Journal of Child Psychology and Psychiatry 46:7 (2005), pp 774–803 doi:10.1111/j.1469-7610.2005.01476.x

Are endophenotypes based on measures of executive functions useful for molecular genetic studies of ADHD?

Alysa E. Doyle,[1] Stephen V. Faraone,[2] Larry J. Seidman,[3] Erik G. Willcutt,[4] Joel T. Nigg,[5] Irwin D. Waldman,[6] Bruce F. Pennington,[7] Joanne Peart,[8] and Joseph Biederman[1]

[1]Massachusetts General Hospital, Harvard Medical School, USA; [2]SUNY Upstate Medical University, USA; [3]Massachusetts Mental Health Center and Harvard Medical School, USA; [4]University of Colorado at Boulder, USA; [5]Michigan State University, USA; [6]Emory University, USA; [7]University of Denver, USA; [8]Formerly at Massachusetts General Hospital, USA

Background: Behavioral genetic studies provide strong evidence that attention-deficit/hyperactivity disorder (ADHD) has a substantial genetic component. Yet, due to the complexity of the ADHD phenotype, questions remain as to the specific genes that contribute to this condition as well as the pathways from genes to behavior. Endophenotypes, or phenotypes that are more closely linked to the neurobiological substrate of a disorder, offer the potential to address these two issues simultaneously (Freedman, Adler, & Leonard, 1999). Thus far, potential endophenotypes for ADHD have not been systematically studied. **Method:** The current paper reviews evidence supporting the use of deficits on neurocognitive measures of executive functions for this purpose. **Results:** Such deficits are a correlate of ADHD and show preliminary evidence of heritability and association with relevant candidate genes. Nonetheless, studies that have assessed the familial and genetic overlap of neurocognitive impairments with ADHD have yielded inconsistent results. **Conclusions:** In order for executive function deficits to be used as an endophenotype for ADHD, we recommend greater attention to the neurocognitive heterogeneity of this disorder and to the precision of measurement of the neuropsychological tests employed. We also discuss empirical strategies that may be necessary to allow such research to progress prior to full resolution of the pathophysiological basis of ADHD. **Keywords:** ADHD, endophenotype, genetics, neuropsychology, executive functions.

Evidence for genetic influences on attention-deficit/hyperactivity disorder (ADHD) has been accumulating since the 1960s (Lopez, 1965). Despite a changing nosology and the use of a variety of assessment tools, heritability estimates have been strikingly consistent and high (Faraone et al., in press). Although several candidate genes have been implicated with reasonable certainty, our understanding of the genetic architecture of ADHD remains limited, most likely due to the complexity of the phenotype and its potential genetic heterogeneity (Faraone, 2000).

Although there is no definitive pathophysiological model of ADHD, dysfunction in fronto-striatal pathways has been demonstrated by neuroimaging studies (Booth et al., 2005; Durston et al., 2003) and by neuropsychological studies of executive functions that are associated with frontal systems (Willcutt, Doyle, Nigg, Faraone, & Pennington, in press b). Furthermore, some researchers have hypothesized that a particular component of executive functions (e.g., deficient inhibitory control (Barkley, 2000) or working memory (Castellanos & Tannock, 2002)) constitutes a core deficit that lies directly in the causal pathway leading to the behavioral symptoms of ADHD. Because neurobehavioral phenotypes may be more closely linked to gene expression than clinical phenotypes, interest has grown in using phenotypes that reflect fronto-striatal brain system functions to facilitate the genetic dissection of this condition.

In the current paper, we review evidence for the utility of executive function measures as an 'endophenotype' for ADHD. We start by defining endophenotypes and justifying their utility by summarizing evidence from molecular genetic studies that ADHD is a complex phenotype. In the bulk of the paper, we describe key criteria that must be met for an endophenotype to be useful and assess the extent to which executive function deficits meet each criterion. Finally, we highlight areas in which additional research is needed and offer several recommendations for future studies.

Endophenotypes

Although the term 'endophenotype' has been used in different ways, virtually all conceptualizations refer to a phenotype that is more proximal to the biological etiology of a clinical disorder than its signs and symptoms and influenced by one or more of the same genes that confer susceptibility to the condition (Almasy & Blangero, 2001; Gottesman & Gould,

Published by Blackwell Publishing, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main Street, Malden, MA 02148, USA

2003; Skuse, 2001). Endophenotypes may be particularly useful for understanding the etiology of complex disorders in which several genes and environmental factors influence the phenotype. The power of these biologically based phenotypes is based on several assumptions, but most importantly that the endophenotype is less genetically complex than the disorder it underlies. This reduced complexity is due both to the endophenotype's relative proximity to gene products in the chain of events leading from gene to behavior and to its potential to target one of possibly several pathophysiological deficits that combine to create the overall condition. Theoretically, because the endophenotype is influenced by fewer genetic and environmental risk factors than the disorder as a whole, its use would result in greater statistical power to detect the effects of individual genes.

Because it is conceptualized as an expression of the genetic liability for a disorder, the endophenotype should appear in individuals who carry genes for a condition but do not express the disorder itself, i.e., unaffected relatives of individuals with the diagnosis. The presence of an endophenotype in these relatives may further augment the statistical power of genetic linkage and association studies due to its increased prevalence compared with the disease entity, its suitability for quantitative trait analyses and its ability to clarify affected versus unaffected status in relatives. If such phenotypes reflect aspects of the pathophysiology of the disorder among well relatives, they can also provide a window into neurobiological risk mechanisms not confounded by treatment or chronicity.

