

## HYPERACTIVITY AND INATTENTION (ADHD)

---

# Attention Deficit Hyperactivity Disorder and Cognition

**Nanda Rommelse, PhD**

Radboud University Medical Center, Department of Psychiatry, Netherlands

February 2010

### 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.

## **References**

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV*. 4<sup>th</sup> ed. Washington, DC.: American Psychiatric Association; 1994.
2. Faraone S, Biederman J, Mick E. The age dependent decline of attention-deficit/hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine* 2006;36(2):159-165.
3. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2005;57(11):1313-1323.
4. Lezak MD, Howieson DB, Loring DW. *Neuropsychological assessment*. 4th ed. New York, NY: Oxford University Press; 2004.
5. Rommelse NN, Altink ME, Oosterlaan J, Buschgens CJ, Buitelaar J, Sergeant JA. Support for an independent familial segregation of executive and intelligence endophenotypes in ADHD families. *Psychological Medicine* 2008;38(11):1595-1606.
6. Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nature Reviews Neuroscience* 2002;3(2):617-628.
7. Durston S. A review of the biological bases of ADHD: what have we learned from imaging studies? *Mental Retardation and Developmental Disabilities Research Reviews* 2003;9(3):184-195.
8. Biederman J, Monuteaux MC, Doyle AE, Seidman LJ, Wilens TE, Ferrero F, Morgan CL, Faraone SV. Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children. *Journal of Consulting and Clinical Psychology* 2004;72(5):757-766.
9. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Journal of Abnormal Child Psychology* 2009;37(11):551-564.
10. Wåhlstedt C, Thorell LB, Bohlin G. Heterogeneity in ADHD: neuropsychological pathways, comorbidity and symptom domains. *Journal of Abnormal Child Psychology* 2009;37(4):551-564.
11. Nigg JT, Willcutt EG, Doyle AE, Sonuga-Barke EJ. Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes? *Biological Psychiatry* 2005;57(11):1224-1230.
12. Anokhin AP, Heath AC, Ralano A. Genetic influences on frontal brain function: WCST performance in twins. *Neuroreport* 2003;14(15):1975-1978.
13. Taylor J. Heritability of Wisconsin Card Sorting Test (WCST) and Stroop Color-Word Test performance in normal individuals: implications for the search for endophenotypes. *Twin Research and Human Genetics* 2007;10(6):829-834.
14. Polderman TJ, Posthuma D, De Sonneville LM, Stins JF, Verhulst FC, Boomsma DI. Genetic analyses of the stability of executive functioning during childhood. *Biological Psychology* 2007;76(1-2):11-20.
15. Doyle AE, Faraone SV, Seidman LJ, Willcutt EG, Nigg JT, Waldman ID, Pennington BF, Peart J, Biederman J. Are endophenotypes based on measures of executive functions useful for molecular genetic studies of ADHD? *Journal of Child Psychology and Psychiatry* 2005;46(7):774-803.
16. Polderman TJ, Gosso MF, Posthuma D, Van Beijsterveldt TC, Heutink P, Verhulst FC, Boomsma DI. A longitudinal twin study on IQ, executive functioning, and attention problems during childhood and early adolescence. *Acta Neurologica Belgica* 2006;106(4):191-207.
17. Seidman L, Biederman J, Monuteaux M, Weber W, Faraone SV. Neuropsychological functioning in nonreferred siblings of children with attention deficit hyperactivity disorder. *Journal of Abnormal Psychology* 2000;109(2):252-265.
18. Nigg JT, Blaskey LG, Stawicki JA, Sachek J. Evaluating the endophenotype model of ADHD neuropsychological deficit: Results for parents and siblings of children with ADHD combined and inattentive subtypes. *Journal of Abnormal Psychology* 2004;113(4):614-625.
19. Waldman ID, Nigg JT, Gizer IR, Park L, Rappley MD, Friderici K. The adrenergic receptor alpha-2A gene (ADRA2A) and neuropsychological executive functions as putative endophenotypes for childhood ADHD. *Cognitive, Affective, & Behavioral*

*Neuroscience* 2006;6(1):18-30.

