Visuospatial Working Memory in ADHD Patients, Unaffected Siblings and Controls
ABSTRACT

BACKGROUND The aim of this study was to: 1) test the usefulness of visuospatial working memory (VSWM) as an endophenotype for Attention-Deficit/Hyperactivity Disorder (ADHD), and 2) study the developmental trajectory of VSWM in ADHD.

METHODS 110 ADHD patients, 60 unaffected siblings, and 109 controls, aged 8-29 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 to 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.
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 behavioural 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 et al., 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 sub-systems: 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 characterised by a decline in task performance with increasing memory load or task difficulty (Baddeley, 2003; Baddeley et al., 1991). CE dysfunctioning translates into a more general performance deficit, stable over different task difficulties. Applying this model to ADHD research, the group by task difficulty interaction found in some studies (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 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 aetiology 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) behavioural 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 behavioural 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 behavioural 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 to 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 et al., 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 to controls. After controlling for ADHD symptoms, the VSWM impairment in unaffected siblings no longer remained significant. Gau and Shang (Gau & 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 under explored. 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 life-long 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 reorganisation 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 younger children with ADHD, while ADHD remitters show improved VSWM compared to 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, in order 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 to 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, in order 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, in order to be able to draw robust conclusions and provide more insight into these issues.
METHODS

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 (n=60) and normal 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 re-invited 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. In order to balance out gender and age differences between groups, additional girls with ADHD (any subtype) and healthy 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 8-30 years, of European Caucasian descent, have an IQ≥70, and 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 contra-indication 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 semi-structured 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, 1998a) combined with either a teacher-rating (Conners’ Teacher Rating Scale - Revised: Long Version
VISUOSPATIAL WORKING MEMORY IN ADHD, SIBLINGS AND CONTROLS

[CTRS-R:L]; Conners, Sitarenios, Parker, & Epstein, 1998b; 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 were gathered of participants’ functioning off medication. 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 behavioural symptoms defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR; American Psychiatric Association, 2000).

Symptoms of the Conners’ questionnaires were only added to the combined symptom count if at least 2 symptoms were reported, in order 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 behaviour (scale L of the CPRS-R:L/CTRS-R:L; scale E of the CAARS-S:L). DSM Hyperactive/Impulsive behaviour (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 ≥6 symptoms of hyperactive/impulsive behaviour and/or inattentive behaviour 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-5; see (Polanczyk et al., 2010); derived from the K-SADS), c) received a T≥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 labelled ‘inconsistent’, and were evaluated by a team of trained experts, in order to derive a consensus decision. All unaffected participants were required to receive a T<63 on each of the above-mentioned scales of each of the Conners’ ADHD questionnaires, and have a combined symptom count ≤3 symptoms. For young adults (≥18
years), criteria were slightly adapted, such that a combined symptom count of 5 instead of 6 symptoms was sufficient for a diagnosis (in line with Kooij et al., 2005; Murphy & Barkley, 1996), and they required ≤2 symptoms on the combined symptom count for ‘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 hours 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 afterwards. 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 by 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 3 or 6 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 predictable 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 inter-stimulus interval (empty grid display). The response window during which the probe was shown and participants had to press the response button was 2000 ms, followed by a 3000 ms inter-trial interval. The task was administered in 4 blocks with a short break in between blocks in order 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 4 blocks. Total task duration was approximately 16 minutes. A practice task with standardized instructions was administered to all participants, shortly before administering the real task. The practice task consisted of 3 working memory trials and 3 control trials, followed by 4 randomised 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 ≥ 3.29 or ≤ -3.29). Two participants from the ADHD group with outliers were excluded from the dataset due to lack of compliance during assessment. Remaining outliers were transformed to a value one unit smaller than the most extreme non-outlier (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 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 Modelling, taking into account clustering of data at different levels. The model consisted of 3 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 non-independency of observations within the subject- and family level. The dataset 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 (in order to control for basic processing or motivational deficits). At the subject-level (level 2), gender and group (NC, US, 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, in order 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 fitted. Interactions with \( p > .05 \) were dropped from the model, as well as non-significant 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, 2002). 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 re-run with IQ as a covariate. The final model was also re-run 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
Figure 1. Schematic overview of a working memory trial with low memory load on the visuospatial working memory task. Each trial consisted of a sequence of either 3 or 6 circles, displayed on a 4x4 grid for 500 ms each, with a 500 ms inter-stimulus interval in between (a). Subsequently, during a 2000 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 3000 ms inter-trial interval, consisting of a black screen (d).
memory load resulting in better VSWM performance. While adding gender significantly improved the overall fit of the model, the effect of gender was not 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 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 behaviour on the one hand, i.e. overriding automated behaviour 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 behavioural symptoms of the disorder. While this idea is consistent with previous research (Kofler et al., 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 et al., 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’ 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’ model.

In order 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
Table 1. Sample characteristics.

