Does neurocognitive functioning predict future or persistence of ADHD? A systematic review

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HIGHLIGHTS

• We reviewed the predictive value of neurocognitive functions for ADHD persistence.
• Persisters and remitters did not differ on higher nor lower level neurocognitive functions.
• Bothpersisters and remitters were different from controls on neurocognitive functions.
• In young children, future ADHD was predicted based on neurocognitive functions.
• Neurocognitive dysfunctions might be seen as epiphenomena in the course of ADHD.

ABSTRACT

Many children with ADHD remain symptomatic in (young) adulthood. It is important to understand what characterizes this persistent ADHD group. Since ADHD has been associated with neurocognitive dysfunctioning on a variety of neurocognitive domains, and many of these domains are influenced by the same risk genes that influence ADHD, neurocognitive functions are a potential predictor for ADHD persistence. We carried out a systematic literature review on the predictive value of neurocognitive functioning for future ADHD. Based on eighteen studies there was no evidence that either automatically controlled (requiring little mental effort; lower level), or more consciously controlled (requiring high levels of mental effort; higher level) neurocognitive functions differentiated ADHD persistence from remittance. In general, both persisters and remitters showed weaker performance than typically developing controls, although the effect was smaller for remitters. Neurocognitive functions measured in childhood predicted ADHD a few years later, regardless of the type of neurocognitive function. Our findings do not support the model of Halperin and Schulz (2006), which suggests a maturation of more consciously controlled neurocognitive functions in ADHD remitters.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common developmental disorder, affecting around 5% of children and adolescents (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007) and 2.5% of adults (Simon, Czobor, Balint, Mészáros, & Bitter, 2009). The decrease in prevalence from ADHD in childhood to adulthood implies an age-related symptom decline. A meta-analysis on retention of ADHD over time showed that, starting at age nine, every five years the rate of ADHD declines by 50% (Hill & Schoener, 1996). This is particularly true for symptoms of hyperactivity/impulsivity, but much less so for symptoms of inattention. Symptoms of inattention appear relatively stable with advancing age (Hart, Lahey, Loeb, Applegate, & Frick, 1995). When applying strict versus loose definitions of persistence (i.e. meeting full diagnostic criteria for ADHD according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association, 1994) versus meeting DSM-IV ADHD in partial remission criteria), 15% versus 65% of children remain symptomatic at age 25 follow-up (Faraone, Biederman, & Mick, 2006). A more recent study showed that even 70% of children with a childhood diagnosis of ADHD continued to meet full ADHD DSM-IV criteria in adolescence (Langley et al., 2010). These data thus show that large proportions of children have persistent and impairing symptoms of ADHD in young adulthood.

For early detection and intervention of persistent ADHD, it is important to understand what determines whether a child remains symptomatic or not. In other words, can we identify predictive factors for the course of ADHD symptoms and diagnosis? These factors may include genetic risk, structural and functional brain characteristics, neurocognitive functioning, behavior, and environmental factors. Currently, our knowledge on predictive factors is foremost based on behavioral and environmental variables. A large well-described cohort of participants with persistent ADHD measured in adulthood, showed that a family history of ADHD, psychosocial adversity, co-morbidity, and the number and severity of childhood symptoms, predicted persistence of ADHD (Biederman et al., 1996; Biederman, Petty, Clarke, Lombedo, & Faraone, 2011). These findings have been supported by an international World Health Organization (WHO) study (Lara et al., 2009). A large-scale population-based study on adult ADHD, however, found support only for severity of childhood ADHD and childhood treatment as predictors for persistent ADHD (Kessler et al., 2005). Up to now, the causal mechanisms between these behavioral predictors and the persistence of ADHD remain unclear.

Assessing the predictive value of neurocognitive functioning in relation to the persistence of ADHD is potentially of great value, because neurocognitive functioning is robustly associated with ADHD. Several models of neurocognitive impairments in ADHD have been proposed (e.g. Barkley, 1997; Pennington & Ozonoff, 1996; Sergeant, 2000; Sonuga-Barke, 2005), supported by studies showing that children with ADHD generally performed poorly in terms of neurocognitive functioning compared to normally developing children. Three major domains of neurocognitive impairment are found to play a key role in ADHD and appear at least to some degree neurobiologically independent from each other: impairments in cognitive control, reinforcement processing, and temporal processing (Castellanos & Tannock, 2002; Durston, van Belle, & de Zeeuw, 2011; Sonuga-Barke, Bitsakou, & Thompson, 2010; Wåhlstedt, Thorell, & Bohlin, 2009). However, deficits in these three neurocognitive domains do not encompass all neurocognitive impairments observed in ADHD, as for example impairments in IQ, attention, basic information processing speed, perception, and emotion recognition may not be categorized in these three domains, but have also shown to be associated with ADHD (Frazier, Demaree, & Youngstrom, 2004; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Nazari et al., 2010; Uekermann et al., 2010; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

The relation between neurocognitive functioning and ADHD is also demonstrated in studies showing that neurocognitive dysfunctions are potentially useful as endophenotypes (Castellanos & Tannock, 2002; Rommelse, Altink, Martin, et al., 2008; Rommelse, Altink, Oosterlaan, et al., 2008; Rommelse, Altink, et al., 2007; Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007; Uebel et al., 2010). An endophenotype is a quantitative trait lying on the pathway between genes and phenotype, in which variation depends upon fewer genes than variation within the phenotype (Gottesman & Gould, 2003). The true mediating effect of these neurocognitive domains is not yet established, but at least for most domains sufficient evidence is available for heritability in which the domains partly link to the same genes as the ADHD phenotype. Traditionally endophenotypes are used in the search for – and unraveling of – the working mechanisms of specific genes, but established endophenotypes may also be helpful in predicting the behavioral phenotype. The abovementioned characteristics suggest that neurocognitive functions can be valuable predictors for persistence of ADHD symptoms or diagnosis.

Which of the associated neurocognitive deficits is most strongly related to persistence of ADHD is largely unknown. It has been hypothesized that ADHD is caused by a non-cortical (for example basal ganglia, cerebellum: not involving neocortical areas) neural dysfunction that is present early in life, remains relatively stable throughout the lifetime, and is not associated with remission of symptoms that often occurs in adolescence (Halperin & Schulz, 2006). The development of the prefrontal cortex (PFC) and associated circuits in early adolescence and in early adulthood compensates for the behavioral deficits associated with the non-cortical neural dysfunction. This is reflected in the development of improved cognitive control and the reduction of ADHD symptoms in late adolescence and early adulthood in a proportion of ADHD cases (Halperin & Schulz, 2006). In other words, neurocognitive deficits that remain present in both remitted and persistent cases, despite prefrontal cortex development, are suggested to have a core causal effect on the disorder. Neurocognitive deficits that normalize concurrently with behavioral symptom recovery are seen as epiphenomena (Carr, Nigg & Henderson, 2006). This model predicts that children with the greatest developmental improvement in neurocognitive functions that require high levels of effort, such as cognitive control functions, are those who show remission from ADHD in adulthood.
The aim of this review was to investigate the predictive value of neurocognitive functioning for ADHD persistence, ADHD remittance and control status, and for future ADHD diagnosis and symptoms. We hypothesized that there are differences in predictive value between domains of neurocognitive functions, as indicated by the model of Halperin and Schulz (2006). This model indicates that (changes in) neurocognitive functions requiring a high level of effort (from here on referred to as ‘higher level’ neurocognitive functions) are predictive for ADHD persistence and ADHD remittance, as ADHD remitters are predicted to show normalization of these functions. This is shown at the left side of Fig. 1. In contrast, less consciously controlled, more automatic neurocognitive functions (from here on referred to as ‘lower level’ neurocognitive functions) are poorly developed in both ADHD persisters and ADHD remitters, and thus have no predictive value for differentiating between the two groups, which is shown at the right side of Fig. 1. Studies on the predictive value of neurocognitive functions would deepen our understanding of the mechanisms involved in the persisting course of ADHD.

![Fig. 1. Schematic of the expected differences between ADHD persisters, ADHD remitters, and controls in terms of neurocognitive functions, according to study design (see main text for explanation of study designs). Neurocognitive functions requiring a high level of effort are referred to as ‘higher level’ neurocognitive functions, and less consciously controlled, more automatic neurocognitive functions are referred to as ‘lower level’ neurocognitive functions. Hypotheses are based on the model postulated by Halperin and Schulz (2006). The dotted circle(s) indicate the time of measurement of neurocognitive functions that were used as a predictor for ADHD persistence or future ADHD. Two dotted circles in one graph indicate that the different times of neurocognitive measurement were studied separately for its predictive value.](image-url)
more practical level, it would provide us a tool to identify children with ADHD who are at risk for future ADHD or for a persistent course into adulthood.

2. Method

The computerized databases PubMed, Web of Knowledge and PsycInfo were used to retrieve relevant studies. The following search terms and equivalents generated by the search engines were used to search in both title and text: follow-up, longitudinal, ADHD, attention-deficit/hyperactivity disorder, attention deficit disorder with hyperactivity, attention deficit disorder, hyperkin#, AD/HD, ADDH, neuropsych*, neurocognitive, cognitive. The reference lists of retrieved articles were used to locate other relevant studies.

Three different study designs were of interest: (a) the development of childhood neurocognitive functioning (multiple assessments of neurocognitive functioning over time) differentiating ADHD persistence, ADHD remittance, and control status, or predicting ADHD symptom development, (b) early neurocognitive functioning or current neurocognitive functioning (single assessment of neurocognitive functioning), differentiating ADHD persistence, ADHD remittance, and control status, or predicting ADHD symptom development, and (c) early neurocognitive functioning predicting future ADHD diagnosis and/or symptoms (see also Fig. 1). These type-c studies thus will not report on the (symptom) persistence of ADHD. Type-b studies also include studies investigating neurocognitive functions that are measured concurrently with the assessment of ADHD persistence and ADHD remittance, to get insight into which neurocognitive deficits may ameliorate in the ADHD remittance group. Regardless of premorbid neurocognitive performance of ADHD persisters and remitters, it is very unlikely that a neurocognitive function that is currently still affected, is related to the remission of ADHD behavior. Current neurocognitive functioning thus is of additional relevance in characterizing ADHD persistence and remittance.

