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Neuropsychological endophenotypes in attention-deficit/hyperactivity disorder: a review of genetic association studies

Oussama Kebir · Ridha Joober

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Abstract As a relatively large body of research has been published up to now, it may be informative to explore whether the use of endophenotypes has produced consistent findings in attention-deficit hyperactivity disorder (ADHD). We reviewed the results of genetic studies investigating associations between putative susceptibility genes for ADHD and neuropsychological traits relevant for this disorder. A PubMed database search identified 47 studies. Most of them ($n = 36$) examined a single candidate gene, while seven studies examined two or three genes and only four studies examined 10 genes or more. The most investigated genes were *DRD4*, *DAT1*, *COMT*, *MAOA, and DBH*. Regarding *DRD4*, association of high reaction time variability with the 7-R allele absence appears to be the most consistent result. Speed of processing, set shifting, and cognitive impulsiveness were less frequently investigated, but seem to be altered in the 7-R allele carriers. Regarding *DAT1*, majority of studies reported negative results indicating that this gene may have a modulating effect rather than direct influence on cognitive functioning. The other genes were investigated in fewer studies, and the reported findings need to be replicated. The principal methodological issues that could represent confounding factors and may explain conflicting results are discussed.

Keywords ADHD · Association study · Cognitive · Genetics · Neuropsychological endophenotype

O. Kebir
INSERM, U894, University Paris Descartes, Paris, France

R. Joober
Department of Psychiatry, McGill University, Montreal, QC, Canada

R. Joober
Douglas Hospital Research Centre, Montreal, QC, Canada

R. Joober (✉)
Douglas Mental Health University Institute, McGill University, 6875 boul. Lasalle, Montréal, QC H4H 1R3, Canada
e-mail: ridha.joober@douglas.mcgill.ca

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most frequent childhood onset disorders with an average prevalence of 5% worldwide [70]. It is characterized by age inappropriate levels of inattention, hyperactivity and impulsivity and impairs social, academic, and occupational functioning in children, adolescents, and adults. A strong genetic contribution to ADHD was evidenced through twin, family and adoption studies, and considerable efforts have been made to identify genes involved in its etiology [17]. However, results of candidate gene associations for ADHD yielded largely inconsistent results. Since it was advanced that this inconsistency could be at least in part due to the heterogeneity and complexity of this clinical syndrome [31, 95], it has been proposed that the use of simpler phenotypes as endophenotypes might increase detection of genetic effects [21, 39, 97]. Endophenotypes refer to measurable components that reduce the complexity of the phenotype and lie closer to basic mechanisms than the visible diagnosis [39].

Many neuropsychological models of ADHD were proposed and could represent candidate endophenotypes. Deficit in response inhibition is thought to impair the capacity of the individual to withhold a prepotent response when engaged in a task [8] and was proposed as an endophenotype by several studies [16, 25, 38, 88]. Other deficits in executive function are also retrieved in children

with ADHD namely impairments on measures of working memory, planning and organization, set shifting, and processing speed [98]. Several of these deficits have been validated as endophenotypes [16, 28, 40, 80, 82]. Alternatively, many features of ADHD are described as related to problems with regulating allocation of energy and effort [86]. In a "cognitive–energetic" model, this state regulation is defined as the allocation of extra effort to sustain performance in the presence of stressors such as high presentation rates of stimuli. Reaction time (RT) variability, one of the most replicated deficits in ADHD across a variety of tasks, is thought to be one of the best indices of state regulation difficulties and has been recently examined as an endophenotype with consistent findings [3, 16, 79]. Additionally, it has also been proposed that ADHD may result from emotional deregulation in the form of delay aversion [91]. According to this model, waiting is associated with a negative emotional tone in children with ADHD. This negative emotion associated with delaying gratification can be appreciated using tasks that require them to wait longer to maximize gain. However, this model is not yet established as a valid endophenotype [16, 18].

The purpose of the current study is, therefore, to offer an updated review of the results of association studies using neuropsychological endophenotypes in ADHD that we have previously published [46]. In addition to the limitations of the included studies, the present review addresses particularly the question of genotype–endophenotype–phenotype relations.

Methods

We undertook a search of English-language journal abstracts available online through the National Library of Medicine's PubMed database using the keywords "ADHD" and "gene". All abstracts of human studies indexed prior to July 2010 were screened ($n = 839$). The search was completed with a screening of the references of the selected papers. Minimum selection criteria for these genetic association studies were the use of clinically established diagnoses and of neuropsychological measures. When multiple publications from a particular research group reported data for overlapping sample, results for the study that presented the largest dataset were included. Studies that selected samples based on a disorder other than ADHD were not considered.

Results

We included in our review 47 studies. Most of them ($n = 36$) examined a single candidate gene, while seven studies examined two or three genes and only four studies examined 10 genes or more. Only four studies comprised adult samples.

Candidate gene approach with substantial findings: *DRD4*, *DAT1*, *COMT*, *MAOA, DBH*

Dopamine receptor 4 (DRD4)

The *DRD4* gene been widely investigated in ADHD because D4 receptors are mainly expressed in brain regions such as the anterior cingulate cortex that are known to be important for attention and inhibition [5, 71]. A meta-analysis of 26 studies showed that the 7-R allele of the polymorphic variable number tandem repeat (VNTR) within exon 3 was associated with ADHD (OR = 1.33, 95% CI 1.15–1.54) [37].

Initially, it was expected that the 7-R risk allele will be associated with poor cognitive scores. However, five studies reported opposite results (Table 1). A first study reported that probands carrying at least one copy of the 7-R allele did not display neuropsychological deficits ($n = 44$) [92]. In this study, a three task battery was used and consisted of a color-word task based on conflict resolution, a cued-detection task requiring shifting and maintenance of attention and a go-change task. Moreover, probands without the 7-R allele showed longer RTs and greater standard deviations. The authors invoked the possibility that in these children, ADHD develops through alternative nongenetic risk factors and that the 7-R allele may have been associated with behavioral features rather than cognitive deficits. A second study using the test of variables of attention (TOVA) reported that children with ADHD carrying the 7-R allele exhibited better commission and omission scores and lower RT variability compared with those carrying the 2-R allele ($n = 132$) [62]. Additionally, a "dose effect" across the different alleles was found with a trend for an inverse correlation between number of repeats and impaired performance. A third study reported that carriers of the 7-R allele performed significantly better than noncarriers in terms of commission errors and had less RT variability on the sustained attention to response task (SART) ($n = 51$) [13]. Furthermore, the probands with the 7-R allele did not differ from a control group with respect to their SART performances. In another study from the same group, spectral analysis of RT variability suggested that the association of this pattern of attentional scores with the absence of the 7-R allele was somewhat specific to ADHD ($n = 68$) [42]. In adults with ADHD, participants with the 7-R allele performed better on a verbal short-term memory task (digit span) than noncarriers ($n = 45$). However, absence of this allele was associated with nonaltered