|                        | ADHD (n=110) | Unaffected Siblings (n=60) | Controls (n=109) | Test statistic | p-value | Contrasts  
<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Age (M, SD)</td>
<td>17.5 (3.2)</td>
<td>17.2 (4.0)</td>
<td>17.6 (3.7)</td>
<td>$F_{2,276} = 0.18$</td>
<td>0.838</td>
<td>ADHD&gt;US=NC</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>69.1%</td>
<td>45.0%</td>
<td>41.3%</td>
<td>$\chi^2_{2, N=279} = 18.98$</td>
<td>&lt;.001</td>
<td>ADHD&gt;US=NC</td>
</tr>
<tr>
<td>IQ (M, SD)</td>
<td>97.9 (15.9)</td>
<td>101.6 (13.1)</td>
<td>105.2 (12.9)</td>
<td>$F_{2,276} = 7.15$</td>
<td>&lt;.001</td>
<td>ADHD&lt;NC</td>
</tr>
</tbody>
</table>
| Parent-rated ADHD symptoms (M, SD)  
  Inattentive            | 66.7 (11.1) | 47.5 (7.0)               | 46.9 (5.9)       | $F_{2,270} = 183.51$ | <.001   | ADHD>US=NC   |
  Hyperactive/Impulsive  | 70.0 (14.4) | 46.4 (5.5)               | 47.2 (5.9)       | $F_{2,270} = 152.83$ | <.001   | ADHD>US=NC   |
  Total                  | 70.5 (12.7) | 46.8 (6.3)               | 46.5 (5.8)       | $F_{2,270} = 214.62$ | <.001   | ADHD>US=NC   |
| Teacher- or self-rated ADHD symptoms (M, SD)  
  Inattentive            | 64.2 (12.5) | 49.5 (9.2)               | 46.9 (8.8)       | $F_{2,270} = 183.51$ | <.001   | ADHD>US=NC   |
  Hyperactive/Impulsive  | 60.9 (14.1) | 48.4 (11.5)              | 45.1 (9.0)       | $F_{2,270} = 152.83$ | <.001   | ADHD>US=NC   |
  Total                  | 64.8 (13.3) | 48.9 (11.6)              | 45.5 (8.6)       | $F_{2,270} = 214.62$ | <.001   | ADHD>US=NC   |

* Group contrasts represent Tukey post-hoc results.
* ADHD symptoms represent T-scores on CPRS-R:L.
* ADHD symptoms represent T-scores on CTRS-R:L (for participants <18 years) or CAARS-S:L (for participants ≥18 years).
elevated levels of ADHD symptoms compared to controls. Unaffected siblings did not show impaired VSWM performance compared to 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 as 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, motor problems have contributed to impaired VSWM performance in ADHD patients and their unaffected siblings. It should be noted that

Table 2. Multilevel model for VSWM performance.

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Coefficient</th>
<th>SE</th>
<th>Test statistics</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline accuracy</td>
<td>0.700</td>
<td>0.156</td>
<td>$t_{407} = 4.48$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Memory load (high versus low)</td>
<td>-5.948</td>
<td>0.705</td>
<td>$t_{277} = -8.43$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gender (F versus M)</td>
<td>-1.724</td>
<td>1.265</td>
<td>$t_{233} = -1.36$</td>
<td>.174</td>
</tr>
<tr>
<td>Age</td>
<td>4.106</td>
<td>1.256</td>
<td>$t_{261} = 3.27$</td>
<td>.001</td>
</tr>
<tr>
<td>Age x Age</td>
<td>-0.088</td>
<td>0.035</td>
<td>$t_{261} = -2.52$</td>
<td>.012</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD versus NC</td>
<td>-4.522</td>
<td>1.553</td>
<td>$t_{237} = -2.91$</td>
<td>.004</td>
</tr>
<tr>
<td>US versus NC</td>
<td>-0.574</td>
<td>1.743</td>
<td>$t_{230} = -0.33$</td>
<td>.742</td>
</tr>
<tr>
<td>ADHD versus US</td>
<td>-3.947</td>
<td>1.672</td>
<td>$t_{222} = -2.36$</td>
<td>.019</td>
</tr>
</tbody>
</table>

Random effects

| Family | 25.237 | 1.056 | Wald $Z = 2.51$ | .012 |
| Deviance | 4239.864 |     |               |     |
| Deviance empty model | 4364.915 |     |               |     |

Note: indented group contrasts represent Fisher’s LSD post-hoc results.
Abbreviations: ADHD=Attention Deficit Hyperactivity Disorder; F=Female; M=Male; NC=Normal Controls; SE=Standard Error; US=Unaffected Siblings.
Figure 2. Performance on working memory trials with 3 or 6 circles (low or high memory load, respectively) of the visuospatial working memory (VSWM) task, controlling for gender, age, and baseline performance. ADHD patients were significantly impaired compared to controls ($p=0.004$) and unaffected siblings ($p=0.019$), with no significant difference between the latter two groups ($p=0.742$).
Figure 3. Developmental trajectory of performance on the visuospatial working memory (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 3 and 6 circle (low and high memory load) working memory trials.
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 5-19 years). Therefore, another possible explanation for the discrepant findings is that unaffected siblings did show some deficits in VSTM at a younger age, but these deficits have subsided as they grew older, which would indicate a catch-up of VSTM 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.

Conclusions

The current study investigated VSTM performance in a large group of carefully assessed participants with and without ADHD across a uniquely broad age range. While ADHD patients showed impaired VSTM performance, their unaffected siblings performed similar to controls. The latter finding questions the usefulness of VSTM as a neurocognitive endophenotype for ADHD. Current data showed parallel developmental trajectories of VSTM functioning in ADHD patients, unaffected siblings, and controls, indicating no catch-up of VSTM 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 VSTM impairments in ADHD. Patients with ADHD were impaired on both memory loads, indicative of Central Executive 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 behavioural symptoms of the disorder. We propose that the field move forward beyond investigating the presence of VSTM deficits in ADHD, toward identifying the possible cause of impaired VSTM performance, and the directionality of its association with the behavioural symptoms of the disorder. Longitudinal studies could provide unique insights into these mechanisms. Understanding the causal relationship between VSTM impairment and ADHD symptoms might help us clarify whether VSTM is a neurocognitive core deficit of the disorder or, alternatively, is better understood as an epiphenomenon or a result of its behavioural symptoms and comorbid problems (e.g. impulsive behaviour, motivational deficits or motor coordination difficulties during assessment).
REFERENCES