Studies were included that (1) used a longitudinal design in which neurocognitive measures were obtained in relation to ADHD persistence/remittance or ADHD symptom development, or in relation to future ADHD diagnosis or symptoms, (2) used a follow-up period of at least six months between sequential assessments to avoid overlap between symptom reports (since the DSM requires ADHD symptoms to exist for at least six months), (3) used DSM-III-Revised (DSM-III-R) or DSM-IV/DSM-IV-Text Revision (DSM-IV-TR) criteria to establish concurrent ADHD diagnosis or symptoms, (4) compared ADHD persisters with ADHD remitters, compared ADHD remitters with controls, or compared ADHD persisters with controls when using group comparisons (for type-a and type-b studies); used a typically developing control group when using group comparisons (for type c-studies); (5) were not confounded by effects of treatment trials, and (6) were published in an English language peer-reviewed journal.

From the 827 studies that were retrieved through the search, fourteen studies met inclusion criteria. Additionally, we found four studies using the reference lists of retrieved studies, resulting in a total of eighteen studies meeting inclusion criteria, covering thirteen independent study samples. As a result of our focus on studies using DSM-III-R and DSM-IV-(-TR) criteria at study entry, included studies were published between 1990 and 2011. Some studies were excluded because these studies reported on the same data already covered by a more comprehensive study report. Specifically, the studies of Biederman et al. (2011) and Von Stauffenberg and Campbell (2007) were not included in the review because results reported in these studies were covered in Biederman et al. (1996), Biederman, Petty, Ball, et al. (2009), and Campbell and von Stauffenberg (2009), respectively. If multiple studies reported on different aspects of neurocognitive functioning in the same sample, these studies were all included (Milwaukee study: Barkley & Fischer, 2011; Fischer, Barkley, Smallish, & Fletcher, 2005 — New York study: Bédard, Trampush, Newcorn, & Halperin, 2010; Halperin, Trampush, Miller, Marks, & Newcorn, 2008 — Boston study: Biederman et al., 1996; Biederman, Petty, Ball, et al., 2009 — Uppsala study: Brocki, Eninger, Thorell, & Bohlin, 2010; Brocki, Nyberg, Thorell, & Bohlin, 2007 — Maastricht study: Kalff et al., 2005; Kalff et al., 2002).

We describe results for several neurocognitive domains reported on in the literature, grouping results in terms of type-a, -b, and -c studies. First, we show the results for the three main domains of neurocognitive functioning: cognitive control, reward processing and temporal processing. Thereafter, we describe findings for other domains of neurocognitive functioning, including intelligence, attention, visual information processing, and basic information processing speed. In the interest of readability, four points are of importance. First, this review describes the prediction of ADHD persistence, rather than remittance, keeping in mind that cases that do not persist are those cases that show remittance. Also, if no results are reported for a particular study design, this indicates that no literature was retrieved for that particular study design. Third, for type-a and type-b studies, we describe how many studies investigated the design, and then report how many studies showed differences between (two) groups. This implicates that, if not otherwise stated, the studies that are not described, did not find differences between the (two) groups. When none of the studies showed differences between (two) groups, we report which studies did not find differences between the groups. Last, although included studies used several terms and definitions to describe ADHD persistence (see Biederman, Mick, & Faraone, 2000 for a discussion), in our main text we use the terms (ADHD) persisters and (ADHD) remitters. Table 1 includes nuanced definitions. It should be noted that many neurocognitive tasks tap into multiple domains of functioning and that for some task measures consensus is lacking which primary function is assessed. We have used the most widely accepted measurement potential of a task measure to decide which domain was assessed by that particular task. We report results without adjustment for IQ, since IQ can remove ADHD related variance when used as covariate (Dennis et al., 2009). However, for one study that did not report results without adjustment for IQ, results were reported with IQ adjustment (Kalff et al., 2002).

3. Results

For each of the studies included in this review, Table 1 displays the study design, follow-up period, number of participants and selection procedure, age of the participants, neurocognitive measures, behavioral (criterion) measures, and results. For each neurocognitive domain, we describe the relevant studies ordered by the design employed (type-a, -b, or -c studies) as reported in the first column of Table 1. Thus, for each domain, first, we report on type-a studies (Biederman, Petty, Ball, et al., 2009; Fischer et al., 2005; Vaughn et al., 2011). Second, we report on type-b studies, starting with studies on the predictive value of early neurocognitive functions (Bédard et al., 2010; Biederman et al., 1996; Biederman, Petty, Ball, et al., 2009; Hart et al., 1995; Langley et al., 2010; Mick et al., 2011), followed by studies on concurrently measured neurocognitive functions (Barkley & Fischer, 2011; Bédard et al., 2010; Biederman, Petty, Ball, et al., 2009; Fischer et al., 2005; Halperin et al., 2008; Mick et al., 2011). Finally, we report on type-c studies (Berlin, Bohlin, & Rydell, 2003; Brocki et al., 2010, 2007; Campbell & von Stauffenberg, 2009; Kalff et al., 2005, 2002; Langley et al., 2010; Marakovitz & Campbell, 1998; Wålstedt, Thorell, & Bohlin, 2008). In the study of Halperin et al. (2008), ADHD persisters and remitters were not compared to each other because of limited group numbers. Results reported from that study (in the neurocognitive domains of inhibition, interference control, working memory, aggregated executive functioning (EF), temporal processing, alerting attention, intelligence, and basic information processing speed) thus only contain
comparisons between persisters and controls, and between remitters and controls, respectively.

3.1. Cognitive control

Cognitive control is the ability to flexibly adjust behavior to changing environmental demands (Nigg & Casey, 2005). Inhibition, working memory, interference control, set-shifting and planning are functions covered by this overarching term. Studies investigating these domains are discussed below. From a neurobiological perspective, cognitive control is thought to rely on the dorsal frontostriatal circuit, involving prefrontal areas, the striatum, and thalamus (Durston et al., 2011). Mainly the prefrontal areas do not mature until late adolescence (Luna, Padmanabhan, & O’Hearn, 2010), making cognitive control one of the latest maturing neurocognitive domains described in this review (Casey, Jones, & Somerville, 2011). Frontal dysfunction and cognitive control deficits are present in both children (Martinussen et al., 2005; Willcutt et al., 2005) and adults with ADHD (Bâlint et al., 2009; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Cubillo, Halari, Giampietro, Taylor, & Rubia, 2011; Desjardins, Scherzer, Braun, Godbout, & Poissant, 2010; Kobel et al., 2010), suggesting that cognitive control deficits remain present in at least some cases with persisting symptoms. However, studies are cross-sectional in design, not investigating the developmental aspects. In the light of testing the model of Halperin & Schulz, we consider cognitive control as ‘higher order’ neurocognitive functions.

3.1.1. Inhibition

Inhibition is the ability to suppress an ongoing dominant response (Nigg, 2000). Measures of inhibition used in the included studies of this review (see Table 1) are commission errors on the Continuous Performance Task (CPT), the Go/No-Go Task, and the Cancellation Task; number of cards, and earnings on the Card Playing Test; latency to first response on the Matching Familial Figures Test (MFF). Two type-a studies investigated the predictive value of inhibition (Vaughn et al., 2011; Fischer et al., 2005). Results showed that inhibition did not predict symptom change in children with and without ADHD (Vaughn et al., 2011), and inhibition in childhood did not differentiate between young adult persistence, remittance, or control status (Fischer et al., 2005). In other words, all three groups (persisters, remitters, and controls) showed the same developmental pattern of inhibition. Two type-b studies reported on current inhibition in young adulthood (Fischer et al., 2005; Halperin et al., 2008). There was no evidence for differences between persisters and remitters (Fischer et al., 2005). Both studies showed similar levels of current inhibition for remitters and controls, while persisters performed worse than controls on two out of five measures of inhibition (Fischer et al., 2005; Halperin et al., 2008). As indicated earlier, Halperin et al. (2008) did not compare ADHD persisters and remitters because of limited group numbers. Type-c studies (five out of six) showed that inhibition in childhood predicted future ADHD symptoms or diagnosis assessed still in childhood (Berlin et al., 2003; Brocki et al., 2010; Brocki et al., 2007; Campbell & von Stauffenberg, 2009; Marakovitz & Campbell, 1998), although this was not true for all measures of inhibition (Brocki et al., 2010; Marakovitz & Campbell, 1998). One of six studies showed that inhibition was not a significant predictor for ADHD diagnosis assessed still in childhood (Kalff et al., 2002).

3.1.2. Interference control

Interference control is another measure of cognitive control slightly different from inhibition. Interference control is the ability to suppress a distractive stimulus or response option that might slow a primary response (Nigg, 2000). Measures of interference control that were used are interference score on the Stroop Color Word Test; reaction time (RT) and accuracy on the Stimulus and Response Conflict Task (SRCT); number of correct responses on both a Stroop-like task and the Knock and Tap Test; number of intervals on the Statue Subtest. Three type-b studies investigated current interference control in (young) adulthood in persisters, remitters, and controls (Barley & Fischer, 2011; Bédard et al., 2010; Halperin et al., 2008). One study showed that persisters performed worse than remitters (Barley & Fischer, 2011). In one study, remitters performed worse than controls (Bédard et al., 2010), and in two studies, persisters performed worse than controls as well (Barley & Fischer, 2011; Bédard et al., 2010). Type-c studies (two out of two) showed predictive value for ADHD symptoms in young children, with somewhat larger effect sizes at one year (Brocki et al., 2010) than at two year follow-up (Brocki et al., 2007).

3.1.3. Working memory

Working memory refers to the ability to temporarily maintain and manipulate information necessary for achieving a certain goal (Baddeley, 2003). Measures of working memory that were used are the Digit Span scaled score (WISC/WAIS); the Digit Span forwards and backwards combined raw score (WAIS); the Working Memory Index (WAIS); number correct and longest sequence completed on the Kaufman Hand Movement Test (KHM); the longest correctly reproduced sequence on the Simon game, total number of pairs ordered correctly on the Children’s Size-Ordering Task (CSOT); number of pictures in correct order on the Kaufman-ABC (K-ABC) Word Order; total points forward and total points backward on a Wordspan task; number of digits on the K-ABC Number Recall; and total points on the Pig Stsy Task. One out of one type-a study did not differentiate between persisters, remitters or controls based on the development of verbal working memory from childhood/adolescence into (young) adulthood (Biederman, Petty, Ball, et al., 2009). One type-b study investigated early working memory performance in late childhood and adolescence, for outcome in adulthood (Biederman, Petty, Ball, et al., 2009). Remitters and persisters showed similar levels of verbal working memory, and both ADHD groups performed worse than controls, independent from the time of measurement (Biederman, Petty, Ball, et al., 2009). Three type-b studies investigated current working memory abilities in (young) adulthood (Barley & Fischer, 2011; Biederman, Petty, Ball, et al., 2009; Halperin et al., 2008). Two studies showed that current verbal and non-verbal working memory did not differentiate persisters and remitters (Barley & Fischer, 2011; Biederman, Petty, Ball, et al., 2009). Two studies also showed that remitters performed worse than controls (Barley & Fischer, 2011; Biederman, Petty, Ball, et al., 2009). In addition, three studies differentiated persistence from control status (Barley & Fischer, 2011; Biederman, Petty, Ball, et al., 2009; Halperin et al., 2008). Three type-c studies showed mixed results. One study found predictive value of early verbal working memory still in childhood, but only for the inattentive type (ADHD-I), not for the hyperactive type (ADHD/H) (Brocki et al., 2010). In a second study, one of two measures of verbal working memory predicted ADHD diagnosis in early childhood (Kalff et al., 2002), and another study showed no evidence for the predictive value of early verbal working memory as well as non-verbal working memory on ADHD symptoms (Brocki et al., 2007).