Finally, endophenotypes may help clarify the suspected pathophysiological basis of a condition in addition to identifying the gene or genes that contribute to it (Freedman et al., 1999; Gottesman & Gould, 2003). If an association between a gene and the candidate pathophysiological mechanism is found, expression studies may allow for further elaboration or revision of the hypothesized mechanism. Moreover, endophenotypes could be useful for identifying processes that mediate/moderate the influence of early environmental events on the later development of the disorder.

Although their use in ADHD is relatively new, endophenotypes have aided the clarification of the etiology and pathophysiology of several other conditions in medicine and psychiatry (e.g., Borecki, Rao, Yaouanq, & Lalouel, 1990; Freedman et al., 1997, 2001). Such findings signal the promise of endophenotypes to better identify and characterize the nature of the genetic contributions to complex disorders.

ADHD as a complex phenotype

In behavioral genetic studies of ADHD, the greater similarity of monozygotic (MZ) versus dizygotic (DZ) twins, coupled with closer resemblance of biological versus adoptive relatives for the disorder, provides clear evidence that liability to ADHD is under substantial genetic influence (Thapar, Holmes, Poulton, & Harrington, 1999; Waldman & Rhee, 2002). Heritability estimates suggest that over 70% of the phenotypic variability in ADHD is due to genetic factors (Faraone et al., in press). To identify the specific genes that increase susceptibility to ADHD, researchers have used two main methods – candidate gene studies and genetic linkage studies (for details about these methods, see Pennington, 2002).

Candidate gene studies. Genes from catecholamine systems are etiological candidates for ADHD because these neurotransmitters have been implicated in the pharmacotherapy of the disorder (Biederman, 1997), animal models of hyperactivity (e.g., de Villiers et al., 1995; Russell, de Villiers, Sagvolden, Lamm, & Taljaard, 1995; Shaywitz, Cohen, & Shaywitz, 1978) and studies of attention in humans (Clark, Geffen, & Geffen, 1989) and animals (Arnsten, 2001). Recently, animal and human studies have generated interest in serotonin as having both a direct impact on ADHD as well as an indirect role through its regulatory influence on dopaminergic pathways (Quist & Kennedy, 2001).

A recent meta-analytic review concluded that several genes from the catecholamine and serotonin systems confer susceptibility to ADHD (Faraone et al., in press). These include genes for two postsynaptic dopamine receptors (DRD4 and DRD5), the dopamine transporter protein (DAT1), dopamine beta hydroxylase (DBH; an enzyme involved in the conversion of dopamine to norepinephrine), a postsynaptic serotonin receptor (5HTR1B), the serotonin transporter protein (5HTT), and a protein identified via animal models of hyperactivity that is involved in neurotransmitter release (SNAP-25). These genes showed significant associations with the ADHD phenotype, with pooled odds ratios ranging from 1.2 to 1.5. Results suggest that these effects are real but that the impact of the individual genes on ADHD is likely to be small.

Additionally, inconsistencies across studies are notable (Faraone et al., in press). One explanation for inconsistencies is that non-significant findings may result from low statistical power to detect small effects. Yet, a close look at the data suggests that power may account for some (e.g., Payton et al., 2001) but not all (e.g., Smith et al., 2003) negative findings. Inconsistencies may also reflect the polygenic nature of ADHD and/or the genetic heterogeneity of the disorder that has been suggested by twin and family studies (Faraone, 1999; Rasmussen et al., 2002; Todd et al., 2001). Although this heterogeneity has not been definitively parsed, promising subtypes include those delineated by comorbidity with conduct disorder and bipolar disorder (Doyle & Faraone, 2002; Faraone, Biederman, & Monuteaux,

2000b), persistence of ADHD into adolescence (Faraone, Biederman, Feighner, & Monuteaux, 2000a; Faraone et al., 2000b), empirically derived latent classes (Todd, 2000) and, in population but not clinical samples, DSM-IV subtypes (Faraone, 2002). Genetic heterogeneity would be consistent with the phenotypic heterogeneity that has long been recognized for ADHD (e.g., American Psychiatric Association, 1980, 1994; Biederman, Newcorn, & Sprich, 1991). Recently, molecular genetic studies have begun to explore sources of heterogeneity, such as DSM-IV subtypes (McCracken et al., 2000; Rowe et al., 1998; Waldman et al., 1998), with intriguing but not definitive results, suggesting that large samples are needed to guard against Type II errors in subgroup analyses.

Linkage studies. Linkage studies of ADHD show inconsistencies with one another, as well. In linkage analysis, broad sections of the genome are screened systematically to identify chromosomal regions that are shared by affected relatives more often than expected by chance. To date, three research groups have published whole genome scans for genetic loci involved in ADHD. In the first study of this kind, researchers from UCLA (Fisher et al., 2002) examined 126 affected sibling pairs (ASPs) with DSM-IV ADHD. Four chromosomal regions emerged as showing some evidence of linkage (5p13, 10q26, 12q23, and 16p13). In a second genome-wide scan with a larger sample of 270 sibling pairs (Ogdie et al., 2003), the UCLA group found stronger evidence for linkage on 16p13 and 17p11. