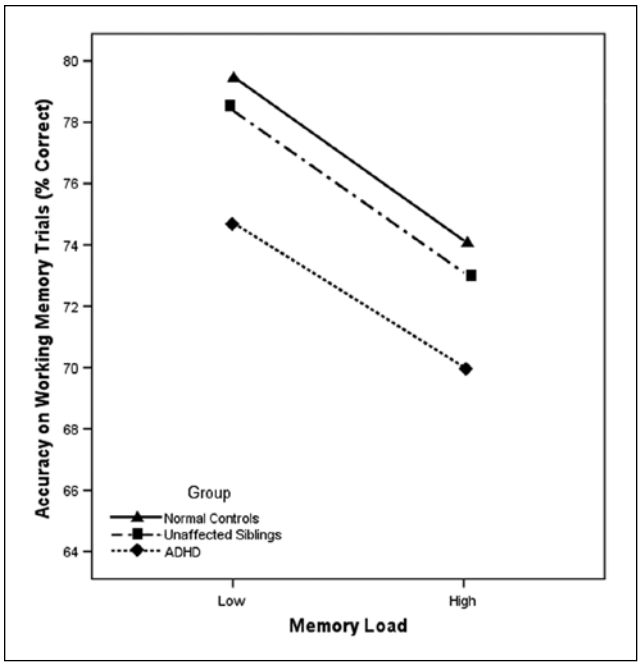

Figure 2. Performance on working memory trials with three or six circles (low or high memory load, respectively) of the VSWM task, controlling for gender, age, and baseline performance. ADHD patients were significantly impaired compared with controls (p = .004) and unaffected siblings (p = .019), with no significant difference between the latter two groups (p = .742).
Note: VSWM = visuospatial working memory.

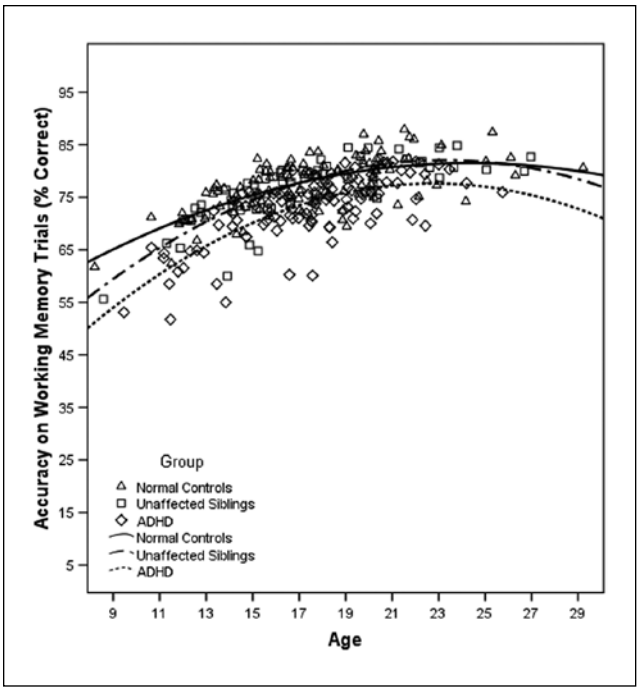

Figure 3. Developmental trajectory of performance on the VSWM task, controlling for gender, age, and baseline performance. Age was best described as an inverse quadratic effect (p = .012) and did not interact with group (p > .05). For illustration purposes, in this figure, accuracy is expressed as the mean accuracy across both the three- and six-circle (low and high memory load) working memory trials.
Note: VSWM = visuospatial working memory.

significance (p = .056), but the group contrasts remained unchanged.

Discussion

Our results show impaired VSWM functioning in ADHD patients. For all participants, performance was corrected for baseline accuracy during the task, thereby minimizing the possibility that ADHD patients showed performance deficits due to secondary processes such as inattention, motivational deficits, or impulsive response patterns. Importantly, the impairment in performance for ADHD patients did not increase with higher memory loads, signifying a rather general processing or executive deficit in ADHD patients. In terms of Baddeley's model of working memory (Baddeley, 2007), this deficit would be most consistent with CE dysfunctioning, rather than decreased storage capacity of visuospatial information. This finding is in line with previous meta-analytic results on working memory in ADHD, in which it was shown that CE demand was one of the strongest moderators of the observed ADHD effects on VSWM performance (Kasper et al., 2012). The CE is described as an "attentional controller" and is thought to be important for the *control of behavior* on the one hand, that is, overriding automated behavior by less routine actions, and *attentional* functions on the other hand, such as the ability to focus, and to divide and switch attention (Baddeley, 2003). Given the overlap between the nature of the CE and ADHD symptoms, impaired CE functioning is not surprising in ADHD patients and may very well lie at the core of the behavioral symptoms of the disorder. While this idea is consistent with previous research (Kofler, Rapport, Bolden, Sarver, & Raiker, 2010; Rapport et al., 2009), the causality of the association between CE dysfunctioning and ADHD symptoms cannot be determined based on currently available data, and warrants further research.