3.1.4. Set-shifting

Set-shifting is the ability to rapidly alternate between mental sets. One measure of set-shifting was used: time to finish on the Progressive Figures Test. One out of one type-c study found that the ability to shift in young children differentiated ADHD diagnosis, borderline ADHD (children meeting symptomatic criteria but not meeting the criteria of impairment), and controls one year later (Kalff et al., 2002).

3.1.5. Planning

Planning is the ability to sequence and control behavior, and take certain precautions in order to achieve a specified goal (Unterrainer & Owen, 2006). Measures of planning that were used are total score,
Table 1

Prospective studies into the predictive value of neurocognitive measures for future (persistence of) ADHD diagnosis or symptoms.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Follow-up period</th>
<th>Participants and selection procedure</th>
<th>Mean age (age range, SD)</th>
<th>Neurocognitive measures (measurement potential; dependent variable)</th>
<th>Behavioral measures (criterion)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Barkley &amp; Fischer, 2011</td>
<td>Type-b study</td>
<td>T0 baseline</td>
<td>158 hyperactive children. Clinical sample. 81 controls. Community sample.</td>
<td>n.a. (4-12 years)</td>
<td>No measurements</td>
<td>P and T ratings DSM-IV criteria for: ADHD DSM-III-R criteria.</td>
</tr>
<tr>
<td>2. Vaughn et al., 2011</td>
<td>Type-a study</td>
<td>T0 baseline</td>
<td>579 children with ADHD. Clinical sample. 204 children with incomplete data dropped out leaving 375 children with ADHD (80.3% boys). 220 controls (81.0% boys) were additionally selected from a population sample chosen to be proportional to ADHD sample in terms of relevant characteristics.</td>
<td>n.a. (7.0-9.9 years)</td>
<td>No measurements</td>
<td>P and T ratings DSM-IV criteria for: ADHD DSM-III-R criteria for: ADHD-I symptoms ADHD hyperactivity symptoms ADHD impulsivity symptoms</td>
</tr>
<tr>
<td>3. Mick et al., 2011</td>
<td>Type-b study</td>
<td>T0 baseline</td>
<td>140 girls with ADHD. Clinical sample. 122 girls controls. Population sample.</td>
<td>(6-17 year)</td>
<td>No measurements</td>
<td>P DSM-III-R structured interview (ADHD) and P DSM-III-R telephone questionnaire (controls).</td>
</tr>
</tbody>
</table>
After adjustment for age effects at follow-up:

- Full/partial persisters = full remitters vs controls
- Full/partial persisters = full remitters vs controls
- Other predictor effects were not significant.
<table>
<thead>
<tr>
<th>Study design*</th>
<th>Follow-up period</th>
<th>Participants and selection procedure</th>
<th>Mean age (age range, SD)</th>
<th>Neurocognitive measures (measurement potential; dependent variable)</th>
<th>Behavioral measures (criterion)³</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td><strong>Type-a study</strong></td>
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<tr>
<td>T₀ baseline</td>
<td>260 boys. Clinical and random (controls) population sample.</td>
<td>(6–17 year)</td>
<td>WISC-R/WAIS-R Vocabulary, Block Design (verbal IQ measured by a scaled score on the Vocabulary subtest — Performance IQ measured by a scaled score on the Block Design subtest — IQ measured by an aggregated measure of standard scores (TIQ))</td>
<td>Both ADHD diagnosis and a symptom change score were used as outcome.</td>
<td>After adjustment for medication and age effects: No predictor effects were significant.</td>
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<td><strong>Type-b study</strong></td>
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<td>N₀ → B₁</td>
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<td>N₁ → B₂</td>
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<tr>
<td>N₂ → B₃</td>
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<tr>
<td>T₁ 4 year follow-up</td>
<td>33 children with incomplete data dropped out leaving 237 children for follow-up.</td>
<td>14.33 years</td>
<td>Same as T₀, and in addition: WISC-R/WAIS-R Arithmetic, Digit Span, Digit Symbol, ROCF, computerized WCST, Stroop Color Word Test (neuropsychological aggregate measured by a composite z-score)</td>
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<td><strong>Type-c study</strong></td>
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<td>N₁ → B₁</td>
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<tr>
<td>N₂ → B₃</td>
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<tr>
<td>T₀ baseline</td>
<td>1364 children. Random population sample.</td>
<td>1 m (n.a.)</td>
<td>No measurements</td>
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<tr>
<td>T₁</td>
<td>35 month follow-up</td>
<td>Not reported.</td>
<td>3 year (n.a.)</td>
<td>Forbidden Toy Situation (reward delay aversion measured by latency to first active engagement)</td>
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<tr>
<td>T₂</td>
<td>53 month follow-up</td>
<td>Not reported.</td>
<td>4.5 year (n.a.)</td>
<td>Delay of Gratification Task (reward delay aversion measured by waiting time)</td>
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</tbody>
</table>

³ P & T semi-structured interview for DSM-IV: 88 ADHD, 33 no ADHD — Both ADHD diagnosis and a symptom change score were used as outcome.
<table>
<thead>
<tr>
<th>Time Point</th>
<th>Grade</th>
<th>Follow-up</th>
<th>Note</th>
<th>Measure</th>
</tr>
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<tbody>
<tr>
<td>T1 1st grade</td>
<td>Not reported.</td>
<td>Not reported.</td>
<td>—</td>
<td>Tower of Hanoi (planning measured by total planning efficiency score) — CPT (different version as compared to 53 months) (inhibition and alerting attention measured by commission errors and omission errors, respectively)</td>
</tr>
</tbody>
</table>

T2 3rd grade follow-up

<table>
<thead>
<tr>
<th>Note</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>281 children with incomplete data dropped out leaving 1082 children for follow-up.</td>
<td>No measurements</td>
</tr>
</tbody>
</table>

T4 3rd grade follow-up

<table>
<thead>
<tr>
<th>Note</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>281 children with incomplete data dropped out leaving 1082 children for follow-up.</td>
<td>No measurements</td>
</tr>
</tbody>
</table>

Membership of one of three ADHD groups:

- Subsample derived on the basis of T & P DSM-IV questionnaires:
  - 57 ADHD/C (70% boys)
  - 80 ADHD/I (64% boys)
  - 790 Controls (44% boys)

After adjustment for maternal education and gender effects:

- ADHD/C > ADHD/I > controls:
  - T2 waiting time (Delay of Gratification Task) (OR ADHD/C vs. ADHD/I = 0.742. OR ADHD/C vs. controls = 0.650. OR ADHD/I vs. controls = 0.877.)
  - ADHD/C = ADHD/I < controls:
    - T1 latency to first active engagement (Forbidden Toy Situation) (OR ADHD/C vs. controls = 0.995. OR ADHD/I vs. controls = 0.996.)
    - ADHD/I = controls:
      - T1 total planning efficiency score (Tower of Hanoi) (OR ADHD/C vs. controls = 0.901. OR ADHD/I vs. controls = 0.926.)
      - ADHD/C = ADHD/I > controls:
        - T2 commission errors (CPT) (OR ADHD/C vs. controls = 1.051. OR ADHD/I vs. controls = 1.046.)
        - ADHD/C > ADHD/I = controls:
          - T3 omission errors (CPT) (OR ADHD/C vs. controls = 1.085. OR ADHD/I vs. controls = 1.076.)
          - Other predictor effects were not significant.

9. Halperin et al., 2008

Type b study

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Note</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0 baseline</td>
<td>169 children with ADHD. Clinical sample.</td>
<td>No measurements</td>
</tr>
<tr>
<td>T1 9.3 year follow-up</td>
<td>80 children dropped out leaving 89 children originally diagnosed with ADHD for follow-up. 85 controls were additionally selected from a population sample chosen to be proportional to ADHD sample in terms of relevant characteristics. (88% boys in complete sample)</td>
<td>— WAIS-III Vocabulary, Similarities and Information (verbal comprehension measured by an aggregated measure of standard scores (VCI)) — WAIS-III Picture Completion, Block Design, Matrix reasoning (perceptual organization measured by an aggregated measure of standard scores (POI)) — WAIS-III Arithmetic, Digit Span, Letter-Number Sequencing (working memory measured by an aggregated measure of standard scores (WMII)) — WAIS-III Digit Symbol/Coding, Symbol Search (processing speed measured by an aggregated measure of standard scores (PSI)) — Stroop Color Word Test (basic processing speed measured by word-reading score, color-naming score, and interference control measured by interference score)</td>
</tr>
</tbody>
</table>

P & T DSM-III-R interview/ questionnaires.

P & C DSM-IV semi-structured interview:

<table>
<thead>
<tr>
<th>Note</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full persisters and full remitters &gt; controls</td>
<td>T1 SD of RT (CPT).</td>
</tr>
<tr>
<td>Full persisters &gt; controls</td>
<td>T1 WMI scores (WAIS-III).</td>
</tr>
<tr>
<td>Full remitters &gt; controls</td>
<td>T1 number of correct responses (CPT).</td>
</tr>
<tr>
<td>Controls</td>
<td>T1 RT (CPT).</td>
</tr>
<tr>
<td>Full persisters &gt; controls</td>
<td>T1 commission errors (CPT).</td>
</tr>
<tr>
<td>Full remitters &lt; controls</td>
<td>T1 word-reading scores (Stroop Color Word Test).</td>
</tr>
<tr>
<td>No other predictor effects were significant.</td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Study design</th>
<th>Follow-up period</th>
<th>Participants and selection procedure</th>
<th>Mean age (age range, SD)</th>
<th>Neurocognitive measures (measurement potential; dependent variable)</th>
<th>Behavioral measures (criterion)</th>
<th>Results</th>
</tr>
</thead>
</table>
| 10. Wåhlstedt et al., 2008 | T0 baseline | T0 2 year follow-up | ADHD: 6.3 years (SD = 9.4 m) | – CPT (inhibition measured by commission errors — stability of temporal processing measured by SD or RT — alerting attention measured by mean reaction time (RT) and correct responses) | No measurements | Composite of P and T ratings of DSM-IV criteria for:  
• ADHD/H symptoms  
• ADHD/I symptoms |
| Type-c study | | Same as baseline (no attrition) | ADHD: 6.3 years (SD = 9.4 m) | – Stroop-like task, verbal WM task, spatial WM task and verbal fluency (groups divided in ‘good EF’ versus ‘poor EF’ based on their scores on these four tasks) | ADHD: 6.3 years (SD = 9.4 m) | After adjustment for gender, age and SES effects:  
• Positively predicting ADHD/H symptoms:  
T0 poor EF and little ADHD symptoms (vs. controls: $\eta^2 = .07$).  
T0 poor EF and more ADHD symptoms (vs. controls: $\eta^2 = .12$).  
• Positively predicting ADHD/I symptoms:  
T0 poor EF (vs. good EF: $\eta^2 = .05$).  
T0 poor EF and little ADHD symptoms (vs. controls: $\eta^2 = .16$).  
T0 poor EF and more ADHD symptoms (vs. controls: $\eta^2 = .18$).  
• Other predictor effects were not significant. |
| | | T1 2 year follow-up | ADHD + poor EF: 6.9 years (SD = 9.4 m) |  | ADHD: 6.3 years (SD = 9.4 m) |  |
| | | | Poor EF: 6.0 years (SD = 8.8 m) |  | ADHD: 6.3 years (SD = 9.4 m) |  |
| | | | Controls: 7.1 years (SD = 7.9 m) |  | ADHD: 6.3 years (SD = 9.4 m) |  |
| | | | 5.4 years (SD = 0.69) | – Stroop-like task + Knock and Tap subtest NEPSY (interference control measured by an aggregated score of number of correct responses on both tasks) | ADHD: 6.3 years (SD = 9.4 m) |  |
| | | |  | – Statue subtest NEPSY (interference control measured by number of intervals) | ADHD: 6.3 years (SD = 9.4 m) |  |
| | | |  | – Go/No-Go task (inhibition measured by commission errors) | ADHD: 6.3 years (SD = 9.4 m) |  |
| | | |  | – Pig Sty (spatial working memory measured by total points) | ADHD: 6.3 years (SD = 9.4 m) |  |
| | | |  | – Wordspan forward (verbal working memory measured by total points forward) | ADHD: 6.3 years (SD = 9.4 m) |  |
| | | |  | – Wordspan backward (verbal working memory measured by total points backward) | ADHD: 6.3 years (SD = 9.4 m) |  |
| | | |  | – WISC-III Block Design + Information (IQ measured by an aggregated measure of standard scores (TIQ)) | ADHD: 6.3 years (SD = 9.4 m) |  |
| | | |  | 7 children dropped out leaving 65 children for follow-up. | ADHD: 6.3 years (SD = 9.4 m) |  |
| | | |  | 6.3 years (SD = 0.68) | ADHD: 6.3 years (SD = 9.4 m) |  |
| 11. Brocki et al., 2007 | T0 baseline | T1 26 month follow-up | ADHD: 6.3 years (SD = 9.4 m) | – WISC-III Block Design + Information (IQ measured by an aggregated measure of standard scores (TIQ)) | No measurements | P and T ratings of DSM-IV criteria for:  
• ADHD symptoms (mean score of ADHD/H and ADHD/I) |
| Type-c study | | | ADHD: 6.3 years (SD = 9.4 m) | | ADHD: 6.3 years (SD = 9.4 m) |  |
| | | | ADHD + poor EF: 6.9 years (SD = 9.4 m) | | ADHD + poor EF: 6.9 years (SD = 9.4 m) |  |
| | | | Poor EF: 6.0 years (SD = 8.8 m) | | Poor EF: 6.0 years (SD = 8.8 m) |  |
| | | | Controls: 7.1 years (SD = 7.9 m) | | Controls: 7.1 years (SD = 7.9 m) |  |
T0 number of intervals (Statue subtest) \( (r = -0.45) \).
T1 IQ (WAIS-III Block Design and XInformation) \( (r = -0.32) \).

Other predictor effects were not significant.

12. Fischer et al., 2005

Type-a study

\( N_1 \rightarrow B_0 \)

\( N_1 \rightarrow B_0 \)

158 hyperactive children.
Clinical sample.
81 controls.
Community sample.

\( T_0 \) baseline

\( T_0 \) baseline

n.a.
(4–12 years)

No measurements

P questionnaires combined with additional information, highly likely fulfilling ADHD DSM-III-R criteria.

\( T_1 \) 8 year follow-up

Not reported
n.a. (12–20 years)

– CPT
  (inhibition and alerting attention measured by commission errors and omission errors respectively)
  – WAIS-III Vocabulary and Block Design
    (IQ measured by an aggregated measure of standard scores (TIQ))
  – CPT
    (same as \( T_1 \))
    – Cancellation Task
      (inhibition and alerting attention measured by commission errors and omission errors respectively)
    – Card Playing Test
      (inhibition measured by number of cards and earnings)

\( T_2 \) +/- 12 year follow-up

37 originally hyperactive children and 11 controls with incomplete data dropped out.
21 years
(19–25 years)

\( T_2 \) TIQ (WAIS Vocabulary and Block Design).

\( T_2 \) omission and commission errors (CPT).

Other predictor effects were not significant.

13. Kalff et al., 2005

Type-c study

\( N_1 \rightarrow B_2 \)

\( N_1 \rightarrow B_2 \)

452 children derived from a random population sample on basis of CBCL scores.

Not reported.

– ANT Baseline Speed Task
  (basic processing speed measured by reaction time (RT) (ms) – alerting attention measured by mean percentage of errors – stability of temporal processing measured by SD of RT)
– ANT Sustained Attention Task
  (alerting attention measured by reaction time (RT) (ms) and mean percentage of errors – stability of temporal processing measured by SD of RT)
– ANT Divided Attention Task
– ANT Focused Attention Task
  (for both tasks: orienting attention measured by reaction time (RT) (ms) and mean percentage of errors – stability of temporal processing measured by SD of RT)
– ANT Go/No-Go Task
  (inhibition measured by mean percentage of commission errors – alerting attention measured by RT (ms) and mean percentage of omission errors – stability of temporal processing measured by SD of RT)

\( T_0 \) baseline

\( T_0 \) baseline

452 children derived from a random population sample on basis of CBCL scores.

Not reported.

– ANT Baseline Speed Task
  (basic processing speed measured by reaction time (RT) (ms) – alerting attention measured by mean percentage of errors – stability of temporal processing measured by SD of RT)
– ANT Sustained Attention Task
  (alerting attention measured by reaction time (RT) (ms) and mean percentage of errors – stability of temporal processing measured by SD of RT)
– ANT Divided Attention Task
– ANT Focused Attention Task
  (for both tasks: orienting attention measured by reaction time (RT) (ms) and mean percentage of errors – stability of temporal processing measured by SD of RT)
– ANT Go/No-Go Task
  (inhibition measured by mean percentage of commission errors – alerting attention measured by RT (ms) and mean percentage of omission errors – stability of temporal processing measured by SD of RT)
<table>
<thead>
<tr>
<th>Study design</th>
<th>Follow-up period</th>
<th>Participants and selection procedure</th>
<th>Mean age (age range, SD)</th>
<th>Neurocognitive measures (measurement potential; dependent variable)</th>
<th>Behavioral measures (criterion)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. Kalff et al., 2005</td>
<td>T&lt;sub&gt;2&lt;/sub&gt; 18 month follow-up</td>
<td>89 children with incomplete data dropped out leaving 363 children (205 boys) for follow-up.</td>
<td>About 7–8 years</td>
<td>Assignment to one of following groups based on P structured DSM-IV&lt;sup&gt;a&lt;/sup&gt; interview:</td>
<td></td>
<td>Results were comparable after adjustment for baseline speed.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>• 33 ADHD</td>
<td>• 75 borderline ADHD</td>
<td>• 122 pathological controls</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>• 133 healthy controls</td>
<td></td>
<td>• Simple contrasts were made with ADHD as the reference group.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• ADHD &gt; healthy controls:</td>
</tr>
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<td></td>
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<td></td>
<td>• T&lt;sub&gt;1&lt;/sub&gt; RT (Baseline Speed, Divided Attention, Focused Attention,).</td>
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<td></td>
<td>• T&lt;sub&gt;1&lt;/sub&gt; SD (Baseline Speed, Divided Attention, Go/No-Go).</td>
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<td></td>
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<td></td>
<td>• ADHD &gt; pathological controls:</td>
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<td></td>
<td></td>
<td>• T&lt;sub&gt;1&lt;/sub&gt; SD (Baseline Speed, Divided Attention, Focused Attention).</td>
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<td></td>
<td>• ADHD &gt; Borderline ADHD:</td>
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<td></td>
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<td></td>
<td>• T&lt;sub&gt;1&lt;/sub&gt; percentage of omission errors (Go/No-Go).</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Other predictor effects were not significant.</td>
</tr>
<tr>
<td>14. Berlin et al., 2003</td>
<td>Type-c study</td>
<td>N&lt;sub&gt;0&lt;/sub&gt; → B&lt;sub&gt;1&lt;/sub&gt;</td>
<td>T&lt;sub&gt;0&lt;/sub&gt; baseline</td>
<td>151 children (53 boys). Random population sample.</td>
<td>5.3 years (SD = 1.12 m)</td>
<td>T ratings of DSM-IV criteria for:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N&lt;sub&gt;0&lt;/sub&gt; → B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>T&lt;sub&gt;1&lt;/sub&gt; 3 year follow-up</td>
<td>16 children dropped out leaving 135 children for follow-up.</td>
<td>8.0 years (SD = 2.4 m)</td>
<td>• ADHD/H symptoms at school</td>
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<td></td>
<td>• ADHD/I symptoms at school</td>
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<tr>
<td>15. Kalff et al., 2005</td>
<td>Type-c study</td>
<td>N&lt;sub&gt;1&lt;/sub&gt; → B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>T&lt;sub&gt;0&lt;/sub&gt; baseline</td>
<td>443 children (252 boys) derived from random population sample on basis of CBCL.</td>
<td>Not reported.</td>
<td>No measurements</td>
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</tbody>
</table>
### 16. Marakovitz & Campbell, 1998

**Type-c study**  

<table>
<thead>
<tr>
<th>T&lt;sub&gt;0&lt;/sub&gt; baseline</th>
<th>T&lt;sub&gt;1&lt;/sub&gt; 2 year follow-up</th>
<th>T&lt;sub&gt;2&lt;/sub&gt; 5 year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>N&lt;sub&gt;0&lt;/sub&gt; → B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>112 boys.</td>
<td>In sum 17 boys with incomplete data dropped out leaving 85 boys for follow-up.</td>
</tr>
<tr>
<td>N&lt;sub&gt;1&lt;/sub&gt; → B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Subsample from random population sample on basis of ADHD checklist plus matched controls.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 boys with incomplete data dropped out leaving 100 boys for follow-up.</td>
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<tr>
<td></td>
<td>n.a. (6.5–11.4 years)</td>
<td></td>
</tr>
</tbody>
</table>

**Measures:**  
- Progressive Figures Test (set shifting measured by time to finish)  
- VMI Beery (visual processing measured by number of correctly drawn forms)  
- No measurements

**Assignment to one of following groups based on P structured DSM-IV interview:**  
- 33 ADHD  
- 75 borderline ADHD  
- 258 controls

**Results:**  
- Borderline ADHD < controls:  
  - T<sub>0</sub> IQ (RAKIT Vocabulary subtest).  
- Other predictor effects were not significant.