Table 1 Summary of association studies of *DRD4* VNTR polymorphism

Study	*N*	Population	Cognitive tests	Results
Swanson et al. 2000 [92]	44	Children	Stroop task, Cued-detection task, Go-change task	7-R allele associated with long RTs and great SD
Manor et al. 2002 [62]	132	Children	TOVA	7-R allele associated with nonaltered commission and omission scores and low RT variability
Bellgrove et al. 2005 [13]	51	Children	SART	7-R allele associated with nonaltered commission score and low RT variability
Johnson et al. 2008 [42]	68	Children	SART	7-R allele associated with high RT variability
Boonstra et al. 2008 [20]	45	Adults	CPT, Verbal and figural fluency, TOL, SOPT, WCST, WAIS	7-R allele associated with nonaltered visuo-constructive ability and set shifting
Langley et al. 2004 [55]	78	Children	CPT, MFFT, Stop task, go-nogo task	7-R allele associated with great impulsiveness but did not influence response inhibition or CPT scores
Waldman 2005 [97]	137	Children	TMT	7-R allele associated with long response times
Kieling et al. 2006 [48]	90	Children	CPT	7-R allele associated with high commission errors
				4/4 genotype associated with low commission and omission errors
Barkley et al. 2006 [7]	80	Adolescents	MFFT, GDS, WCST	No association
DeYoung et al. 2006 [26]	29	Adults	IQ	No association
Kollins et al. 2008 [50]	180	Children	CPT	No association

CPT continuous performance test, *DRD4 VNTR* dopamine receptor 4 variable number tandem repeat, *GDS* Gordon detection system, *IQ* intelligence quotient, *MFFT* matching familiar figures test, *RT* reaction time, *SART* sustained attention to response test, *SOPT* self-ordered pointing test, *TMT* trail making test, *TOL* tower of London, *TOVA* test of variables of attention, *WAIS* Wechsler adult intelligence scale, *WCST* Wisconsin card sorting test

visuo-constructive ability (WAIS-III subtest) and set shifting (Wisconsin card sorting test, WCST) [20].

Three other subsequent studies reported opposite results. The first study included medication-naive children with ADHD ($n = 78$) and found that the group with the 7-R allele appeared to show greater impulsiveness (faster and less accurate responses in the matched familiar figures test, MFFT, and faster RTs in the stop task) than those without this allele [55]. However, the 7-R allele did not influence response inhibition (stop and go/no-go tasks) or continuous performance test (CPT) measures. In the second study, performances on the trail making test (TMT, A: processing speed; B: set-shifting ability) were examined as an endophenotype in a sample of children with ADHD ($n = 137$) and their siblings [97]. Performances in the two parts of the TMT were associated with *DRD4* genotypes. Participants carrying two copies of the 7-R allele exhibited longer response times, independently of diagnostic status. The third study reported that probands with one or more 7-R alleles displayed more commission errors on the CPT, whereas 4-R homozygosity was associated with reduced commission and omission errors ($n = 90$) [48].

Three negative studies were published. Barkley et al. [7], in a longitudinal study, reported no differences between ADHD adolescents with and without the 7-R allele on the MFFT, the Gordon diagnostic system (GDS), and the WCST ($n = 80$). DeYoung et al. [26] did not found relation between the IQ and the 7-R allele in an adult sample ($n = 29$). Similarly, Kollins et al. [50] failed to find an association between the 7-R allele and the CPT scores in 180 children.

Apart from the VNTR polymorphism, one study reported a significant association with a single nucleotide polymorphism (SNP) located in *DRD4*. Bellgrove et al. [13] found that probands' homozygosity for the A allele at rs1800955 (in the promoter region at position –521) was associated with greater RT variability in the SART ($n = 51$). Moreover, family-based analysis showed that high errors in a composite score of commission and omission errors predicts transmission of the A allele from heterozygous parents to affected children. Results were negative for rs747302 (position–616). In adults with ADHD, homozygous for the long allele of the 120 bp duplicated repeat polymorphism performed better on a measure for verbal memory (California Verbal Learning test) than other genotypes ($n = 45$) [20]. Two subsequent studies with larger samples failed to show significant association with a number of SNPs. CPT scores were not associated with five SNPs (HCV1611535, rs35134589, rs3758653, rs936461, rs11246226) in 180 affected children

[50]. Equally, attention network test scores were not associated with three SNPs (rs6350, rs403636, rs463379) in 181 children [51].

In summary, the CPT and derived tasks (SART, TOVA, and GDS) were the most used cognitive tests. Association of high RT variability with the 7-R allele absence appears to be the most consistent result. Other cognitive markers as speed of processing (TMT A), set shifting (TMT B), and cognitive impulsiveness (MFFT) seem to be altered in the 7-R allele carriers, but these results need replication. No effect of genotype was found on response inhibition (the stop and go/no-go tasks). For other polymorphisms, four studies found no or only few associations.

Dopamine transporter (DAT1)

The *DAT1* gene codes for a solute carrier protein responsible for the reuptake of dopamine from the synaptic cleft back to the presynaptic neuron. Homozygosity for the 10-R allele of VNTR polymorphism located in the 3′-untranslated region was reported to be associated with high dopamine transporter protein in the striatum [22, 41] a region where it is heavily expressed [52, 53] and where it serves as the primary means of dopamine reuptake [34]. A meta-analysis of 34 studies found a significant but modest association between this allele and ADHD (OR = 1.12, 95% CI: 1.00–1.27) [37].

Five studies investigating several executive tasks in relation to *DAT1* polymorphisms in ADHD children reported negative results [7, 20, 58, 74, 100]. However, a sixth study reported that while there was no association with WCST measures of performance, better performance on other indices such as the tower of London (TOL), the self-order pointing task, and the Wechsler intelligence scale for children-III (WISC-III) arithmetic and digit span subtests were found to be associated to the 10/10 genotype compared with the 9/10 genotype ($n = 196$) [44] (Table 2).

In regard to attention tests, two studies reported negative results. Barkley et al. [7] reported that the 10-R allele was not associated with performance on the GDS, a continuous performance, like test in adolescents and adults with ADHD ($n = 147$). A second study using tag SNPs failed to find significant association between CPT scores and *DAT1* in 180 children [50]. However, four other studies provide conflicting results in relation to omission and commission errors from CPT and related tasks (SART, TOVA, and GDS). Loo et al. [57] reported that children carrying two copies of the 10-R allele exhibit higher commission errors, impulsive responses (β score), and RT variability on the CPT compared with carriers of the 9-R allele ($n = 27$). Bellgrove et al. [12], using the SART, found high RT variability in children who were homozygous for the 10-R allele. However, in this study, the two groups did not differ in omission and commission errors ($n = 22$). In contrast, Oh et al. [69] reported fewer omission errors in the TOVA in patients with two copies of the 10-R allele compared with carriers of one copy ($n = 44$). No significant differences were observed between the two groups with regard to commission errors, RTs or RT variability. In a fourth study, probands with the 10/10 genotype made less commission errors in the CPT than those with 9/10 genotype but no differences in omission errors, RT, or in IQ were observed ($n = 85$) [49] (Table 2).