Studying the developmental trajectory of VSWM in ADHD should ideally be undertaken by following a large sample longitudinally, from childhood into adulthood. While our analyses are set up cross-sectionally and are thus not ideally suited for studying the developmental trajectory, our large sample size and broad age range nevertheless allow us to provide some exploratory insights into this issue. The inverse quadratic effect of age suggests a development of VSWM functions over time, which gradually decelerates as children grow older, reaching maturity

during mid to late adolescence (see Figure 3). This is consistent with previous research into the development of visual working memory in healthy children and adolescents (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006). While age significantly contributed to VSWM performance, no interactions with group were found, indicating that the developmental trajectory of VSWM of ADHD patients and their unaffected siblings was similar to that of controls. Given the large age range in our sample (8-29 years), current results suggest that VSWM deficits in ADHD patients are relatively stable and pervasive into young adulthood. To our knowledge, this is the first study to describe VSWM deficits in ADHD patients in a large-enough age range to study the developmental trajectory of VSWM impairment. While current results are based on cross-sectional data and are in need of replication in a longitudinal sample, they do provide interesting insight into the development of VSWM deficits in ADHD from childhood into young adulthood. Notably, current findings are in line with Halperin and Schultz's developmental model of ADHD (Halperin & Schulz, 2006). Based on this model, it is expected that patients with persisting symptoms of ADHD, as opposed to those with remitting symptoms, show persisting deficits in more effortful executive functions. While our sample did not allow us to compare ADHD "remitters" versus "persisters," our finding of continuing VSWM impairment in adolescents and adults with *persisting* ADHD does lend support for Halperin and Schultz's model.

To gain more insight into the usefulness of VSWM as an endophenotype for ADHD, unaffected siblings were compared with ADHD patients and controls. All groups were carefully defined, and it was ascertained that unaffected siblings did not experience elevated levels of ADHD symptoms compared with controls. Unaffected siblings did not show impaired VSWM performance compared with controls, consistent with previous studies (Bidwell et al., 2007; Seidman et al., 2000). The absence of impairment in unaffected siblings suggests that VSWM deficits mainly co-occur with the presence of ADHD symptoms, and that VSWM may not be a genetically mediated vulnerability (i.e., an endophenotype) for the disorder. However, our findings are inconsistent with one previous study (Rommelse, Altink, Oosterlaan, et al., 2008), in which a slightly different task was used. The authors used a computerized visuospatial sequencing task, in which participants had to use the computer mouse to click on the same locations on a grid where cues had been presented. Given the unambiguous presence of motor difficulties in many children with ADHD (Barkley, 1990; Piek, Pitcher, & Hay, 1999), and the fact that there is some evidence of similar motor problems in unaffected siblings (Slaats-Willemse, de Sonneville, Swaab-Barneveld, & Buitelaar, 2005), it is possible that in the study of Rommelse and colleagues (2008), motor problems have contributed to impaired VSWM performance in ADHD patients and their unaffected siblings. It should be noted that the current sample is for a large part overlapping with the sample used by Rommelse and colleagues, in which participants were tested 5 to 6 years prior to the current study (ages ranging from 5 to 19 years). Therefore, another possible explanation for the discrepant findings is that unaffected siblings did show some deficits in VSWM at a younger age, but these deficits have subsided as they grew older, which would indicate a catch-up of VSWM functioning in adolescent unaffected siblings. However, this explanation seems unlikely, given the fact that we did not find different developmental trajectories between ADHD patients, unaffected siblings, and controls in a broad age range. Evidently, more research is needed to shed more light on this issue.

Conclusion

The current study investigated VSWM performance in a large group of carefully assessed participants with and without ADHD across a uniquely broad age range. While ADHD patients showed impaired VSWM performance, their unaffected siblings performed similar to controls. The latter finding questions the usefulness of VSWM as a neurocognitive endophenotype for ADHD. Current data showed parallel developmental trajectories of VSWM functioning in ADHD patients, unaffected siblings, and controls, indicating no catch-up of VSWM deficits for ADHD patients in adolescence or young adulthood. Given the broad age range of our sample, we provide unique insights into the developmental trajectory of VSWM impairments in ADHD. Patients with ADHD were impaired on both memory loads, indicative of CE dysfunctioning, rather than limitations in storage or rehearsal capacity. These results implicate a rather general processing deficit in ADHD, which may lie at the core of the behavioral symptoms of the disorder. We propose that the field move forward beyond investigating the presence of VSWM deficits in ADHD, toward identifying the possible cause of impaired VSWM performance, and the directionality of its association with the behavioral symptoms of the disorder. Longitudinal studies could provide unique insights into these mechanisms. Understanding the causal relationship between VSWM impairment and ADHD symptoms might help us clarify whether VSWM is a neurocognitive core deficit of the disorder or, alternatively, is better understood as an epi-phenomenon or a result of its behavioral symptoms and comorbid problems (e.g., impulsive behavior, motivational deficits, or motor coordination difficulties during assessment).

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