**After adjustment for gender, age, parental occupation, IQ and CBCL group assignment effects:**  
- ADHD < controls  
- T<sub>1</sub> number of correct drawings (RAKIT Embedded Figures).  
- T<sub>1</sub> number of pictures in correct order (K-ABC Word Order).  
- T<sub>1</sub> number of correctly drawn forms (VMI Beery).  
- Borderline ADHD < controls T<sub>1</sub> number of correct drawings (RAKIT Embedded Figures).  
- More time to finish (Progressive Figures Test) at T<sub>1</sub> differentiated ADHD, Borderline ADHD and No ADHD.  
- Other predictor effects were not significant.

### 17. Biederman et al., 1996

**Type-b study**  

<table>
<thead>
<tr>
<th>T&lt;sub&gt;0&lt;/sub&gt; baseline</th>
<th>T&lt;sub&gt;1&lt;/sub&gt; 4 year follow-up</th>
</tr>
</thead>
</table>
| N<sub>0</sub> → B<sub>0,1</sub> | 260 boys.  
  Clinical and random (controls) population sample. | 33 children with incomplete data dropped out leaving 237 children for follow-up. |
| | n.a. (6–17 years) | Not reported. |

**Measures:**  
- WISC Vocabulary, Block Design (IQ measured by an aggregated measure of standard scores (TIQ))

**Assignment to one of following groups based on P and C structured DSM-III-R interviews:**  
- 140 boys with ADHD  
- 120 controls

**Results:**  
- Same as baseline

**After adjustment for age and baseline GAF score effects:**  
- No predictor effects were found.
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Study designa</th>
<th>Follow-up period</th>
<th>Participants and selection procedure</th>
<th>Mean age (age range, SD)</th>
<th>Neurocognitive measures (measurement potential; dependent variable)</th>
<th>Behavioral measures (criterion)b</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. Hart et al., 1995</td>
<td>Type-b study</td>
<td>( T_0 ) baseline ( N_0 \rightarrow B_{0.1} )</td>
<td>177 boys. Clinical sample.</td>
<td>( n.a. ) (7–12 years)</td>
<td>WISC-R (IQ measured by an aggregated measure of standard scores (FSIQ))</td>
<td>P, C and T structured DSM-III-R interview.</td>
</tr>
<tr>
<td></td>
<td>1 year follow-up</td>
<td>6 boys dropped out leaving 171 boys for follow-up.</td>
<td></td>
<td></td>
<td>No measurements</td>
<td>Assignment to one of following groups based on P, C and T structured DSM-III-R interview:</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>‧ 75 ADHD full persisterb</td>
<td>• 22 ADHD moderate full/partial remitterb</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>• 9 ADHD full/partial remitterb</td>
<td>• 19 controls</td>
</tr>
</tbody>
</table>

Note. ADHD Attention Deficit Hyperactivity Disorder; ADHD/C Attention Deficit Hyperactivity Disorder/Combined subtype; ADHD/H Hyperactivity-impulsive subtype; ADHD/J Attention Deficit Hyperactivity Disorder/Inattentive subtype; ANT Amsterdam Neuropsychological Tasks; CBCL Child Behavior Checklist; CPT Continuous Performance Task; CVLT California Verbal Learning Test; DS Digit Span; DSM (III-R); Diagnostic and Statistical Manual of Mental Disorders (3rd edition-revised); DSy/Co Digit Symbol/Coding; EF Executive Functioning; FFD Freedom from Distractibility; FSIQ Full Scale Intelligence Quotient; K-ABC Kaufman Assessment Battery for children; RHK Kaufman Hand Movements Test; MMF Matching Familiar Figures Test; n.a. not assessed; NEPSY Developmental Neuropsychological Assessment Battery; POI Perceptual Organization Index; RAKIT Revised Amsterdam Child Intelligence Test; ROCF Rey-Osterrieth Complex Figure; SES socioeconomic status; SRC Stimulus and Response Conflict Tasks; SS Symbol Search; T Teacher; TIQ total intelligence quotient; P Parent; PSI Processing Speed Index; VCI Verbal Comprehension Index; VMI Beery Developmental Test of Visual-Motor Integration; WAIS-III WAIS-III Revised; WIAT Wisconsin Card Sorting Test; WISC WAIS-III WAIS-III Revised; WMI Working Memory Index.

a The predictive relation investigated in each study is provided in this column. N = neurocognition and B = behavior. Subscripts show at which time point N or B were assessed, with ‘0’ representing baseline measurement. \( N_0 \rightarrow N_1 \) means ‘the development of neurocognition from \( T_0 \) to \( T_1 \)’. The same applies to \( B_0 \rightarrow B_1 \) for example.

b Definitions of ADHD persistence or remittance are based on definitions that were used in included studies. (I) Cases meeting full ADHD DSM criteria at follow-up are referred to as ‘ADHD full persists’. (II) Cases meeting either full or subthreshold criteria for ADHD at follow-up are referred to as ‘ADHD full/partial persists’, defined as meeting at least three or four symptoms of hyperactivity/impulsivity or inattention with significant impairment. This symptom threshold varies across studies. Thus, studies reporting on ADHD full/partial persists did not distinguish between cases meeting full diagnostic criteria for ADHD and cases meeting only subthreshold criteria. (III) Cases meeting less than four or three symptoms of hyperactivity/impulsivity or inattention at follow-up are referred to as ‘ADHD full remitters’. (IV) Cases that did not meet full criteria for ADHD at follow-up were referred to as ‘ADHD full/partial remitters’, containing both fully remitted cases as well as ADHD subthreshold cases. Thus, there is overlap between the ADHD full/partial persists group (II) and the ADHD full/partial remitters group (IV), since both groups contain children meeting subthreshold criteria at follow-up.

c See text for a full description of the different study designs.

c Not clear which number exactly was included in relevant analyses.

d Authors claimed that the ADHD classification is highly comparable with DSM-IV criteria.

e Group main effect was not further tested because of too large differences in variance.

f Children in the non-ADHD/1 group had no diagnosis of ADHD at follow-up, but were recruited at baseline measurement as ‘problem boys’, with elevated levels of hyperactivity, inattentive problems or non-compliance.

h Moderate full/partial remitters met full/partial ADHD remitting criteria three or four years after baseline measurement, and met full ADHD criteria at the other of these two measurements.
number of correct to first trial, and time to first move on the Tower of London (ToL); and total planning efficiency score on the Tower of Hanoi (ToH). One type-b study investigated current planning measures in adulthood, and showed that persisters, remitters and controls were not differentiated from each other on current planning measures (Barkley & Fischer, 2011). One out of one type-c study showed that in young children, planning abilities predicted ADHD diagnosis two years later (Campbell & von Staffenburg, 2009). In that study the inattentive type (ADHD/I) and combined type (ADHD/C) were differentiated from controls, but not from each other.

3.1.6. Fluency

Fluency refers to the ability to quickly generate responses (solutions) to a certain problem (Pennington & Ozonoff, 1996). Measures of fluency were number of unique designs from the Five-Points Test of Design Fluency; and number of words from the RAKIT verbal fluency subtest. One type-b study investigated current (non-verbal) fluency, and showed that current fluency did not differentiate persisters from remitters in adulthood, and both ADHD groups were differentiated from controls (Barkley & Fischer, 2011). One out of one type-c study showed that verbal fluency did not predict ADHD diagnosis in very young children one year later (Kalff et al., 2002).

3.1.7. Aggregated executive functioning

Since cognitive control is closely linked to the concept of EF (Dramsdahl, Westerhausen, Haavik, Hugdahl, & Plessen, 2011), these findings are outlined here as well. Table 1 shows details of the measures that were used for the aggregated EF measures. For instance, one of the studies used performance on four different tasks (Stroop-like task, verbal WM task, spatial WM task, and verbal fluency) to divide groups in ‘good EF versus poor EF’. Poor EF was defined as scoring in the lowest 30% on at least two tasks, and good EF was defined as scoring in the highest 50% on all four tasks (Wahlstedt et al., 2008). Together, four studies investigated the predictive value of aggregated EF measures (Biederman, Petty, Ball, et al., 2009; Halperin et al., 2008; Mick et al., 2011; Wahlstedt et al., 2008). One type-a study investigated the predictive value of the development of an aggregated measure of EF from childhood to adulthood, and found no differences between persistence, remittance, and control status (Biederman, Petty, Ball, et al., 2009). Two type-b studies investigated the predictive value of early aggregated EF measures in young adulthood (Biederman, Petty, Ball, et al., 2009; Mick et al., 2011). Both studies showed that an aggregated EF measure did not differentiate persisters from remitters in adolescence and in young adulthood, and both ADHD groups were different from controls (Biederman, Petty, Ball, et al., 2009; Mick et al., 2011). Three type-b studies investigated current measures of aggregated EF in (young) adulthood (Biederman, Petty, Ball, et al., 2009; Halperin et al., 2008; Mick et al., 2011), and reported similar effects as for early measures of aggregated EF; two studies showed that persisters and remitters did not differ from each other (Biederman, Petty, Ball, et al., 2009; Mick et al., 2011). In two studies, both ADHD groups performed worse than controls (Biederman, Petty, Ball, et al., 2009; Mick et al., 2011), while in the third study persisters and remitters were not differentiated from controls (Halperin et al., 2008). One out of one type-c study showed predictive value for an aggregated EF measure on both ADHD-I symptoms and ADHD-H symptoms compared to control status in early childhood (Wahlstedt et al., 2008).