Some studies reported a relation of *DAT1* with measures of spatial attentional asymmetry. Bellgrove et al. [12], using the gray-scale task, reported that probands with two copies of the 10-R allele showed an attenuated spatial asymmetry, whereas heterozygous children showed the typical leftward attentional asymmetry ($n = 22$). In a subsequent study with an extended sample ($n = 96$), they reported that left-sided inattention was associated with the 10-R allele of the 3'UTR VNTR but not with the intron 8 VNTR polymorphism [9]. A recent study reported that children with ADHD homozygous for the 10/3 haplotype (formed by the 10-R allele of the 3'UTR VNTR and the 3-R allele of the intron 8 VNTR) had more spatial reorienting deficits for left visual field targets ($n = 50$) [14]. Lastly, a study using the attention network test that evaluates simultaneously alerting, orienting, and executive control reported a tendency for an association between alerting and executive control performance and a SNP (rs 6350) on *DAT1* in 181 children [51].

In summary, majority of studies reported negative results. This suggests that the effect of *DAT1* on the ADHD phenotype is not mediated by neuropsychological performance and that this gene may have a modulating effect rather than direct influence on cognitive functioning.

DRD4 × DAT1 interactions

It was speculated that the combination of the two dopaminergic risk genotypes (a copy of the *DRD4* 7-R allele and homozygosity for the *DAT1* 10-R allele) may lead to an extreme hypodopaminergic state correlated with poor cognitive function. In a longitudinal investigation of two independent birth cohorts, there was a significant association between the IQ and the number of risk genotypes in the *DRD4* and *DAT1* genes [66]. Children with ADHD symptoms carrying the two risk genotypes scored in average 8.2 IQ points lower than children with no risk genotypes. In contrast, three association studies implicating children with clinically diagnosed ADHD (total $n = 1{,}553$) failed to replicate such influence of *DAT1* and *DRD4* polymorphisms on full-IQ score [36, 45, 90]. However, an interaction between the two dopaminergic polymorphisms

Table 2 Summary of association studies of *DAT1*

Study	*N*	Population	Cognitive tests	Results
Association with executive functions				
Barkley et al. 2006 [7]	74	Adolescents	WCST, MFFT	No association
Wohl et al. 2008 [100]	146	Children	TMT, Stroop test	No association
Loo et al. 2008 [58]	540	Children	Stop-signal task, Stroop color-word test, TMT, FDI, IQ	No association
Rommelse et al. 2008 [74]	350	Children	Stop-signal task, shifting attentional set, time test, visuo-spatial sequencing, digit span, motor tasks	No association
Boonstra et al. 2008 [20]	45	Adults	Verbal and figural fluency, TOL, SOPT, WCST, WAIS	No association
Karama et al. 2008 [44]	196	Children	WCST, TOL, SOPT, WISCIII arithmetic and digit span subtests	No association with WCST 10/10 genotype associated with good performance on the TOL, the SOPT, and WISC-III subtests
Association with attentional tasks				
Barkley et al. 2006 [7]	147	Adolescents and adults	GDS	No association
Kollins et al. 2008 [50]	180	Children	CPT	No association
Loo et al. 2003 [57]	27	Children	CPT	10-R allele associated with high commission errors, impulsive responses, and RT variability
Bellgrove et al. 2005 [12]	22	Children	SART	10/10 genotype associated with high RT variability No association with omission and commission errors
Oh et al. 2003 [69]	44	Children	TOVA	10/10 genotype associated with low omission errors No association with commission errors, RTs or RT variability
Kim et al. 2006 [49]	85	Children	CPT	10/10 genotype associated with low commission errors No association with omission errors or RT

CPT continuous performance test, *FDI* freedom from distractibility index, *DAT1* dopamine transporter, *GDS* Gordon detection system, *IQ* intelligence quotient, *MFFT* matching familiar figures test, *RT* reaction time, *SART* sustained attention to response test, *SOPT* self-ordered pointing test, *TMT* trail making test, *TOL* tower of London, *TOVA* test of variables of attention, *WAIS* Wechsler adult intelligence scale, *WCST* Wisconsin card sorting test, *WISCIII* Wechsler intelligence scale for children

was reported in relation with verbal IQ—externalizing behavior correlation in 130 affected boys [45].

Catechol-O-methyltransferase (COMT)

The *COMT* gene codes for an enzyme responsible for the degradation of the catecholamines dopamine and norepinephrine. Given that DAT1 may play a reduced role in the control of synaptic dopamine within the prefrontal cortex (PFC) [68, 87], it has been suggested that the variation of COMT activity may modulate largely synaptic availability of dopamine in the PFC where it is highly expressed. However, the majority of association studies have reported negative results [37].

Two studies failed to find an association between Val158Met polymorphism and performance on a set of cognitive tasks known to tap into the PFC. The first study included 124 children and used the MFFT, the CPT, and the stop and go/no-go tasks [67]. The second study included 118 children and obtained cognitive scores from the WCST, the TOL, and the self-order pointing task evaluating a range of executive functions including working memory, planning, and set shifting [94]. A third study examined sustained attention capacity (estimated from performance on 2 subtests of the "test of everyday attention for children") in relation to Val158Met polymorphism ($n = 61$) [10]. Contrary to expectation, the Met allele was associated with impairment in sustained attention. Given that performances on tasks mediated by the PFC can be impaired by both hypo- and hyper-dopaminergic states [4], the authors hypothesized that the slower clearance of dopamine associated with the Met allele of the *COMT* may

be disadvantageous to cognition in ADHD [10]. A fourth study showed a trend for an association when transmission of the *COMT* Val allele was examined in probands who scored better than the 50th percentile on the CPT commission errors score ($n = 48$) [30]. Only participants with the Met/Met genotype had markedly fewer commission errors, whereas no significant differences were observed between Val/Val and Val/Met genotypes. In affected adults, subjects homozygous for the Val allele showed lower IQ than heterozygous subjects ($n = 45$) [20].

Monoamine oxidase A (MAOA)

The *MAOA* gene encodes a protein involved in the metabolism of dopamine, serotonin, and norepinephrine. The 2- and 3-R alleles of the 30-bp VNTR polymorphism located 1.2 kb upstream of the coding region (*MAOA*-uVNTR) have been associated with low transcriptional efficiency of the gene and with impulsivity and aggressive behavior [64, 85]. A recent meta-analysis was negative but found an important heterogeneity across studies [37].

Manor et al. examined the role of *MAOA*-uVNTR in the TOVA in a population of 112 affected children [63]. In this study, participants carrying the long *MAOA* alleles (4- and 5-R) made more commission errors than those without the alleles. This association was markedly attenuated after administration of methylphenidate. Recently, Rommelse et al. [75] examined the relationship between a common haplotype based on three SNPs (rs12843268, rs3027400, and rs1137070) and neuropsychological functioning evaluated by a battery of 10 tasks chosen for their psychometric qualities as evidenced by previous endophenotypic analyses. They reported a differential association in boys and girls with ADHD. In boys ($n = 265$), the ATT haplotype was associated with poor motor control, whereas in girls ($n = 85$) it was associated with nonaltered visuo-spatial working memory.

