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Working memory arrest in children with high-functioning autism compared to children with attention-deficit/hyperactivity disorder: Results from a 2-year longitudinal study

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Abstract
The aim of this study was to analyse the development of verbal working memory in children with high-functioning autism compared to children with attention-deficit/hyperactivity disorder and typically developing children. A total of 34 children with high-functioning autism, 72 children with attention-deficit/hyperactivity disorder and 45 typically developing children (age 9–16 years) were included at baseline and followed up approximately 25 months later. The children were given a letter/number sequencing task to assess verbal working memory. The performance of children with high-functioning autism on verbal working memory did not improve after 2 years, while improvement was observed in children with attention-deficit/hyperactivity disorder and typically developing children. The results indicate a different developmental trajectory for verbal working memory in children with high-functioning autism compared to children with attention-deficit/hyperactivity disorder and typically developing children. More research is needed to construct a developmental framework more suitable for children with autism spectrum disorder.

Keywords
Asperger’s syndrome, attention-deficit/hyperactivity disorder, autism spectrum disorder, development, pervasive developmental disorder—not otherwise specified, working memory

Introduction
Recent research in psychopathology, neurocognition, brain imaging and genetics has suggested a possible pathophysiological link between autism spectrum disorders (ASDs, i.e., autistic disorder, Asperger’s syndrome (AS) and pervasive developmental disorder—not otherwise specified) and attention-deficit/hyperactivity disorder (ADHD; Gargaro et al., 2011; Taurines et al., 2012; Vorstman and Ophoff, 2013). Neurocognitive deficits are common in both ASD and ADHD and have been linked to prefrontal and temporal brain regions which are crucial for executive functions (EFs) and memory functions (Gargaro et al., 2011; Rommelse et al., 2011; Taurines et al., 2012). ASD and ADHD are both thought of as developmental disorders (American Psychiatric Association (APA), 2013), but their developmental trajectories have not been sufficiently studied. In this longitudinal study, we compare working memory (WM) development of children with ASD compared to children with ADHD and typically developing children (TDC). Knowledge about neurocognitive development in ASD is also important for intervention planning and monitoring (Conklin et al., 2007).

There is no consensus on the definition of WM and which tasks measure the concept best (Best and Miller,
The most commonly used definition of WM defines the construct as the active maintenance and manipulation of information within a limited time span (Baddeley, 2003). Optimal WM performance in TDC seems to take place in ages 13–15 years for maintenance and ages 15–17 years for manipulation (Conklin et al., 2007). Maintenance refers to tasks that require memory for strings of information (i.e. forward span), whereas manipulation refers to more complex tasks that involve a higher load on EF processing and require rearranging information in memory (i.e. letter/number sequencing (LNS); Best and Miller, 2010; Travers et al., 2011). The development of both appears to be linear from preschool years through adolescence in TDC. Improvements through adolescence seem to be related to degree of manipulation rather than modality (i.e. verbal or visual information; Conklin et al., 2007). It is unclear whether the development of WM seen in TDC also applies to the ASD population.

Findings regarding differences in verbal WM between children with ASD and children with ADHD are inconsistent. Some have found deficits in children with ADHD, but not in children with ASD (Alloway et al., 2009). Others have found the opposite or no differences between the groups (for an overview, see Pennington and Ozonoff, 1996). A recent study revealed that both ASD and ADHD children were significantly impaired compared with TDC on verbal WM, but there were no significant differences between the ASD and ADHD children (Andersen et al., 2013).

A developmental lag in spatial WM has been found in children with ASD (Luna et al., 2007; Ozonoff and McEvoy, 1994; Travers et al., 2011). Moreover, in a recent study, a decrease in WM performance in everyday settings along with increased age in ASD was observed (Rosenthal et al., 2013). Travers et al. (2011) speculated that in children with ASD, the emerging spatial WM impairments with increasing age may be due to increased manipulation demands. Contrary to these findings, Happe et al. (2006) found similar development of spatial WM in children with ASD and TDC. However, except for Ozonoff and McEvoy (1994), all of the above-mentioned studies are cross-sectional, which implies that the aforementioned conclusions regarding the development of WM should be interpreted cautiously. It is, for example, always a risk that the composition of ASD groups may differ at different ages, and thus falsely give the impression of changes in effect size of neurocognitive impairment during development. Following the same group of children in longitudinal designs is considered more valid and reliable for assessing developmental changes. Hence, longitudinal studies are needed to verify the impression given in cross-sectional studies. With respect to ADHD, impaired verbal and spatial WM have been reported in both cross-sectional and longitudinal studies. In contrast to the pattern of findings for spatial WM in ASD, children with ADHD display a similar linear development of WM to that found in TDC (for review, see Best and Miller, 2010; Øie et al., 2010; Qian et al., 2013; Vaidya, 2012).