Summarizing the different subdomains of cognitive control, none of three type-a studies predicted ADHD (symptom) persistence (inhibition, working memory, aggregated EF): the development of cognitive control abilities was similar for persisters, remitters, and controls. None of the two type-b studies investigating early cognitive control measures differentiated persisters from remitters, and both persisters and remitters were differentiated from controls (early measures of working memory, aggregated EF). Six type-b studies investigated current cognitive control measures. In only one of these studies were persisters differentiated from remitters; four studies differentiated ADHD remitters from controls (interference control, working memory, fluency, and aggregated EF), and all six studies differentiated persisters from controls. The majority of measures in eight type-c studies showed that cognitive control capacities (inhibition, interference control, set- shifting, planning, and aggregated EF) in early childhood predict future ADHD symptoms or diagnosis (still in childhood). However, verbal and non-verbal working memory was not predictive in five out of seven measures.

3.2. Reward processing

Reward processing refers to the sensitivity to reinforcement which influences the degree of motivation to perform and is related to orbito-fronto-striatal loops as described above (Brenhouse & Andersen, 2011; Durston et al., 2011). It also refers to the processing of delayed rewards, which relies on ventral fronto-striatal circuits (Sonuga-Barke et al., 2010). The activation of these circuits is quite different in adolescents and adults, suggesting that these systems do not mature before adolescence (Casey et al., 2011). At the behavioral level, it is known that children with ADHD have a stronger preference for smaller immediate rewards over larger delayed rewards compared to controls. In addition, it appeared that the positive effect of reward contingencies on task performance is somewhat more prominent in children with ADHD than in control children (Luman, Oosterlaan, & Sergeant, 2005). Although literature on reward processing in adults is scarce, evidence suggests that adults with ADHD show reward delay aversion compared to controls (Marx et al., 2010). This is in line with findings of similar neurobiological dysfunctions of reward processing in adolescents (Scheres, Milham, Knutson, & Castellanos, 2007) and in adults with ADHD (Plichta et al., 2009; Ströhle et al., 2008). All three studies showed reduced ventral striatal activity in ADHD compared to controls during reward anticipation in a reinforcement reaction time task, indicating that problems with reward processing are present at least in persistent ADHD cases. For the purpose of this review, we consider reward processing as a lower order neurocognitive function.

Measures of reward processing (reward delay aversion) that were used are latency to first active engagement on a Forbidden Toy Situation; waiting time on a Delay of Gratification Task (choosing between a small immediate reward or a larger reward seven minutes later); impulsive responses on another Delay of Gratification Task (waiting for a signal before searching for a cookie hidden under one of three cups); and latency to touch on a Resistance to Temptation Task. Results of type-c studies (two out of two) showed predictive value of reward delay aversion for future ADHD/C and ADHD/I compared to control status, still in childhood (Campbell & von Staffenburg, 2009; Marakovitz & Campbell, 1998), although one measure in the Marakovitz & Campbell study showed no predictive value.

3.3. Temporal processing

Temporal processing is a very broad term which has been used to refer to the ability to order and predict sequential events in time, and show temporal stability of responding (Durston et al., 2011); skills that depend on intact time perception, time discrimination and time (re)production (Castellanos & Tannock, 2002; Ivy, 1996). Even though these processes are quite different and probably reflect diverse neurobiological mechanisms, they all rely at least partially on fronto-cerebellar circuits (Castellanos & Tannock, 2002; Durston et al., 2007; Durston et al., 2011) with the cerebellum as key player (Mackie et al., 2007). The cerebellum appears to increase further in size during adulthood, especially the vermis (Durston et al., 2001) and thus is not a fully matured structure yet early in life. Deficits in different types of temporal processing exist not only in children
with ADHD (time discrimination, time reproduction (Rommelse, Altink, Oosterlaan, et al., 2008; Rommelse, Oosterlaan, Buitema, Faraone, & Sergeant, 2007; Toplak, Dockstader, & Tannock, 2006); predicting sequential events in time (Durston et al., 2007)) but also in adults with ADHD (time estimation and reproduction (Barkley, Murphy, & Bush, 2001; Marx et al., 2010)). Increasing cerebellar dysfunction (again particular in vermal areas) appears during adolescence in children with ADHD relative to normally developing children (Mackie et al., 2007). It is thus suggested that, based on cross-sectional studies, temporal processing deficits are apparent in at least persisting ADHD cases. In terms of testing the Halperin & Schulz model, we consider temporal processing as a lower order neurocognitive function.

Studies into temporal processing are limited to studies using measures of temporal stability (e.g., RT variability). In all studies the SD of RT (SDRT) was used, derived from the CPT, SRCT interference control and inhibition conditions, the Go/No-Go Task, a Divided Attention Task and a Sustained Attention Task. One type-a study investigated the predictive value of the development of RT variability from middle to late childhood, and found no predictive value for ADHD symptom change (Vaughn et al., 2011). Two type-b studies investigated current RT variability in young adulthood (Bédard et al., 2010; Halperin et al., 2008). There was no evidence for differences between persisters and remitters (Bédard et al., 2010). One study showed that remitters were differentiated from controls (Halperin et al., 2008), and both studies differentiated persisters from controls (Bédard et al., 2010; Halperin et al., 2008). One type-c study showed predictive value for future ADHD diagnosis (ADHD versus control status) one year later for four out of five measures of RT variability (Kalff et al., 2005).

3.4. Intelligence

Another domain potentially relevant in ADHD research is intelligence. Intelligence indicates a general mental capability encompassing a wide range of cognitive abilities including, for example, reasoning, planning, problem solving and abstract thinking. Here we will focus on the most commonly used division between verbal and performance intelligence (Wechsler, 1997). There is no defined brain network subserving intelligence since intelligence is a heterogeneous concept, but of interest is that the developmental maturation of cortical thickness appears to be related to intelligence; a faster, but more basic lower level functions (e.g. basic information processing speed), depending on which subtest measure of IQ is used (for example full scale IQ [FSIQ]), of which processing speed is a part, versus Block Design as a measure of Performance IQ (PIQ).

Measures of intelligence that were used are Total IQ (TIQ, estimated from Vocabulary or Information, and Block Design, sometimes supplemented with other subtests of the WISC or WAIS), FSIQ (using all subtests of an intelligence scale); PIQ (estimated from Block Design of the WISC or WAIS), Verbal IQ (VIQ, estimated from Vocabulary of the WISC or WAIS, estimated from Verbal Comprehension Index from the WAIS, or estimated from Vocabulary from the RAVLT); and Freedom from Distractibility Index (FFD, from WISC/ WAIS subtests Arithmetic and Digit Symbol Coding). One type-a study investigated the predictive value of the development of PIQ and VIQ from childhood/adolescence into (young) adulthood, and showed no predictive value of the decrease in PIQ for differentiating persisters from remitters (Biederman, Petty, Ball, et al., 2009). Both ADHD persisters and remitters were differentiated from controls (Biederman, Petty, Ball, et al., 2009). Persisters, remitters and controls all showed a similar increase in VIQ (Biederman, Petty, Ball, et al., 2009). Results of Total IQ should be taken with some caution, since PIQ and VIQ showed different results (see Table 1 for results on TIQ) (Biederman, Petty, Ball, et al., 2009). Six type-b studies investigated early measures of IQ in childhood and adolescence (Bédard et al., 2010; Biederman et al., 1996; Biederman, Petty, Ball, et al., 2009; Hart et al., 1995; Langley et al., 2010; Mick et al., 2011). There was no evidence for differences between adolescent or young adult persisters and remitters. Two of six studies differentiated both ADHD persisters and remitters from controls in adolescence and young adulthood (Biederman, Petty, Ball, et al., 2009; Mick et al., 2011), while the other four studies did not differentiate persisters and remitters from controls, or did not predict ADHD symptom change (Bédard et al., 2010; Biederman et al., 1996; Hart et al., 1995; Langley et al., 2010). Four studies investigated current measures of IQ in adolescence or (young) adulthood (Barkley & Fischer, 2011; Biederman, Petty, Ball, et al., 2009; Halperin et al., 2008; Mick et al., 2011). Similarly, no studies differentiated persisters from remitters (Barkley & Fischer, 2011; Biederman, Petty, Ball, et al., 2009; Mick et al., 2011). Three studies differentiated persistence and remittance from control status (Barkley & Fischer, 2011; Biederman, Petty, Ball, et al., 2009; Mick et al., 2011), while one study did not differentiate persisters and remitters from controls (Halperin et al., 2008). Three type-c studies showed mixed findings. One study demonstrated that IQ was predictive for future ADHD symptoms in very young childhood (Brocki et al., 2007). In another study, only the borderline ADHD group was differentiated from controls using IQ, while children with ADHD performed similar to controls (Kalff et al., 2002). In one study, IQ measured in childhood did not predict ADHD at follow-up in adolescence (Langley et al., 2010).

3.5. Attention

Another neurocognitive domain that plays an important role in ADHD is attention. Although consensus is lacking, a large body of literature distinguishes between three sub-domains of attention including alerting, orienting and executive attention (Posner & Petersen, 1990; Raz & Buhle, 2006). Alerting can be defined as the ability to attain and maintain a state of high sensitivity in anticipation of a stimulus. This alertness or vigilance is required to react without delay to an impending stimulus (Posner, 2008; Raz & Buhle, 2006), and is thought to be mediated by frontal and (inferior) parietal regions, as well as the locus coeruleus (Raz, 2004; Raz & Buhle, 2006). Orienting allows the selection of information from sensory input, sometimes also referred to as ‘scanning’ or ‘selection’ (Posner, 2008; Raz & Buhle, 2006) and is thought to rely on both subcortical structures (e.g. part of thalamus) and cortical structures (superior parietal lobe, frontal eye fields and temporoparietal junction) (Raz, 2004; Raz & Buhle, 2006). Executive attention is often equated to interference control and is discussed in Section 3.1. Normal maturation of the attentional networks appears to continue after childhood, since between the age of 12 years and adulthood these brain areas are matured (Konrad et al., 2005). This is in line with behavioral developmental studies (Konrad et al., 2005; Rueda et al., 2004). In adults with ADHD, functional and structural brain deficits as well as phenotypic expression of attentional problems related to alerting, orienting and executive attention are still present, although possibly to a lesser extent than in children with ADHD (Amico, Stauber, Koutsouleris, & Frodl, 2011; Cubillo, Halari, Giampietro, Taylor, & Rubia, 2011; Rubia, 2011; Tucha et al., 2008). Although these findings suggest that at least some aspects of attention remain impaired in some persistent ADHD cases, these studies were cross-sectional in design.
We think alerting attentional tasks require little mental effort and are considered as tapping automatically controlled, lower level functions. Attentional demands increase in orienting tasks, therefore we consider performance on orienting tasks as more consciously controlled, higher level neurocognitive functions.

Measures of alerting attention that were used are RT, omission errors, and correct responses on the CPT; omission errors on the Cancellation Task and on the Go/No-Go Task; RT and mean percentage of errors on the Baseline Speed Task. Measures of orienting attention that were used are total score on the Auditory Attention Test; RT and error measures on both the Divided Attention Task and the Focused Attention Task. Two type-a studies investigated the predictive value of the development of alerting attention (Fischer et al., 2005; Vaughn et al., 2011). There was no evidence for the predictive value for ADHD symptom change in childhood (Vaughn et al., 2011), nor for the differentiation between persisters, remitters and controls based on the development of alerting attention from adolescence into young adulthood (Fischer et al., 2005). Two type-b studies investigated current alerting attention capacities in young adulthood (Fischer et al., 2005; Halperin et al., 2008). There was no evidence for differences between ADHD persisters and remitters (Fischer et al., 2005). Two studies found that ADHD remitters did not differ from controls (Fischer et al., 2005; Halperin et al., 2008). ADHD persisters were different from controls in three of four measures in the two studies (Fischer et al., 2005; Halperin et al., 2008). Three type-c studies revealed mixed findings. A large random population study showed that alerting attention capacities measured at two different ages predicted future diagnosis of ADHD compared to control status (Campbell & von Stauffenberg, 2009). However, in another study only one of three measures of alerting attention predicted a diagnosis of ADHD one year later compared to control status (Kalff et al., 2005), and another study did not differentiate at all; children with ADHD/I, children with no diagnosis of ADHD/I but other behavioral problems (attention problems and hyperactivity but not severe enough to warrant a diagnosis), and controls performed similarly on a measure of alerting attention (Marakovitz & Campbell, 1998). Regarding orienting attention, two out of two type-c studies showed predictive value for orienting attention; in one study early orienting attention predicted future ADHD symptoms (Brocki et al., 2010), and two out of four orienting attention measures predicted future ADHD diagnosis, still in childhood (Kalff et al., 2005).

3.6. Visual information processing

Visual information processing can be defined as the capacity to integrate visual input from the outside world into something meaningful (Barclay, 1997). Visual processing capacities rely substantially on a connection between the occipital and temporal lobes. This so-called ‘ventral stream’ is activated when judging ‘what’ an object is. The dorsal stream, linking the occipital lobe and the parietal lobe, is activated when judging ‘where’ an object is, and has more to do with action regarding the object (Goodale & Milner, 1992; Goodale & Westwood, 2004). It appears that visual processing normally improves during childhood (Williams et al., 2011). Research on visual processing deficits in children and adults with ADHD is scarce, with some evidence suggesting that children with ADHD may have problems with visual sensory integration in the occipital lobe compared to controls (Nazari et al., 2010) and that children and adults with ADHD may have problems with central coherence, although findings are inconsistent (Hervey et al., 2004; Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). We consider measures that were used for visual information processing in this review as higher level neurocognitive functions.

Measures of visual information processing that were used are number of correct drawings on the RAKIT Embedded Figures; number of correctly drawn forms on the Visuo-Motor Integration Beery (VMI Beery); and number of correct pictures on the K-ABC Gestalt Closure. One type-c study showed that two of the three visual processing measures differentiated future (still in childhood) ADHD diagnosis and borderline ADHD from control status (Kalff et al., 2002).

3.7. Basic information processing speed

Basic information processing speed is defined as the (mental) speed with which elementary cognitive tasks are executed, commonly measured by reaction time tasks (Coyle, Pillow, Snyder, & Kochunov, 2011; Salthouse, 1996; Takeuchi et al., 2011). Depending on the particular information that is processed, different neural systems are involved in processing speed (Takeuchi et al., 2011). In general however, it appears that myelination of fiber tracts plays an important role in basic processing speed (Brenhouse & Andersen, 2011). A strong increase in myelination is seen in the first decade of life, with ongoing development into adulthood (Tao & Peterson, 2010). Behaviorally, it is found that processing speed increases during childhood and adolescence until adult ages in terms of a quadratic function (Kail & Ferrer, 2007). In general, children with ADHD are found to be slower in processing speed compared to control children (Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008). With regard to adult ADHD, in one meta-analysis it was shown that adults with ADHD performed worse on measures of processing speed compared to controls (Bridgett & Walker, 2006), but this was not confirmed in another meta-analysis (Hervey et al., 2004). We consider basic information processing speed as a typically lower level neurocognitive ability that underlies many other neurocognitive functions.

Measures of basic information processing speed that were used are Digit Symbol score on the WISC/WAIS; both word-reading scores and color-naming score on the Stroop Color Word Test; Processing Speed Index on the WAIS; and RT on a Baseline Speed Task. One type-a study investigated the predictive value of the development of basic information processing speed from childhood into (young) adulthood (Biederman, Petry, Ball, et al., 2009). There was no evidence for differences between ADHD persisters, remitters, and controls (Biederman, Petry, Ball, et al., 2009). One type-b study investigated early measures of processing speed in childhood and adolescence, and showed no differences between young adult persisters and remitters (Biederman, Petry, Ball, et al., 2009). In addition, both ADHD groups performed worse than controls. Two type-b studies investigated current basic information processing speed in young adults (Biederman, Petry, Ball, et al., 2009; Halperin et al., 2008). One study showed no differences between ADHD persisters and remitters, with both remitters and persisters performing worse than controls (Biederman, Petry, Ball, et al., 2009), while in the other study, both remitters and persisters did not differ from controls on a measure of current basic information processing speed (Halperin et al., 2008). One type-c study showed predictive value for future ADHD compared to control status in childhood (Kalff et al., 2005).

4. Summary and discussion

The aim of this comprehensive review was to investigate the predictive value of neurocognitive functioning for persistence or remission of ADHD diagnosis and symptoms, or future ADHD diagnosis or symptoms. We focused first, but not exclusively, on cognitive control, reward processing and temporal processing. It was predicted that children with the largest developmental improvement in functions that rely on prefrontal functioning, such as cognitive control, or other higher level neurocognitive functions, are the ones that show remission from ADHD symptoms. This is based on the suggestion that the development of the prefrontal cortex and associated circuits, and thus the development of higher level neurocognitive functioning, compensates for non-cortical (e.g. striatal), lower level neurocognitive dysfunctions in ADHD (Halperin & Schulz, 2006).
This theory suggests that core neurocognitive deficits of the disorder are those deficits that remain present in subjects with remitted ADHD symptoms, while deficits that disappear in remitted ADHD are seen as epiphenomena, and are not causally related to the disorder (Carr et al., 2006; Halperin & Schulz, 2006).

This review included eighteen studies, encompassing data from thirteen independent samples. Several main findings stand out. Overall, there is no evidence to suggest that ADHD remitters improve on cognitive control functions compared to ADHD persisters, or on other higher level neurocognitive abilities such as intellectual functioning. Both ADHD persisters and remitters, assessed at several ages, showed weaker performance than controls, although there are studies that showed smaller differences when differentiating ADHD remitters from controls compared to when ADHD persisters were differentiated from controls, on some measures (Bédard et al., 2010; Fischer et al., 2005). Findings are somewhat preliminary for lower level neurocognitive functions, because the main focus of most studies was on higher level domains. So far, a similar pattern of results was found for higher and lower level neurocognitive functions: ADHD remitters did not outgrow performance levels of persisters in terms of temporal processing, or other lower level neurocognitive functions, such as alerting attention and basic information processing speed. Our findings suggest that ADHD persisters and remitters remain equally impaired in terms of neurocognitive functioning. Interestingly, measures of both lower and higher level neurocognitive functions in early childhood were predictive for future ADHD symptoms or ADHD diagnosis a few years later. Unfortunately, to what extent these very early neurocognitive measures are able to predict future ADHD outcome in older children, for example in adolescence or even in adulthood, is not known from our review. Further studies are warranted here to unravel the relation between neurocognitive functions measured in very early childhood, development of ADHD symptoms and eventually also remittance or persistence of the disorder in adulthood. Last, no evidence was revealed to suggest specific differences in predictive value between the neurocognitive domains described.

Taking all findings together, it is clear that at this point, we cannot confirm the hypotheses postulated from the Halperin & Schulz model. In this model, several lower level neurocognitive functions were suggested as candidate core deficits in ADHD, thereby suggesting that ADHD remitters would resemble ADHD persisters in terms of these lower level neurocognitive functions, and both groups would show weaker performance than controls. However, not only did ADHD remitters perform at a similar level as ADHD persisters on lower level neurocognitive functions, both groups were also comparable in terms of higher level neurocognitive functions. So far, neurocognitive functioning appears unrelated to the developmental course of the disorder, although not all domains were extensively investigated (e.g. reward processing, temporal processing). The current findings are consistent with the observation that adults with ADHD, despite a fully developed brain, show both lower and higher order neurocognitive dysfunctions (Boonstra et al., 2005; Hervey et al., 2004; Schoechlin & Engel, 2005). Children with ADHD are suggested to show a developmental delay in brain maturation (Shaw, Eckstrand, et al., 2007), indicating that during development brain structure and function would normalize. Our findings suggest that both children with persistent as well as remitted ADHD remain dysfunctional in terms of neurocognitive functioning. This suggests that a delayed brain maturation is not sufficient to explain the course of ADHD. A few studies have been performed on the predictive value of neurobiological measures for persistence of ADHD (for example functional or structural MRI measures). Normalization of the volume of the right parietal cortex accompanied clinical improvement of ADHD in adolescence (Shaw et al., 2006), and a progressive loss of cerebellar volumes is related to persistent symptoms in adolescence (Mackie et al., 2007). However, since there is no one-to-one relation between neurocognitive functions and these kinds of neurobiological measures, it is unclear to what extent we can expect predictive value of neurocognitive functions from these results. Genetic markers of ADHD persistence might be helpful as well, but this type of research is still in its infancy. Three studies so far found a relation between specific alleles and a persistent course of ADHD (Biederman, Petty, Ten Haagen, et al., 2009; Langley et al., 2009; Shaw, Gornick, et al., 2007), and there may be differences in the genetic profiles of ADHD persisters and ADHD remitters (Franke et al., 2012).