COMT × MAOA interactions

Qian et al. [73] tested the hypothesis of the interaction between *COMT* Val158Met and *MAOA*-uVNTR in modulation of intelligence in 264 Chinese affected boys. They found that performance IQ was significantly predicted by this interaction (significance survived Bonferroni correction). The *COMT*(val/val)-*MAOA*(3-R) combined genotype predicted high intelligence, whereas the *COMT*(val/val)-*MAOA*(4-R) predicted low performance.

Dopamine β-hydroxylase (DBH)

The *DBH* gene encodes an enzyme that catalyzes the conversion of dopamine into norepinephrine and is particularly expressed in the PFC [35]. A–1021 C/T polymorphism (rs1611115) was reported to be responsible for up to 50% of the variation of plasma DBH activity [101]. However, it is the intron 5. TaqI polymorphism (rs2519152) that has been often tested in clinical samples of patients with consistent findings.

In a study using a temporal order judgment task, children with ADHD displayed impairments in allocating attention to visual targets that appeared in close temporal proximity (50 ms) compared with controls [15]. Homozygous probands for the A2 allele of the TaqI polymorphism (T allele) exhibited poorer performances on this task than noncarriers of this allele ($n = 37$). Furthermore, performance on this task predicted distorted transmission of A2 alleles from parents to affected children. In a second study, homozygous probands for the A2 allele had significantly more commission and omission errors and greater RT variability (on the SART) than those who did not carry this allele ($n = 51$) [11]. A third study reported neuropsychological correlates of the *DBH* TaqI polymorphism in a large group of adolescents with ADHD and a matched control group ($n = 80$) [7]. Whereas no genotype effect was found on any measures in the control group, probands homozygous for the A2 allele made more errors on the WCST (problem-solving) and the MFFT (cognitive impulsiveness). Apart form the TaqI polymorphism, one study reported a positive association between the –1021 C/T polymorphism and executive function, as reflected by a composite measure (CPT and WCST) in children and adolescents with ADHD ($n = 64$) [47].

Candidate gene approach with sparse data: *DRD5*, *ADRA2A*, *GRIN2A, GRIN2B, TPH2, NET1, BDNF, SYN3*

Eleven studies investigated association between various cognitive markers and some markers from these genes. No consistent findings were described. Results are summarized in Table 3.

Multi-markers approach

Bobb et al. [19] studied 20 polymorphisms from 12 genes (*5-HT1B, 5-HT2A, 5-HT2C, ADRA2A, CHRNA4, COMT, DAT1, DRD1, DRD4, DRD5, NET1,* and *SNAP-25*) in a sample of 74 children with ADHD. The risk alleles of two *NET1* SNPs (rs998424, rs3785157) were associated with high performance on the similarities subtest of the WISC-III, and the risk alleles of two *DRD1* SNPs (rs4532, rs265981) were each associated with decreased RT on the computerized response inhibition task. However, none reached significance after correction for multiple testing. Sonuga-Barke et al. [90] investigated the possible

Table 3 Summary of association studies of candidate genes with sparse data

Study reference	Gene	Polymorphisms	*N*	Population	Cognitive tests	Results
Manor et al. 2004 [60]	*DRD5*	148 bp repeat	102	Children	TOVA	Association with commission errors, omission errors, RTs, and RT variability
Loo et al. 2008 [58]	*DRD5*	148 bp repeat	540	Children and adolescents	Stop-signal task, Stroop task, TMT, FDI, IQ	No association
Waldman et al. 2006 [96]	*ADRA2A*	rs1800544, rs553668	176	Children	TOL, TMT, stop-signal task	Association of rs1800544 with TOL and TMT and with RT variability on the stop-signal task Association of rs553668 with TMT
Cho et al. 2008 [23]	*ADRA2A*	rs1800544	128	Children	CPT	Association of CC genotype with high RT variability
Adams et al. 2004 [1]	*GRIN2A*	rs1070503, rs8049651, rs727605, rs1014531	59	Children	Stop task, forward digit span, backward digit span	No association
Dorval et al. 2006 [27]	*GRIN2B*	rs2268115, rs2300256, rs2284411, rs2284407	92	Children	Digit span	No association
Manor et al. 2008 [61]	*TPH2*	rs1386488, rs6582072	344	Children	TOVA	Association between rs1386488 and rs1386497 and total RT scores and with total RT variability scores
Baehne et al. 2009 [6]	*TPH2*	rs4570625, rs11178997	122	Adults	CPT	Association of homozygous genotypes (G and T, respectively) with high omissions errors
Cho et al. 2008 [24]	*NET1*	rs5569, rs28386840	131	Children	CPT	No association
Lee et al. 2007 [56]	*BDNF*	rs2049046, rs11030104, rs6265	315	Children	Digit span	No association
Makkar et al. 2007 [59]	*SYN3*	rs133946, rs133945, rs9862, rs1056484	177	Children	Digit span	No association

ADRA2A adrenergic receptor 2A, *BDNF* brain-derived neurotropic factor, *CPT* continuous performance test, *DRD5* dopamine receptor 5, *FDI* freedom from distractibility index, *GRIN2A* glutamate receptor ionotropic N-methyl-D-aspartate 2A, *GRIN2B* glutamate receptor ionotropic N-methyl-D-aspartate 2B, *IQ* intelligence quotient, *NET1* norepinephrine transporter, *RT* reaction time, *SYN3* synapsin III, *TMT* trail making test, *TOL* tower of London, *TOVA* test of variables of attention, *TPH2* trypotphan hydroxylase 2

association between full IQ, and 55 SNPs in 18 genes (including *DRD4*, *DAT1*, *TPH2*, *ARRB2*, *SYP*, *ADRB2*, *HES1*, *MAOA*, *NET1*, and *PNMT*) that were previously shown to have nominal level of association within the studied sample ($P < 0.05$). Results were negative in the 702 cases and in the group of 694 siblings. A third study used haplotype-tagging SNP analyses (100 SNPs) to identify possible genetic association between 10 candidate genes (*DRD1*, *DRD2*, *DRD3*, *DRD4*, *DAT1*, *HTR1B*, *SLC6A4*, *NET1*, *DBH*, and *SNAP-25*) and CPT performance in a population of 364 individuals from 152 families ascertained on the basis of at least one child having ADHD [50]. After multiple testing corrections, significant associations were found between commission errors and two SNPs in *DRD2* (rs2075654, rs1079596), and between RT variability and one SNP in *NET1* gene (rs3785155). More recently, a genome-wide association study (investigating 438 783 SNPs after quality control) focused on association with IQ performance in a sample of 627 children with ADHD. Whereas SNP-by-SNP analysis failed to detect robust associations, an analysis based on grouping genes according to cellular function detected an association of the group of genes of synaptic heterotrimeric G proteins with IQ score which was validated in a second clinical sample of 1507 children [84].