To the best of our knowledge, no longitudinal studies have investigated the development of verbal WM in children with ASD. Furthermore, no studies have compared the development of verbal WM in children with ASD compared to children with ADHD. Such studies are needed as the differences and overlap between these two groups may change during development. Knowing their developmental course is important in order to design better interventions. The aim of this study was to investigate the developmental trajectory of verbal WM over a 2-year period in children with high-functioning autism (HFA; children with ASD with unimpaired intellectual abilities) compared with children with ADHD and TDC. Similar to what has been reported for the development of spatial WM in a review by Travers et al. (2011), we expected to find less improvement over time in verbal WM in children with HFA compared to children with ADHD and TDC.

**Method**

**Participants**

The children with HFA and ADHD were recruited from the Child and Adolescent Mental Health Centres in Innlandet Hospital Trust (IHT) in Norway. The participants were part of a larger research project investigating cognitive and emotional development in children and adolescents with neuropsychiatric disorders. The age span in this part of the project has been restricted to 9–16 years instead of 8–17 years for larger age homogeneity. All participants underwent a diagnostic assessment at baseline (T1) based on separate interviews of the children and parents using the Schedule for Affective Disorders and Schizophrenia for School Age Children/Present and Lifetime version 2009 (K-SADS-PL; Kaufman et al., 1997). Validity and reliability have been reported as good to excellent for K-SADS-PL with test–retest reliability from .63 to 1.00 and inter-rater reliability from 93% to 100% (Kaufman et al., 1997; Kim et al., 2004). The diagnostic evaluations were supplemented with information from the Autism Spectrum Screening Questionnaire (ASSQ; Ehlers and Gillberg, 1993). The ASSQ offers excellent test–retest reliability and inter-rater reliability, and sensitivity and specificity range from .62 to .91 (Ehlers et al., 1999; Posserud et al., 2009). In addition, the ADHD Rating Scale IV (DuPaul et al., 1998) and the Child Behaviour Checklist (CBCL) ADHD scale (Achenbach and Rescorla, 2001) were filled out by the parents. Clinical significance was assessed by applying normative data from the ASSQ (Ehlers et al., 1999), the ADHD Rating Scale IV (DuPaul et al., 1998) and T-scores above 65 on the syndrome and Diagnostic and Statistical
Manual of Mental Disorders (DSM)-oriented scales in CBCL (Achenbach and Rescorla, 2001). A diagnosis was assigned if Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV; APA, 2000) criteria were met through a comprehensive evaluation involving K-SADS-PL, parent reports, self-reporting and information from teachers regarding academic and social functioning. All participants underwent a comprehensive neuropsychological assessment. Results from these are reported elsewhere. See Andersen et al. (2013) for more details regarding the recruitment procedure.

A total of 34 children with HFA (28 males, mean age = 12.2 years, range = 9.1–15.9), 72 participants with ADHD (38 males, mean age = 12.0 years, range = 9.1–15.9) and 45 TDC (29 males, mean age = 11.8 years, range = 9.5–15.2) from T1 were available at follow-up (T2). Demographic and clinical characteristics are presented in Table 1. One participant in the HFA group and two in the ADHD group refused to participate at T2, and one participant with ADHD was excluded from the analyses because he refused to complete the neuropsychological testing. The four participants who were lost to follow-up did not differ significantly from the clinical groups with regard to age, CBCL total problems score or IQ at T1.

At T1, 28 participants in the HFA group were diagnosed with AS and 6 with pervasive developmental disorder–not otherwise specified (PDD-NOS). One of the children used a small dose of antipsychotics (aripiprazole = 5 mg) due to aggressive behaviour at T1. Another child was medicated with stimulants (methylphenidate dosage of 30 mg – 2.4 mg/kg). Two children used stimulant (methylphenidate) medication at T1, but medication was discontinued 24 h before assessment. At T1, 40 children in the ADHD group were diagnosed with ADHD inattentive subtype and 32 with combined subtype. The ADHD diagnostic subgroups were treated as one group in the analyses as there were no significant differences between them on the neurocognitive measures at T1 (see Skogli et al., 2013). All ADHD children except one were medication naïve at T1, as they, in contrast to medicated children in the HFA group, were newly referred for ADHD assessment. The medicated child in the ADHD group was prescribed a small dose of quetiapine (100 mg) due to aggression. No participants with ADHD had ever used stimulants at inclusion (T1). The TDC were recruited from local schools and attended regular classes. Separate K-SADS-PL interviews with the children and parents revealed no mental disorders. The TDC were given a small compensation for their participation.
participation. Exclusion criteria for all groups at T1 were prematurity (< 36 weeks), IQ estimate below 70 and neurological disease. For the TDC, an additional criterion was no history of psychiatric disorder, dyslexia or head injury (with loss of consciousness).

There were no significant differences between the groups with regard to age at T1. There were significantly (p = .013) fewer girls in the HFA group compared to the other groups. The ratio of males to females is close to that found in prevalence studies (Kadesjö et al., 1999; Surén et al., 2012). The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) was administered to estimate IQ. At T1, there was a significant difference between the groups with regard to IQ (F = 4.8, p = .009). Post hoc analysis revealed that the ADHD group had significantly lower IQ scores than the TDC. The HFA group did not differ significantly from the TDC or from the ADHD group in IQ.

Mothers of TDC had a significantly higher education level than the mothers of the TDC was nearly equal to that of mothers of ADHD or HFA group in IQ. Similar to T1, there was a significant difference between the groups with regard to IQ (F = 4.8, p = .009). Post hoc analysis revealed that the ADHD group had significantly lower IQ scores than the TDC. The HFA group did not differ significantly from the TDC or from the ADHD group in IQ. Mothers of TDC had a significantly higher education level than mothers of the children in the clinical groups (for details, see Table 1). However, the education level of the mothers of the TDC was nearly equal to that of mothers of TDC in other studies in Norway (Heiervang et al., 2010).

The CBCL (Achenbach and Rescorla, 2001) was completed by the parents. The CBCL is a 120-item inventory that provides information regarding child/adolescent behaviour or emotional problems during the past 6 months. There was a significant difference between groups on the CBCL total problems scale (F = 123.7, p < .001). In the subsequent post hoc test, both clinical groups scored significantly impaired compared to the TDC. There was no significant difference between the clinical groups on the CBCL total problems scale.

A follow-up assessment (T2) was conducted approximately 25 months after the baseline assessment (HFA: M = 25.6 months, standard deviation (SD) = 3.5; ADHD: M = 24.9 months, SD = 2.1; TDC: M = 25.0 months, SD = 1.2). Procedures for re-assessment at T2 were the same as for T1. Of the 34 participants in the HFA group at T2, all diagnoses from T1 were confirmed (28 with AS and six with PDD-NOS). At T2, one adolescent was taking antipsychotic and antidepressant medication (quetiapine = 75 mg and sertraline = 100 mg), and one was taking antidepressant medication (mianserin hydrochloride = 30 mg). Three adolescents were on psychostimulants (methylphenidate). Psychostimulants for all three of these participants were discontinued at least 24 h prior to neuropsychological re-assessment. At follow-up, the parents were asked whether the children had received any treatment or extra help at school during the past 2 years. A total of 17 children (50%) in the HFA group had received medication and/or psychological treatment from a child and adolescent mental health centre, and 21 (62%) had received extra help in school either alone or in addition to medical and/or psychological treatment. Data regarding psychological treatment or extra help at school were missing for six children.

A total of 72 participants from the ADHD group were included at T2. Two of these participants no longer met the criteria for ADHD at T2. Of these, 40 participants were prescribed psychostimulants (methylphenidate), but medication was discontinued 24 h prior to re-assessment. One participant with ADHD forgot to discontinue stimulant medication prior to re-assessment. At follow-up, the parents were asked whether the children had received any treatment or extra help at school during the past 2 years. A total of 48 (67%) children in the ADHD group had received medication and/or psychological treatment from a child and adolescent mental health centre, and 49 (68%) children had received extra help in school either alone or in addition to medical and/or psychological treatment. Data regarding psychological treatment or extra help at school were missing for six children. All TDC participants were reassessed at T2 (n = 45).

Similar to T1, there was a significant difference between groups on the CBCL total problems scale at T2 (F = 78.7, p < .001). In the subsequent post hoc test, both clinical groups scored significantly impaired compared to the TDC. However, a mixed between–within subjects analysis of variance (ANOVA) revealed a significant interaction effect of time × group (F(2, 144) = 4.7, p = .011, η² = .061). A repeated-measures ANOVA for each group and time on CBCL total problems revealed a significant effect of time (p ≤ .001), with lower problem scores at T2, for both clinical groups. The TDC also had a lower CBCL total problems score over time, but the reduction was not significant. With regard to IQ, there was neither effect of time nor an interaction effect of time × group on IQ.

Both children (12 years and older) and parents gave informed consent prior to inclusion at T1 and T2. The study was conducted in accordance with the Helsinki Declaration of the World Medical Association Assembly. It was approved by the Regional Committee for Medical Research Ethics in Eastern Norway (REK-Øst), and by the Privacy protection ombudsman for research at IHT in advance.

**Measures**

The LNS test from the Wechsler Intelligence Scales for Children-IV (WISC-IV) was used to measure verbal WM (Wechsler, 2004). The LNS consists of 10 items, each containing 3 trials with the same number, but different combinations of digits and letters. Following a verbal presentation of each trial, the participant is asked to recall the numbers in ascending order and the letters in alphabetical order (Wechsler, 2004). In the present study, total correct recalled trials were examined. Lower raw scores indicated difficulties with the task.

**Data analyses**

Significant results are reported at the p ≤ .05 level. Demographic characteristics were investigated using the
Chi-squared test for independence (gender) and one-way ANOVA (age, mother’s education and IQ). Post hoc tests with a Bonferroni correction were conducted for the group comparisons.

Mixed between–within subjects ANOVAs (mixed ANOVA) were conducted to assess the impact of diagnosis on LNS across time and group. Significant differences were followed up with Bonferroni post hoc test and repeated measures ANOVAs for each group. Pearson’s correlations were conducted for the T1–T2 change scores on the LNS and the T1–T2 change scores on the CBCL total problems to check for a possible association between WM and behaviour. We did a mixed ANOVA for each clinical group (ADHD group on stimulants/ADHD group not on stimulants) to assess the impact of being on stimulant medication on the LNS results. We also performed a separate mixed ANOVA excluding the children that were prescribed antidepressants and/or antipsychotics. To control for a possible confounding effect of gender and IQ, mixed ANOVAs using sex, mothers’ education and IQ as a covariate were conducted.

**Results**

The mixed ANOVA examining performance on the LNS revealed a significant interaction effect of group × time ($F(2, 142) = 4.8, p = .009, \eta^2_p = .064$). A repeated measures ANOVA for each group and time on LNS did not reveal a significant effect of time for the children with HFA. Furthermore, the T1–T2 change scores on LNS and CBCL total problems in the HFA group were not significantly ($r = .111, p = .55$) related. The children with ADHD had a significant improvement over time ($F(1, 66) = 25.2, p < .001, \eta^2_p = .28$) as did the TDC ($F(1, 44) = 31.8, p < .001, \eta^2_p = .42$), see Figure 1. For the ADHD group, the increase in LNS T1–T2 change score correlated with a decrease in CBCL total problems T1–T2 change score ($r = -.242, p = .05$). Tests of between-subject effects showed a significant effect of group ($F(2, 142) = 28.4, p < .001, \eta^2_p = .286$). The Bonferroni post hoc test showed that the participants with HFA scored significantly impaired compared to participants with ADHD ($p = .007$) and TDC participants ($p < .001$) on the LNS. The ADHD participants scored significantly ($p < .001$) impaired compared to the TDC.

When controlling for the confounding effects of Full Scale Intelligence Quotient (FSIQ) in mixed ANOVAs, there was no significant ($p = .090$) interaction effect of time × FSIQ for LNS. Furthermore, we did not find any significant ($p = .162$) interaction effects of gender × time or for mothers’ education × time ($p = .350$) on the LNS. Mixed ANOVAs excluding those using antipsychotics or antidepressants and the one on stimulants at T2 did not change the results. Furthermore, it did not seem to be an effect of stimulant medication on the LNS results in the ADHD group either.

**Discussion**

Consistent with our hypothesis, we found a differential developmental trajectory for verbal WM among the groups. Whereas WM capacity continued to develop in the TDC and the ADHD groups, the HFA group displayed a developmental arrest. The lack of improvement in verbal WM over time is similar to what has been found for spatial WM in children with HFA (Luna et al., 2007; O’Hearn et al., 2008; Travers et al., 2011). To our knowledge, no other longitudinal studies have examined verbal WM in HFA, and cross-sectional studies examining different age groups are inconclusive (Lind and Williams, 2011). Cross-sectional research designs indicate increasing WM impairments with age in children with ASD as a result of increased requirements for manipulation (Travers et al., 2011). Furthermore, the capacity for WM manipulation in ASD has been found to develop later than the capacity for WM maintenance in TDC (Travers et al., 2011). It is not clear whether this decrease in capacity lasts into adulthood or if a maturation of WM capabilities takes place later in adolescence or early adulthood. Results from cross-sectional studies of development of spatial WM in ASD indicate that the impairments continue into adulthood (Luna et al., 2007; O’Hearn et al., 2008). If the manipulation aspect and not the modality is the cause of developmental differences, as suggested by Conklin et al. (2007), it is plausible to expect a similar transition of problems into adulthood for verbal WM. EF in general and WM processes in particular are linked to the functioning of the prefrontal cortex (Barendse et al., 2013). Our results are consistent with results from brain imaging studies, indicating atypical...
brain growth of prefrontal cortex in ASD (Courchesne and Pierce, 2005; Taurines et al., 2012). However, as no longitudinal studies have confirmed the results from the cross-sectional studies on development of WM capabilities, developments might appear later if WM capabilities were longitudinally tracked into adulthood.

The executive subfunctions shifting and planning develop later than WM in TDC (for review, see Best and Miller, 2010). WM processes seem to be necessary for successful mental shifting in TDC (Senn et al., 2004). Before TDC can successfully shift between response sets, for example, they must be able to maintain a response set in WM (Garon et al., 2008). Thus, the early phase of development of one component (WM) may facilitate the development of other components. The early arrest in WM in children with HFA may contribute to possible later impairments of the executive subfunctions shifting and planning. Shifting and planning are generally reported as impaired in ASD (Best and Miller, 2010; Gargaro et al., 2011; Lind and Williams, 2011) and have been proposed to play a significant role in problems with forming meta-representations and practising. Forming meta-representations and practising social communication are two deficits thought to be central problems in ASD (Lind and Williams, 2011). Given the central role of WM in the development of other EF, a review article of Barendse et al. (2013) suggests that WM may have an impact on ASD symptoms in general.

The CBCL total problems score at baseline was significantly elevated in the clinical groups. However, there was a significant improvement on the CBCL total problems score from baseline to follow-up. Both clinical groups scored below cut-off for borderline clinical values at follow-up. For the ADHD subjects, the decrease in emotional and behavioural problems (the CBCL total problems score) was associated with an increase in WM capacity. A similar association was not found in the HFA group. The improvement over time in total problems score in the ADHD group may reflect a positive treatment outcome affecting symptoms, behaviour and WM. In contrast, behavioural and emotional improvement over time was not associated with increased WM capacity in the children with HFA. Several reasons may explain this finding. One possibility is that it is a statistical artefact due to less improvement in the HFA group, resulting in less variance in the correlational analysis for that group. A more substantial explanation is that WM capacity is more directly linked to overall functioning among subjects with ADHD, whereas also other deficits, cognitive or emotional, explain changes in daily life functioning in HFA. The decrease in emotional and behavioural problems in spite of a developmental arrest in WM on a group level in HFA points to this possibility. We will analyse this further in a new study, since it might have important implications for treatment. The implication of scarce improvement in WM might suggest the need for more emphasis on WM training. Recent research shows that WM can be trained using specifically designed computer programs (Hovik et al., 2013; Loosli et al., 2011; Prins et al., 2011). On the other hand, if improvement in function can be attained without improvement in WM in children and adolescents with HFA, then a treatment focus in other areas might be more constructive. An enhanced understanding of the development of WM in children with HFA compared to ADHD and TDC may be of particular relevance for clinicians. Knowledge of developmental trajectories may also help parents and educators anticipate developmental challenges and plan accordingly (Conklin et al., 2007). Furthermore, neurocognitive deficits may have a negative effect on academic achievement and make school facilitation necessary. Social skills training strategies are a widely used therapeutic approach in treating children with ASD. It is possible that difficulties with WM may complicate such interventions (Antshel et al., 2011; Thomson et al., 2011).

Strengths of this study are inclusion of relatively large groups of children with HFA, ADHD and TDC in the same study. Another strength is the longitudinal design and low dropout rate (4%). The large age span (9–16 years at T1) might represent a limitation, but small SD in age reflect the fact that most participants were pre-adolescents at T1. Stimulant medication may have a positive impact on cognition (Coghill et al., 2013b) even when tested in a drug-free status (Huang et al., 2012). However, the clinical effect of methylphenidate typically lasts for 3–12 h (Coghill et al., 2013a). Like in most ADHD studies, in this study, stimulant medication for the ADHD children was discontinued 24 h before assessment (e.g. Alloway et al., 2009; Øie et al., 2010). Our exploratory analyses suggest that this was sufficient to avoid any impact on the WM findings. Another potential limitation is that the sample was drawn from a clinical population, and represents those who are willing to seek help. Furthermore, we did not have control for interventions in the follow-up period.

The results of our study seem to indicate a different developmental trajectory for WM in children with HFA compared to children with ADHD and TDC. This suggests that more research is needed to construct a developmental framework more suitable for the trajectory of development exhibited by children with ASD.

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