The findings in this review have implications for theoretical models on the development of ADHD. It has been suggested that neurocognitive deficits act as intermediate factors between genetic factors and ADHD symptoms (Castellanos & Tannock, 2002; Rommelse, Altink, Martin, et al., 2008; Uebel et al., 2010), implicating that neurocognitive deficits are related to the development of ADHD. The true mediating effect of these neurocognitive deficits is not yet established however, and the finding that ADHD remitters cannot be differentiated from ADHD persisters, and ADHD remitters do not normalize in at least some domains of neurocognitive functioning, despite a decrease in ADHD symptoms, indicates that there is no one-to-one relation between neurocognitive and symptomatic development. This may lead to the very tentative conclusion that neurocognitive deficits in ADHD may be seen as epiphenomena instead of core causal deficit. In other words, neurocognitive dysfunctions may be related to the same etiological factors as the ADHD symptoms, but may not mediate between genes and behavior (Kendler & Neale, 2010; Walters & Owen, 2007). This could explain the apparent existence of children with ADHD without any neurocognitive problems (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005), the lack of association between neurocognitive dysfunctioning and severity of ADHD symptoms (Rommelse et al., 2011), and similar neurocognitive problems in affected and unaffected siblings while unaffected siblings clearly have less behavioral problems (Rommelse, Altink, Oosterlaan, et al., 2008; Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007). The postulation that neurocognitive problems can be seen as epiphenomena in ADHD contrasts with the Halperin & Schulz model, that suggests that remaining symptoms are core deficits in ADHD.

But is there any predictive value of neurocognitive functioning? The studies that were performed in early childhood showed predictive value of neurocognitive functions for future ADHD. These studies, however, are only of practical value if neurocognitive functioning can explain some of the variance over and above ADHD symptoms at baseline. When failing to adjust for early ADHD symptoms, the neurocognitive functions may, at best, be viewed as a good proxy of early ADHD severity. In four of the nine studies that investigated the predictive value of early neurocognitive functioning on future ADHD symptoms or diagnosis, baseline behavioral characteristics were taken into account, ranging from baseline Global Assessment of Functioning (GAF-) scores to early ADHD symptoms. These studies showed that predictive value for future ADHD remains for cognitive control (inhibition, switching and planning, verbal working memory, executive functioning), reward delay aversion, alerting attention, and visual processing (Biederman et al., 1996; Campbell & von Stauffenberg, 2009; Kalff et al., 2002; Wåhlstedt et al., 2008). These findings indicate that both lower and higher order neurocognitive functions measured in young childhood, predict ADHD diagnosis or symptoms a few years later and above ADHD symptoms at baseline. This is of clinical relevance, since neurocognitive weaknesses in young children are thus a risk factor in the development of ADHD diagnosis or symptoms. There is one point of importance. Studies predicting future ADHD were all performed in very young childhood, thus although neurocognitive functions are risk factors for ADHD diagnosis or symptoms, these studies were not informative in terms of ADHD persistence or remittance.

Since ADHD persisters and remitters could not be differentiated based on neurocognitive functioning in this review, the question of the actual value of neurocognitive functioning in the development
of ADHD remains. Although it is possible that neurocognitive functioning in general acts as an epiphenomenon in ADHD, it has been shown that it is valuable to define neuropsychologically impaired subtypes in ADHD (Durston et al., 2011; Nigg, Wilcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke et al., 2010; Van der Meer et al., 2012). These neurocognitive subtypes can add to the broader definition of ADHD at the behavioral level, creating more homogeneous groups that may profit from more specialized and individualized treatment (Nigg et al., 2005). A related question is whether remitters need to be treated or monitored for apparent neurocognitive problems, because these problems might impact outcomes that may be associated with ADHD, such as substance abuse, social functioning, and school performance (see for example Diamantopoulou, Rydell, Thorell, & Bohlin, 2007; Latimer et al., 2003; Miller & Hinshaw, 2010; Molina & Pelham, 2001). Thus, even though ADHD symptoms may be in remission, neurocognitive deficits may negatively impact on other important outcomes, which were not reviewed in this study.

4.1. Limitations and future recommendations

This review has some limitations. First, our review is limited by the number of studies available in the literature, especially studies that take into account reward processing and temporal processing. Also, in some domains only one aspect was investigated, as for example only reward delay aversion was assessed in studies on reward processing, or RTT in studies on temporal processing, while the predictive value of differences in sensitivity to different types of incentives (reward versus response cost or differences in reward intensity) or time discrimination or time (re)production is not investigated so far. Second, studies differed widely in study design, group definitions, or time between assessments and adjustment for possible confounders. In order to minimize issues with regard to different study designs and group definitions, we aggregated results from a similar study design (type-a, -b, or -c, Fig. 1) and aggregated definitions across studies used to define persistence and remittance (i.e., full persister, full/partial persister, full remitter and full/partial remitter; Table 1). Group definitions in terms of persistence/remittance may have an uncalled effect on our results regarding the predictive value of neurocognitive functioning in relation to ADHD. Two studies used strict definitions of ADHD persistence and ADHD remittance and removed subthreshold cases from their analyses (Bédard et al., 2010; Halperin et al., 2008). Other studies combined strict criteria for ADHD persistence with a loose definition of remittance (not fulfilling full criteria for a DSM diagnosis of ADHD) (Fischer et al., 2005; Hart et al., 1995), or combined loose criteria for ADHD persistence (all subjects with more than three or four symptoms of inattention or hyperactivity/impulsivity) with a more strict definition of remittance (Barkley & Fischer, 2011; Biederman et al., 1996; Biederman, Petty, Ball, et al., 2009; Mick et al., 2011). Importantly, differences in persistence and remittance definitions are not a likely explanation of the results in this review, since even the study using the most strict criteria to define ADHD persistence and remittance (Bédard et al., 2010) did not differentiate between these two groups using neurocognitive measures. Third, studies differed in sample selection. Two studies included clinical samples (Hart et al., 1995; Langley et al., 2010), and two studies used samples derived entirely from the general population, with one assessing a large birth cohort (Campbell & von Stauffenberg, 2009) and one investigating a random sample drawn from a full sample (Berlin et al., 2003). The other studies combined clinical samples (subjects with ADHD) with control subjects or drew a selective subsample from a random population sample, based on some behavioral characteristics. The two studies in our review that used clinical samples reported negative results, that is, these studies did not show predictive value of intellectual functioning for ADHD persistence or ADHD symptom change. Studies using participants from a general population sample were able to differentiate ADHD persisters and remitters from controls based on several neurocognitive functions, indicating that findings might be related to the nature of the sample studied, especially regarding patient/control comparisons.

Differences in treatment between ADHD persisters and ADHD remitters may have an uncalled effect on the results. In this review, five out of eighteen studies investigated if medication use influenced the relation between neurocognitive (dys)functioning and ADHD outcome (Barkley & Fischer, 2011; Biederman et al., 1996; Langley et al., 2010; Mick et al., 2011; Vaughn et al., 2011). None of these studies reported contamination by medication of the neurocognitive results. Also, one study reported that the rate of ADHD symptom decline was independent of medication use (Hart et al., 1995). Since results are similar for studies that did and did not take into account the possible effects of medication, this suggests that medication effects are not a cofactor in explaining the findings of our review. Future studies should investigate to what extent medication effects may influence the results, to prevent uncalled effects. In addition, it is important to ensure that findings for complex higher order neurocognitive functions may not be explained by more basic functions such as processing speed or alerting attentional demands. Since there were no differences between lower order and higher order neurocognitive functions (neither of them differentiated between ADHD persisters and ADHD remitters), it is not very likely that differences in lower level functions will have influenced results for higher level neurocognitive functions in this review. This is confirmed in the one study that adjusted results for group differences in basic processing speed (Kaliff et al., 2005). Future studies should carefully consider neurocognitive measures as they usually tap into more than one domain, and include pure measures of lower level neurocognitive functions to check if differences in these lower level components may explain results for higher order functions. Similarly, there may be differences in the interpretation of dependent variables derived from the neurocognitive tasks. For example, SDRT has not only been interpreted as reaction time variability, but it can also reflect little attentional lapses, or state regulation problems (Tamm et al., 2012). In the case of other interpretations, SDRT may nevertheless be considered as reflecting a more automatically controlled, lower level neurocognitive function. In addition, in future studies, follow-up intervals should be wide enough for predicting future ADHD (persistence), as to make sure that the child may have entered another developmental phase. Further, neurocognitive predictive effects should be separately examined for the three symptom domains of ADHD, which was done only in a minority of studies incorporated in our review (Berlin et al., 2003; Brocki et al., 2010; Campbell & von Stauffenberg, 2009; Marakovitz & Campbell, 1998; Wahlstedt et al., 2008). Future studies should ideally include both behavioral and neurocognitive assessments in childhood, adolescence and/or adulthood, as to investigate the additive predictive effect of neurocognitive functioning beyond behavioral functioning over time and different developmental phases. Efforts should be made to use identical measures over time.

5. Conclusion

Despite the heterogeneity of included studies, it can be concluded that ADHD persistence and ADHD remittance cannot be reliably differentiated based on either higher or lower level neurocognitive functioning: both groups generally show poorer functioning compared to typical controls. Furthermore, higher and lower order neurocognitive functions are comparably predictive for the development of future ADHD symptoms (still in childhood), with some predictive effect over and above baseline ADHD. The apparent disentanglement of the age-related changes in neurocognitive deficits and ADHD symptoms may cautiously suggest that neurocognitive deficits can be best seen as episphemomena, i.e., related to the same etiological factors as the ADHD symptoms but not directly mediating between
etiological factors and phenotype. Nevertheless, neurocognitive functions may still be useful in creating more homogeneous subgroups of children with ADHD with distinct prognoses and treatment benefits (Nigg et al., 2005). Better designed studies (longitudinal studies following children from early childhood into adult age, measuring cognition, ADHD and other relevant indicators, thereby also targeting neglected domains such as reward processing, temporal processing, basic information processing speed), are needed to firmly support our conclusions.

References

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders (4th ed.).

Bridgett, D. J., & Walker, M. E. (2006). Intellectual functioning in adults with ADHD: A basic information processing speed), are needed to better designed studies (longitudinal studies following children from early childhood into adult age, measuring cognition, ADHD and other relevant indicators, thereby also targeting neglected domains such as reward processing, temporal processing, basic information processing speed), are needed to firmly support our conclusions. Better designed studies (longitudinal studies following children from early childhood into adult age, measuring cognition, ADHD and other relevant indicators, thereby also targeting neglected domains such as reward processing, temporal processing, basic information processing speed), are needed to firmly support our conclusions.


References marked with an asterisk indicate studies included in the meta-analysis.