

## HYPERACTIVITY AND INATTENTION (ADHD)

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# Attention Deficit Hyperactivity Disorder and Cognition

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### Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is characterized by a triad of symptoms of inattention, hyperactivity and impulsivity.<sup>1</sup> The disorder is highly heritable and affects around 3-5% of school-aged children.<sup>2,3</sup> In recent decades, the cognitive problems of ADHD have been widely studied. Cognition can be defined as gaining knowledge and comprehension, including thinking, knowing, remembering, judging and problem solving.

### Subject

Several causal pathway models have been proposed, trying to combine the findings of biological and cognitive abnormalities frequently found in ADHD. The cognitive models all have in common that deficits in executive functioning (EF) are one of the most prominent characteristics of ADHD. EF has been defined as "those capacities that enable a person to engage successfully in independent, purposive, self-serving behaviour".<sup>4</sup> EF impairments have been reported in many studies with ADHD patients, with problems in inhibition and working memory being the most

frequently replicated.<sup>5</sup> Deficits in EF are strongly linked to abnormalities in the in the *prefrontal lobe* and *frontal-subcortical circuitry* found in patients with ADHD.<sup>6,7</sup>

## **Problem**

Even though most causative models of ADHD incorporate deficits in EF as an important factor, it is actually unknown if and to what extent deficits in EF *cause* ADHD. In other words, given that ADHD is a highly heritable disorder, is EF a heritable trait that increases the risks of developing ADHD and in what percentage of patients may it pose a causal factor?

## **Key Research Questions**

Two issues are central in order to examine whether EF deficits are causally related to ADHD:

- Given that ADHD is strongly heritable, are EF problems themselves also heritable and linked to the same genes as ADHD?
- What percentage of children with ADHD actually suffers from EF problems?

## **Recent Research Results**

*Are EF problems heritable and linked to the same genes as ADHD?*

A necessary first step in determining if EF deficits are heritable is to study EF performance in a twin design. A twin design allows for disentangling the influence of heritable and environmental influences on EF. Several twin studies have examined EF performance.<sup>12-16</sup> At ages 5 and 12, about 50% of performance on several EF tasks appeared attributable to genetic factors.<sup>16</sup> Other studies have yielded similar percentages of around 40% to 50%,<sup>12,13,15</sup> suggesting performance on EF tasks is moderately heritable. Furthermore, genetic factors appear an important mediator of *stability* of EF during childhood.<sup>14</sup>

A second step in determining if EF deficits are heritable and linked to the same genes as ADHD is to study the EF performance in relatives of ADHD patients. This sheds light on the familiarity of EF deficits in ADHD. Siblings, for instance, share on average 50% of their genes. It is therefore likely that non-affected siblings of a child with ADHD carry risk genes for ADHD without having the phenotypic expression of ADHD. If EF deficits are indeed familiarly linked to ADHD, non-affected siblings will show the same EF deficits, probably to a somewhat lesser extent, than their ADHD

affected siblings.

Several studies have targeted EF within ADHD families and results support the hypothesis that EF deficits are familial and also present (to a lesser extent) in non-affected relatives of ADHD patients.<sup>5,17-21</sup> Studies that have specifically targeted inhibition or interference control as an executive function have also reported promising results, with non-affected relatives displaying subtle deficits in this area and relatives resembling each other in their performance.<sup>22-26</sup> These findings suggest that EF deficits are familial. Although this is not sufficient to suggest that EF problems are heritable; it is at least consistent with it.

A final step in examining whether EF deficits are linked to the same genes as ADHD is to examine EF performance in relation to ADHD candidate genes and/or to use EF performance in linkage analyses using ADHD pedigrees. Both of these strategies have rarely been carried out due to the large sample sizes that are required to generate sufficient power for the analyses. Preliminary results indicate that *polymorphisms* in a gene (*Dopamine Receptor D4* gene) that has been most frequently replicated in relation to ADHD indeed also relates to EF.<sup>15,27-30</sup> One linkage study found a genome-wide significant linkage signal on chromosome 13q12.<sup>11</sup> using an EF measure (verbal working memory) in ADHD pedigrees, suggesting genes on this location may influence both ADHD and EF performance.<sup>31</sup> In addition, another linkage study indicated that a region on chromosome 3q13 was related to both a composite measure of EF and to inattention symptoms of ADHD, suggesting these EF deficits may relate to the same genes as ADHD.<sup>32</sup>

*What percentage of children with ADHD suffer from EF problems?*

The percentage of children suffering from EF problems strongly depends on the definition of an executive function deficit (EFD).<sup>8</sup> There is no consensus on what actually constitutes an EFD, but most definitions entail a performance below the 10th percentile of a matching control group on at least one, two or three EF tasks. On a group level, children with ADHD virtually always perform worse on EF measures than children in the control group. However, on an individual level, a proportion of children with ADHD outperform a proportion of the children in the control group.<sup>9</sup> In other words, not every child with ADHD suffers from an EFD. EF weaknesses are neither necessary nor sufficient to cause all cases of ADHD.<sup>9</sup> Rather, other cognitive functions, motivational problems or, in some cases, response to family distress or peer problems, may constitute pathways to ADHD.<sup>10,11</sup> About a third of the children show a moderately severe EFD, defined as being impaired on three or more EF measures.<sup>11</sup>

## Research Gaps

In order to determine whether EF deficits found in a proportion of ADHD patients are indeed causative of ADHD in this group, a more comprehensive approach is required than that has currently been undertaken. That is, only a few studies examined EF in a familial context and most studies have been underpowered for genetic analyses. An even larger problem is that results are difficult to compare because of the use of different tasks and methods to measure the same executive function. This is particularly troublesome for attempts to combine cognitive datasets across sites for increased statistical power in genetic analyses. Thus, in order to determine whether EF deficits found in a proportion of ADHD patients are indeed causative of ADHD, it is necessary to administer EF tasks that have good validity, reliability, heritability and norm data. Using the same “golden standard” tasks would make it possible to combine different samples across research sites. This would greatly enhance comparability of data and would boost power for genetic analyses, leading to more robust results hopefully applicable in clinical practice.

## Conclusions

Performance on EF tasks is moderately heritable and genetic factors appear an important mediator of *stability* of EF during childhood. EF deficits are familially linked to ADHD and are possibly related to, amongst others, the Dopamine Receptor D4 gene, which is also related to ADHD. In other words, (partly) genetically-based deficits in EF may *cause* ADHD. However, only a subgroup of ADHD patients (about 30%) suffers from moderately severe EF problems, suggesting EF weaknesses are neither necessary nor sufficient to cause all cases of ADHD.

## Implications for Parents, Services and Policy

Cognitive tests are still not sensitive or specific enough to be used in daily practice for diagnosing ADHD. We still have to rely on parents’ and teachers’ reports (or self report in adolescents and adults with suspected ADHD) for diagnosis. However, recent longitudinal data indicates that childhood EF predicts future academic achievement, social functioning and global functioning in ADHD patients.<sup>33</sup> These results suggest it may benefit clinical practice when EF impairments are assessed and treated, particularly in those at high-risk for negative outcomes, in order to prevent long-term difficulties across a range of important functional domains.<sup>33</sup> Intervention strategies for EF deficits are still in their primary phase of development, but already positive results have been obtained.<sup>34,35</sup> A subgroup of children with ADHD that suffers from moderately severe EF deficits (+/-

30%) may benefit from these interventions.

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