Discussion

The criteria for an endophenotype include heritability, independence from fluctuation in behavioral manifestations of the disorder over time, co-segregation with the illness within families and higher occurrence in nonaffected family members than in the general population [39]. Under

the assumption that the endophenotype has a simpler underlying genetic architecture than the phenotype, the focus on endophenotype investigation in genetic studies may help to shed light on the genetic of the disorder that they index. However, investigating endophenotypes that are not validated using the proposed criteria can lead to a plethora of data and results of dubious biological relevance [93].

The use of endophenotypes raises the question of genotype–endophenotype–phenotype relations. Several authors attempted to disentangle the complexity of these relations. First, it is interesting to investigate whether the endophenotype mediates or moderates the relation between genotype and phenotype. Mediation means that the effects of a particular gene or locus on a disorder are expressed either in full or in part through the endophenotype, whereas in the case of moderation those effects are stronger in affected individuals who also show the endophenotype [97]. This can be tested by interpreting comparison between the results of ADHD status regression on the candidate gene and the regression of ADHD status on both the candidate gene and the endophenotype. An example of this analysis showed that TMT A response time seemed to mediate part of the effects of *DRD4* on ADHD status, whereas TMT B response time tended to moderate these effects [97]. Rarely addressed in the current literature, such investigations may clarify in the future the possible moderation and/or mediation effects of neuropsychological endophenotypes on genetic association with ADHD subtypes and symptom dimensions.

A second important point is how to take into account the multiplicity of neuropsychological deficits in regard to genotype–endophenotype–phenotype relations. It was hypothesized that multiple endophenotypes are more likely to mediate the relation between genotype and phenotype and seem to be more powerful in predicting the phenotype [28, 78]. Thus, it was proposed that the use of aggregated composite is useful since it appeared to be correlated more strongly between siblings than most individual task measures [77]. However, construction of such composite remains dependent on heritability of the selected neuropsychological measures, which still not very well studied in the majority of these traits.

Third, nongenetic factors participate in variation of the endophenotype. For example, it has been shown that maternal smoking during pregnancy is a risk factor for both ADHD and executive dysfunctions in offspring [33, 43]. Failure to take these confounding factors into account may result in spurious findings and prevent replicating results from one study to another. Interestingly, a recent study reported that paternal smoking was reported to have a negative effect on attentional control (in a sustained attention test based on visual CPT) in children with ADHD ($n = 79$) and that this effect is mediated by genetic risk factors (strongest effect when *DRD4* 7-R allele and *DAT1* intron 8 6/6 genotype are combined) [2]. Familial studies with testing of parents could also help to reveal epigenetic transmission of the endophenotype. A recent study reported that inhibitory control (stop-signal task) was subject to a differential parental contribution with an evidence of parent-of-origin effects with children's inhibitory control ability influenced more by paternal ability than maternal ability [38].

Finally, some disorders frequently associated with ADHD might interfere with the measurement of neuropsychological performances [83, 89]. For example, reading disability and ADHD co-occur in about 15–40% of patients [99], and it is possible that the two conditions interact to shape neuropsychological performances of affected individuals. Recently, Rommelse et al. [76] examined whether an endophenotype based on executive and motor functioning was related to comorbid conditions with and without adjusting for their interdependence on ADHD. Autistic traits, motor coordination problems, and reading problems were correlated with both executive functions and motor endophenotypes, suggesting that these comorbid problems may share the same neuropsychological substrate with ADHD. Interestingly, oppositional defiant behaviors, which appeared the most important comorbid problem in the studied sample, and anxiety problems, were not related to endophenotypes of interest. This study showed also that the co-occurrence of a comorbid condition with ADHD did not seem to have an independent effect on the relation between ADHD and neuropsychological endophenotypes, suggesting that comorbid problems may result in larger endophenotypic dysfunctions but not in a distinct phenotype.

Limitations

Three important issues in this field of research are the wide variations in age of participants, differences in neuropsychological profiles between males and females with ADHD, and pharmacological treatment received by participants at moment of testing (for a detailed discussion see [46]).

Additionally, some statistical aspects are important to consider. First, many of the associations between polymorphisms of the candidate genes and neuropsychological measures were performed without a control group. Including a control group is highly recommended to ensure sensitivity and specificity of the neuropsychological measures to ADHD. Second, sample sizes of the first published studies were small. The effect of a single genetic polymorphism is thought to be very modest, and its detection will need large sample sizes. Despite significant increase in

sample size in the recent works, some negative findings could be attributed to a lack of statistical power, and positive results should be considered preliminary until they are replicated in extended samples. Moreover, multiple testing is an issue in many studies investigating a high number of cognitive scores and could increase false positive results if not corrected. Lastly, it could be interesting to compare the variance in endophenotypes explained by variation in candidate genes with the proportion of clinical phenotypic variance explained by the associated candidate genes. Indeed, under the main assumption underlying the endophenotype approach (genetic architecture of endophentypes is simpler than the one of the disorders they index), one would expect that the genes associated ADHD and it indexing endophenotypes would explain more variance of the latter than the former. However, the number of studies assessing the same gene and the same neuropsychological endophenotype are small preventing any reliable meta-analytic estimation of these effect sizes. Nonetheless, it is noticeable that, even in somatic diseases with strongly established endophenotypes such as type II diabetes and fasting glucose level the genotype–endophenotype–phenotype does not appear to be a simple one. For example, the recent data from genome-wide association studies indicate SNPs that were associated with Type II diabetes explain 6% of the variance of this disorder [102]. In contrast, SNPs associated with fasting glucose explain only 1.5% of the variance of fasting glucose levels [72]. This suggests that the assumption of a simpler genetic architecture of endophenotypes compared with the phenotypes they index may need to be reconsidered. However, we point out that the present review focused only on pure behavioral measures of cognitive tasks. Genetic approaches combining the study of functional brain activity coupled to a cognitive task performance and stratified by genotypes of a candidate gene have been reported to yield nonnegligible effect sizes that are possibly stronger than those observed with the use of neuropsychological endophenotypes [65]. This might suggest that candidate genes have greater penetrance at the level of certain neurobiological circuitries than at the level of the cognitive performance, which supposes that imaging genetic approaches could achieve a better characterization of the genetic architecture of ADHD, although other authors have questioned this approach [32].

Perspectives

In the era of Genome Wide Association Studies, genetic studies based on endophenotypes rather than behavioral syndromes may be more promising and fruitful. Thus, far two studies have been published in ADHD. Rommelse et al. [81] using 5407 SNPs found two significant genome-wide linkage signals (LOD scores greater than 3.9 in exploratory analyses without correction for multiple testing) on 2q21.1 (motor timing) and 13q12.11 (digit span). Doyle et al. [29] using 4885 SNPs reported suggestive linkage signal between 3q13 with a cognitive inattention composite and a second peak on 22q12 with WCST non-perseverative errors (multivariate analyses with correction for multiple trait testing). Although these results are interesting to follow, it is clear that much larger samples sizes and international efforts in standardizing the measurements of these endophenotypes between collaborative centers are required to achieve this potential promise.

Conflict of interest None.

References

1. Adams J, Crosbie J, Ickowicz A et al (2004) Glutamate receptor, ionotropic, N-methyl D-aspartate 2A (GRIN2A) gene as a positional candidate for attention-deficit/hyperactivity disorder in the 16p13 region. Mol Psychiatry 9:494–499
2. Altink ME, Slaats-Willemse DI, Rommelse NN et al (2009) Effects of maternal and paternal smoking on attentional control in children with and without ADHD. Eur Child Adolesc Psychiatry 18:465–475
3. Andreou P, Neale BM, Chen WAI et al (2007) Reaction time performance in ADHD: improvement under fast-incentive condition and familial effects. Psychol Med 37:1703–1715
4. Arnsten AFT (1998) Catecholamine modulation of prefrontal cortical cognitive function. Trends Cogn Sci 2:436–447
5. Asghari V, Sanyal S, Buchwaldt S et al (1995) Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J Neurochem 65:1157–1165
6. Baehne CG, Ehlis AC, Plichta MM et al (2009) Tph2 gene variants modulate response control processes in adult ADHD patients and healthy individuals. Mol Psychiatry 14:1032–1039
7. Barkley RA, Smith KM, Fisher M et al (2006) An examination of the behavioral and neuropsychological correlates of three ADHD candidate gene polymorphisms (DRD4 7 + , DBH Taq1 A2, and DAT1 40 bp VNTR) in hyperactive and normal children followed to adulthood. Am J Med Genet B Neuropsychiatr Genet 141:487–498
8. Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 121:65–94
9. Bellgrove MA, Barry E, Johnson KA et al (2008) Spatial attentional bias as a marker of genetic risk, symptom severity, and stimulant response in ADHD. Neuropsychopharmacology 33:2536–2545
10. Bellgrove MA, Domschke K, Hawi Z et al (2005) The methionine allele of the COMT polymorphism impairs prefrontal cognition in children and adolescents with ADHD. Exp Brain Res 163:352–360
11. Bellgrove MA, Hawi Z, Gill M et al (2006) The cognitive genetics of attention deficit hyperactivity disorder (ADHD): sustained attention as a candidate phenotype. Cortex 42:838–845
12. Bellgrove MA, Hawi Z, Kirley A et al (2005) Dissecting the attention deficit hyperactivity disorder (ADHD) phenotype: sustained attention, response variability and spatial attentional

asymmetries in relation to dopamine transporter (DAT1) genotype. Neuropsychologia 43:1847–1857
13. Bellgrove MA, Hawi Z, Lowe N et al (2005) DRD4 gene variants and sustained attention in attention deficit hyperactivity disorder (ADHD): Effects of associated alleles at the VNTR and -521 SNP. Am J Med Genet B Neuropsychiatr Genet 136:81–86
14. Bellgrove MA, Johnson KA, Barry E et al (2009) Dopaminergic haplotype as a predictor of spatial inattention in children with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 66:1135–1142
15. Bellgrove MA, Mattingley JB, Hawi Z et al (2006) Impaired temporal resolution of visual attention and dopamine beta hydroxylase genotype in attention-deficit/hyperactivity disorder. Biol Psychiatry 60:1039–1045
16. Bidwell LC, Willcutt EG, Defries JC et al (2007) Testing for neuropsychological endophenotypes in siblings discordant for attention-deficit/hyperactivity disorder. Biol Psychiatry 62:991–998
17. Biederman J, Faraone SV (2005) Attention-deficit hyperactivity disorder. Lancet 366:237–248
18. Bitsakou P, Psychogiou L, Thompson M et al (2009) Delay aversion in attention deficit/hyperactivity disorder: an empirical investigation of the broader phenotype. Neuropsychologia 47:446–456
19. Bobb AJ, Addington AM, Sidransky E et al (2005) Support for association between ADHD and two candidate genes: NET1 and DRD1. Am J Med Genet B Neuropsychiatr Genet 134:67–72
20. Boonstra AM, Kooij JJ, Buitelaar JK et al (2008) An exploratory study of the relationship between four candidate genes and neurocognitive performance in adult ADHD. Am J Med Genet B Neuropsychiatr Genet 147:397–402
21. Castellanos FX, Tannock R (2002) Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 3:617–628
22. Cheon KA, Ryu YH, Kim JW et al (2005) The homozygosity for 10-repeat allele at dopamine transporter gene and dopamine transporter density in Korean children with attention deficit hyperactivity disorder: relating to treatment response to methylphenidate. Eur Neuropsychopharmacol 15:95–101
23. Cho SC, Kim JW, Kim BN et al (2008) Possible association of the alpha-2A-adrenergic receptor gene with response time variability in attention deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 147:957–963
24. Cho SC, Kim JW, Kim BN et al (2008) No evidence of an association between norepinephrine transporter gene polymorphisms and attention deficit hyperactivity disorder: a family-based and case-control association study in a Korean sample. Neuropsychobiol 57:131–138
25. Crosbie J, Schachar R (2001) Deficient inhibition as a marker for familial ADHD. Am J Psychiatry 158:1884–1890
26. DeYoung CG, Peterson JB, Séguin JR et al (2006) The dopamine D4 receptor gene and moderation of the association between externalizing behavior and IQ. Arch Gen Psychiatry 63:1410–1416
27. Dorval KM, Wigg KG, Crosbie J et al (2006) Association of the glutamate receptor subunit gene GRIN2B with attention-deficit/hyperactivity disorder. Genes Brain Behav 6:444–452
28. Doyle AE, Faraone SV, Seidman LJ et al (2005) Are endophenotypes based on measures of executive functions useful for molecular genetic studies of ADHD. J Child Psychol Psychiatry 46:774–803
29. Doyle AE, Ferreira MA, Sklar PB et al (2008) Multivariate genomewide linkage scan of neurocognitive traits and ADHD symptoms: suggestive linkage to 3q13. Am J Med Genet B Neuropsychiatr Genet 147:1399–1411
30. Eisenberg J, Mei-Tal G, Steinberg A et al (1999) Haplotype relative risk study of catechol-Omethyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD): association of the High-enzyme activity Val allele with ADHD impulsive-hyperactive phenotype. Am J Med Genet B Neuropsychiatr Genet 88:497–502
31. Faraone SV, Perlis RH, Doyle AE et al (2005) Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry 57:1313–1323
32. Flint J, Munafò MR (2007) The endophenotype concept in psychiatric genetics. Psychol Med 37:163–180
33. Fried PA, Watkinson B, Gray R (2003) Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 25:427–436
34. Garris PA, Wightman RM (1994) Different kinetics govern dopaminergic transmission in the amygdala, prefrontal cortex, and striatum: an in vivo voltammetric study. J Neurosci 14:442–450
35. Gaspar P, Berger B, Febvret A et al (1989) Catecholamine innervation of the human cerebral cortex as revealed by comparative immunohistochemistry of tyrosine hydroxylase and dopamine-beta-hydroxylase. J Comp Neurol 279:249–271
36. Genro JP, Roman T, Zeni CP et al (2006) No association between dopaminergic polymorphisms and intelligence variability in attention-deficit/hyperactivity disorder. Mol Psychiatry 11:1066–1067
37. Gizer IR, Ficks C, Waldman ID (2009) Candidate gene studies of ADHD: a meta-analytic review. Hum Genet 126:51–90
38. Goos LM, Crosbie J, Payne S et al (2009) Validation and extension of the endophenotype model in ADHD patterns of inheritance in a family study of inhibitory control. Am J Psychiatry 166:711–717
39. Gottesman II, Gould TD (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 160:636–645
40. Gau SS, Shang CY (2010) Executive functions as endophenotypes in ADHD: evidence from the Cambridge Neuropsychological Test Battery (CANTAB). J Child Psychol Psychiatry 51:838–849
41. Heinz A, Goldman D, Jones DW et al (2000) Genotype influences in vivo dopamine transporter availability in human striatum. Neuropsychopharmacol 22:133–139
42. Johnson KA, Kelly SP, Robertson IH et al (2008) Absence of the 7-repeat variant of the DRD4 VNTR is associated with drifting sustained attention in children with ADHD but not in controls. Am J Med Genet B Neuropsychiatr Genet 147:927–937
43. Julvez J, Ribas-Fito N, Torrent M et al (2007) Maternal smoking habits and cognitive development of children at age 4 years in a population-based birth cohort. Int J Epidemiol 36:825–832
44. Karama S, Grizenko N, Sonuga-Barke EJS et al (2008) Dopamine transporter 3'UTR VNTR genotype is a marker of performance on executive function tasks in children with ADHD. BMC Psychiatry 8:45
45. Kebir O, Grizenko N, Sengupta S et al (2009) Verbal but not performance IQ is highly correlated to externalizing behavior in boys with ADHD carrying both DRD4 and DAT1 risk genotypes. Prog Neuropsychopharmacol Biol Psychiatry 33:939–944
46. Kebir O, Tabbane K, Sengupta S et al (2009) Candidate genes and neuropsychological phenotypes in children with ADHD: review of association studies. J Psychiatry Neurosci 34:88–101
47. Kieling C, Genro JP, Hutz MH et al (2008) The −1021 C/T DBH polymorphism is associated with neuropsychological performance among children and adolescents with ADHD. Am J Med Genet B Neuropsychiatr Genet 147:485–490

48. Kieling C, Roman T, Doyle AE et al (2006) Association between DRD4 gene and performance of children with ADHD in a test of sustained attention. Biol Psychiatry 60:1163–1165
49. Kim JW, Kim BN, Cho SC (2006) The dopamine transporter gene and the impulsivity phenotype in attention deficit hyperactivity disorder: a case-control association study in a Korean sample. J Psychiatr Res 40:730–737
50. Kollins SH, Anastopoulos AD, Lachiewicz AM et al (2008) SNPs in dopamine D2 receptor gene (DRD2) and norepinephrine transporter gene (NET) are associated with continuous performance task (CPT) phenotypes in ADHD children and their families. Am J Med Genet B Neuropsychiatr Genet 147:1580–1588
51. Konrad K, Dempfle A, Friedel S et al (2010) Familiality and molecular genetics of attention networks in ADHD. Am J Med Genet B Neuropsychiatr Genet 153:148–158
52. Krause J, la Fougere C, Krause KH et al (2005) Influence of striatal dopamine transporter availability on the response to methylphenidate in adult patients with ADHD. Eur Arch Psychiatry Clin Neurosci 255:428–431
53. Krause KH, Dresel SH, Krause J et al (2003) The dopamine transporter and neuroimaging in attention deficit hyperactivity disorder. Neurosci Biobehav Rev 27:605–613
54. Lachman HM, Papolos DF, Saito T et al (1996) Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenet 6:243–250
55. Langley K, Marshall L, van der Bree M et al (2004) Association of the dopamine D4 receptor gene 7-repeat allele with neuropsychological test performance of children with ADHD. Am J Psychiatry 161:133–138
56. Lee J, Laurin N, Crosbie J et al (2007) Association study of the brain-derived neurotropic factor (BDNF) gene in attention deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 144:976–981
57. Loo S, Specter E, Smolen A et al (2003) Functional effects of the DAT1 polymorphism on EEG measures in ADHD. J Am Acad Child Adolesc Psychiatry 42:986–993
58. Loo SK, Rich EC, Ishii J et al (2008) Cognitive functioning in affected sibling pairs with ADHD: familial clustering and dopamine genes. J Child Psychol Psychiatry 49:950–957
59. Makkar R, Gomez L, Wigg KG et al (2007) The gene for synapsin III and attention-deficit hyperactivity disorder. Psychiatr Genet 17:109–112
60. Manor I, Corbex M, Eisenberg J et al (2004) Association of the dopamine D5 receptor with attention deficit hyperactivity disorder (ADHD) and scores on a continuous performance test (TOVA). Am J Med Genet B Neuropsychiatr Genet 127:73–77
61. Manor I, Laiba E, Eisenberg J et al (2008) Association between trypotphan hydroxylase 2, performance on a continuance performance test and response to methylphenidate in ADHD participants. Am J Med Genet B Neuropsychiatr Genet 147:1501–1508
62. Manor I, Tyano S, Eisenberg J et al (2002) The short DRD4 repeats confer risk to attention deficit hyperactivity disorder in a family-based design and impair performance on a continuous performance test (TOVA). Mol Psychiatry 7:790–794
63. Manor I, Tyano S, Mel E et al (2002) Family-based and association studies of monoamine oxidase A and attention deficit hyperactivity disorder (ADHD): preferential transmission of the long promoter-region repeat and its association with impaired performance on a continuous performance test (TOVA). Mol Psychiatry 7:626–632
64. Manuck SB, Flory JD, Ferrell RE et al (2000) A regulatory polymorphism of the monoamine oxidase-A gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsivity. Psychiatry Res 95:9–23
65. Meyer-Lindenberg A, Weinberger DR (2006) Intermediate phenotypes and genetic mechanisms of psychiatric disorders. Nat Rev Neurosci 7:818–827
66. Mill J, Caspi A, Williams BS et al (2006) Prediction of heterogeneity in intelligence and adult prognosis by genetic polymorphisms in the dopamine system among children with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 63:462–469
67. Mills S, Langley K, Van der Bree et al (2004) No evidence of association between Catechol-Omethyltransferase (COMT) Val158Met genotype and performance on neuropsychological tasks in children with ADHD: A case-control study. BMC Med Genet 4:15
68. Moron JA, Brockington A, Wise RA et al (2002) Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. J Neurosci 22:389–395
69. Oh KS, Shin DW, Oh GT et al (2003) Dopamine transporter genotype influences the attention deficit in Korean boys with ADHD. Yonsei Med J 44:787–792
70. Polanczyk G, de Lima MS, Horta BL et al (2007) The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 164:942–948
71. Primus RJ, Thurkauf A, Xu J et al (1997) Localization and characterization of dopamine D4 binding sites in rat and human brain by use of the novel, D4 receptor-selective ligand [3H]NGD 94–1. J Pharmacol Exp Ther 282:1020–1027
72. Prokopenko I, Langenberg C, Florez JC et al (2009) Variants in MTNR1B influence fasting glucose levels. Nat Genet 41:77–81
73. Qian QJ, Yang L, Wang YF et al (2010) Gene-gene interaction between COMT and MAOA potentially predicts the intelligence of attention-deficit hyperactivity disorder boys in China. Behav Genet 40:357–365
74. Rommelse NN, Altink ME, Arias-Vásquez A et al (2008) A review and analysis of the relationship between neuropsychological measures and DAT1 in ADHD. Am J Med Genet B Neuropsychiatr Genet 147:1536–1546
75. Rommelse NN, Altink ME, Arias-Vásquez A et al (2008) Differential association between MAOA, ADHD and neuropsychological functioning in boys and girls. Am J Med Genet B Neuropsychiatr Genet 147:1524–1530
76. Rommelse NN, Altink ME, Fliers EA et al (2009) Comorbid problems in ADHD: degree of association, shared endophenotypes, and formation of distinct subtypes. Implications for a future DSM. J Abnorm Child Psychol 37:793–804
77. Rommelse NN, Altink ME, Martin NC et al (2008) Neuropsychological measures probably facilitate heritability research of ADHD. Arch Clin Neuropsychol 23:579–591
78. Rommelse NN, Altink ME, Martin NC et al (2008) Relationship between endophenotype and phenotype in ADHD. Behav Brain Funct 4:4
79. Rommelse NN, Altink ME, Oosterlaan J et al (2008) Speed, variability, and timing of motor output in ADHD: which measures are useful for endophenotypic research? Behav Genet 38:121–132
80. Rommelse NN, Altink ME, Oosterlaan J et al (2008) Support for an independent familial segregation of executive and intelligence endophenotypes in ADHD families. Psychol Med 38:1595–1606
81. Rommelse NN, Arias-Vásquez A, Altink ME et al (2008) Neuropsychological endophenotype approach to genome-wide linkage analysis identifies susceptibility loci for ADHD on 2q21.1 and 13q12.11. Am J Hum Genet 83:99–105
82. Rommelse NN, Oosterlaan J, Buitelaar J et al (2007) Time reproduction in children with ADHD and their nonaffected siblings. J Am Acad Child Adolesc Psychiatry 46:582–590