20. Bidwell LC, Willcutt EG, DeFries JC, Pennington BF. Testing for neuropsychological endophenotypes in siblings discordant for attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2007;62(9):991-998.
21. Uebel H, Albrecht B, Asherson P, Börger NA, Butler L, Chen W, Christiansen H, Heise A, Kuntsi J, Schäfer U, Andreou P, Manor I, Marco R, Miranda A, Mulligan A, Oades RD, van der Meere J, Faraone SV, Rothenberger A, Banaschewski T. Performance variability, impulsivity errors and the impact of incentives as gender-independent endophenotypes for ADHD. *Journal of Child Psychology and Psychiatry* 2010;51(2):210-218.
22. Slaats-Willemse D, Swaab-Barneveld H, De Sonneville L, Buitelaar J. Familial clustering of executive functioning in affected sibling pair families with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 2005;44(4):385-391.
23. Slaats-Willemse D, Swaab-Barneveld H, De Sonneville L, Van der Meulen E, Buitelaar J. Deficient response inhibition as a cognitive endophenotype of ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 2003;42(10):1242-1248.
24. Crosbie J, Schachar R. Deficient inhibition as a marker for familial ADHD. *American Journal of Psychiatry* 2001;158(11):1884-1890.
25. Schachar RJ, Crosbie J, Barr CL, Ornstein TJ, Kennedy J, Malone M, Roberts W, Ickowicz A, Tannock R, Chen S, Pathare T. Inhibition of motor responses in siblings concordant and discordant for Attention Deficit Hyperactivity Disorder. *American Journal of Psychiatry* 2005;162(6):1076-1082.
26. Goos LM, Crosbie J, Payne S, Schachar R. Validation and extension of the endophenotype model in ADHD patterns of inheritance in a family study of inhibitory control. *American Journal of Psychiatry* 2009;166(6):711-717.
27. Boonstra AM, Kooij JJS, Buitelaar JK, Oosterlaan J, Sergeant JA, Heister JG, Franke B. An exploratory study of the relationship between four candidate genes and neurocognitive performance in adult ADHD. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 2008;147(3):397-402.
28. Altink ME, Rommelse NNJ, Slaats-Willemse DIE, Arias Vasquez A, Franke B, Buschgens CJM, Fliers EA, Faraone SV, Sergeant JA, Oosterlaan J, Buitelaar JK. The dopamine receptor D4 7-repeat allele influences neurocognitive functioning, but this effect is moderated by age and ADHD status. *Journal of Child Psychology and Psychiatry*. In press.
29. Durston S, de Zeeuw P, Staal WG. Imaging genetics in ADHD: a focus on cognitive control. *Neuroscience and Biobehavioral Reviews* 2009;33(5):674-689.
30. Loo SK, Rich EC, Ishii J, McGough J, McCracken J, Nelson S, Smalley SL. Cognitive functioning in affected sibling pairs with ADHD: familial clustering and dopamine genes. *Journal of Child Psychology and Psychiatry* 2008;49(9):950-957.
31. Rommelse NN, Arias-Vásquez A, Altink ME, Buschgens CJ, Fliers E, Asherson P, Faraone SV, Buitelaar JK, Sergeant JA, Oosterlaan J, Franke B. Neuropsychological endophenotype approach to genome-wide linkage analysis identifies susceptibility loci for ADHD on 2q21.1 and 13q12.11. *American Journal of Human Genetics* 2008;83(1):99-105.
32. Doyle AE, Ferreira MA, Sklar PB, Lasky-Su J, Petty C, Fusillo SJ, Seidman LJ, Willcutt EG, Smoller JW, Purcell S, Biederman J, Faraone SV. Multivariate genomewide linkage scan of neurocognitive traits and ADHD symptoms: suggestive linkage to 3q13. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 2008;147B(8):1399-1411.
33. Miller M, Hinshaw SP. Does childhood executive function predict adolescent functional outcomes in girls with ADHD? *Journal of Abnormal Child Psychology*. In press.
34. Papazian O, Alfonso I, Luzondo RJ, Aragues N. Training of executive function in preschool children with combined attention deficit hyperactivity disorder: a prospective, controlled and randomized trial. *Revista de Neurologia* 2009;48(suppl 2):S119-S122.
35. Klingberg T, Fernell E, Olesen PJ, Johnson M, Gustafsson P, Dahlström K, Gillberg CG, Forsberg H, Westerberg H. Computerized training of working memory in children with ADHD—a randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 2005;44(2):177-186.