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Cognitive heterogeneity in adult attention deficit/hyperactivity disorder: A systematic analysis of neuropsychological measurements

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Abstract
Attention Deficit/Hyperactivity Disorder (ADHD) in childhood is associated with impaired functioning in multiple cognitive domains: executive functioning (EF), reward and timing. Similar impairments have been described for adults with persistent ADHD, but an extensive investigation of neuropsychological functioning in a large sample of adult patients is currently lacking. We systematically examined neuropsychological performance on tasks measuring EF, delay discounting, time estimation and response variability using univariate ANCOVA's comparing patients with persistent ADHD (N=133, 42% male, mean age 36) and healthy adults (N=132, 40% male, mean age 36). In addition, we tested which combination of variables provided the highest accuracy in predicting ADHD diagnosis. We also estimated for each individual the severity of neuropsychological dysfunctioning. Lastly, we investigated potential effects of stimulant medication and a history of comorbid major depressive disorder (MDD) on performance. Compared to healthy adults, patients with ADHD showed impaired EF, were more

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impulsive, and more variable in responding. However, effect sizes were small to moderate (range: 0.05–0.70) and 11% of patients did not show neuropsychological dysfunctioning. The best fitting model predicting ADHD included measures from distinct cognitive domains (82.1% specificity, 64.9% sensitivity). Furthermore, patients receiving stimulant medication or with a history of MDD were not distinctively impaired. To conclude, while adults with ADHD as a group are impaired on several cognitive domains, the results confirm that adult ADHD is neuropsychologically heterogeneous. This provides a starting point to investigate individual differences in terms of impaired cognitive pathways.

1. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is a common and highly heritable neuropsychiatric disorder in childhood that is strongly persistent over time. At least 35% of all childhood patients still meet full ADHD criteria in adulthood (American Psychiatric Association, 2000), and this percentage is much higher (78%) when partial remitted patients are included (Biederman et al., 2010). ADHD has an average prevalence of 2.5–4.9% in the adult population (Simon et al., 2009). The clinical phenotype of ADHD is characterized by persistent, age-inappropriate symptoms of inattention, and/or hyperactivity and impulsivity (American Psychiatric Association, 2000).

ADHD has been associated with neurocognitive dysfunctioning, and over the years, several neuropsychological theories about ADHD etiology have been put forward. One of the most influential theories proposed ADHD to arise from a single core deficit in behavioral inhibition, which leads to secondary impairments in several executive functions (Barkley, 1997). However, this assumption of a central deficit was challenged by data showing that ADHD patients are impaired in multiple neuropsychological domains. It has therefore been proposed that there are distinct pathways to dysfunction, including executive function (EF) deficits, delay aversion, and timing problems (Castellanos et al., 2006; Sonuga-Barke et al., 2010). Although not included in the multiple pathway model, another characteristic of ADHD is performance variability. The inconsistency in performance and the high prevalence of moment-to-moment variability in reaction times is one of the most consistently reported manifestations of ADHD. Reaction time variability (RTV) received extensive discussion as an indicator of cognitive performance, although the exact nature of high RTV in ADHD is still uncertain (Kofler et al., 2013; Tamm et al., 2012).

Studies of cognitive functioning in adults with ADHD suggest that cognitive impairments found in adults resemble those observed in children with ADHD, showing equally moderate effects sizes (for meta-analytic reviews, see Boonstra et al., 2005; Hervey et al., 2004; Schoechlin and Engel, 2005). Similar results were derived from qualitative reviews (Seidman, 2006; Woods et al., 2002). Recent meta-analyses in adult ADHD focused solely on deficits found in working memory (Alderson et al., 2013) and long-term memory (Skodzik et al., 2013). Furthermore, recent experimental studies on adult ADHD show deficits in attention (Fuermaier et al., 2015; Grane et al., 2014), set-shifiting (Boonstra et al., 2010; Halleland et al., 2012; Rohlf et al., 2012) inhibition (Boonstra et al., 2010; Fuermaier et al., 2015), (working) memory (Fuermaier et al., 2015; Lundervold et al., 2015; Rohlf et al., 2012), delay discounting (Marx et al., 2010), and increased reaction time variability (Feige et al., 2013; Gmehlin et al., 2014; Grane et al., 2014).

From the childhood literature, we know that ADHD is characterized by large heterogeneity at the neuropsychological level, which means that only a minority of ADHD patients shows deficits in each domain and that some patients with ADHD will perform in the normal range (Nigg et al., 2005b). Such heterogeneity was illustrated in a recent study on boys with ADHD (Coghill et al., 2013). Per cognitive domain merely 18–36% of the patients had an impairment, while 25% of the sample did not show deficient performance in any of the cognitive domains.

Heterogeneity in cognitive performance within a sample of ADHD patients may also arise from differences in medication use or comorbidity. Stimulants are effective for the treatment of clinical symptoms in adult ADHD (Faraone et al., 2004) and also in neuropsychological studies medication is usually seen as a potential moderator. Many neuropsychological studies in ADHD have included patients who had previously taken, or were receiving stimulant medication at the time of the study. To eliminate the acute effects of medication, most studies used a washout period (24 h or 48 h). However, stimulants may act longer than 48 h (McCarthy et al., 2014). Similarly, ADHD patients with a comorbid psychiatric disorder showed greater neuropsychological deficits than ADHD patients without comorbidity (Hervey et al., 2004) and may represent a distinct subgroup, with different cognitive profiles (Fischer et al., 2007). However, it has also been shown that cognitive deficits in adult ADHD cannot be accounted for by comorbid disorders (Nigg et al., 2005a; Silva et al., 2013). Major depressive disorder (MDD) is the most frequently observed comorbidity, and can co-occur with ADHD in up to 50% of the cases (Wilens et al., 2009). MDD has been associated with cognitive difficulties in memory, attention and problem-solving. Only two studies examined comorbid MDD in ADHD to date, both suggesting that current comorbid MDD symptoms may not influence neuropsychological profiles in ADHD (Katz et al., 1998; Riordan et al., 1999). While potential effects of comorbid MDD on cognition are often controlled for by excluding patients with current MDD from a study, many included patients will have remitted MDD. It is currently not known whether adult ADHD

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