83. Rösler M, Retz W, Yaqoobi K et al (2009) Attention deficit/hyperactivity disorder in female offenders: prevalence, psychiatric comorbidity and psychosocial implications. Eur Arch Psychiatry Clin Neurosci 259:98–105
84. Ruano D, Abecasis GR, Glaser B et al (2010) Functional gene group analysis reveals a role of synaptic heterotrimeric G proteins in cognitive ability. Am J Hum Genet 86:113–125
85. Sabol SZ, Hu S, Hamer D (1998) A functional polymorphism in the monoamine oxidase A gene promoter. Hum Genet 103:273–279
86. Sergeant JA (2005) Modeling attention-deficit/hyperactivity disorder: a critical appraisal of the cognitive-energetic model. Biol Psychiatry 57:1248–1255
87. Sesack SR, Hawrylak VA, Guido MA et al (1998) Cellular and subcellular localization of the dopamine transporter in rat cortex. Adv Pharmacol 42:171–174
88. Slaats-Willemse D, Swaab-Barneveld H, de Sonneville L et al (2003) Deficient response inhibition as a cognitive endophenotype of ADHD. J Am Acad Child Adolesc Psychiatry 42:1242–1248
89. Sobanski E, Brüggemann D, Alm B et al (2007) Psychiatric comorbidity and functional impairment in a clinically referred sample of adults with attention-deficit/hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci 257:371–377
90. Sonuga-Barke EJ, Brookes KJ, Buitelaar J et al (2008) Intelligence in DSM-IV combined type attentiondeficit/hyperactivity disorder is not predicted by either dopamine receptor/transporter genes or other previously identified risk alleles for attention-deficit/hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 147:316–319
91. Sonuga-Barke EJ, Sergeant JA, Nigg J et al (2008) Executive dysfunction and delay aversion in attention deficit hyperactivity disorder: nosologic and diagnostic implications. Child Adolesc Psychiatr Clin N Am 17:367–384
92. Swanson J, Oosterlaan J, Murias M et al (2000) Attention deficit/hyperactivity disorder children with a 7-repeat allele of the dopamine receptor D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention. Proc Natl Acad Sci USA 97:4754–4759
93. Szatmari P, Maziade M, Zwaigenbaum L et al (2007) Informative phenotypes for genetic studies of psychiatric disorders. Am J Med Genet B Neuropsychiatr Genet 144:581–588
94. Taerk E, Grizenko N, Ben Amor L et al (2004) Catechol-O-Methyltransferase (COMT) Val108/158Met polymorphism does not modulate executive function in children with ADHD. BMC Med Genet 5:30
95. Waldman ID, Gizer IR (2006) The genetics of attention deficit hyperactivity disorder. Clin Psychol Rev 26:396–432
96. Waldman ID, Nigg JT, Gizer IR et al (2006) The adrenergic receptor alpha-2A gene (ADRA2A) and neuropsychological executive functions as putative endophenotype for childhood ADHD. Cogn Affect Behav Neurosci 6:18–30
97. Waldman ID (2005) Statistical approaches to complex phenotypes: evaluating neuropsychological endophenotypes for attention-deficit/hyperactivity disorder. Biol Psychiatry 57:1347–1356
98. Willcutt EG, Doyle AE, Nigg JT et al (2005) Validity of the executive function theory of attentiondeficit/hyperactivity disorder: a meta-analytic review. Biol Psychiatry 57:1336–1346
99. Willcutt EG, Pennington BF (2000) Comorbidity of reading disability and attention-deficit/hyperactivity disorder: differences by gender and subtype. J Learn Disabil 33:179–191
100. Wohl M, Boni C, Asch M et al (2008) Lack of association of the dopamine transporter gene in a French ADHD sample. Am J Med Genet B Neuropsychiatr Genet 147:1509–1510
101. Zabetian CP, Anderson GM, Buxbaum SG et al (2001) A quantitative-trait analysis of human plasma-dopamine beta-hydroxylase activity: evidence for a major functional polymorphism at the DBH locus. Am J Hum Genet 68:515–522
102. Zeggini E, Scott LJ, Saxena R et al (2008) Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet 40:638–645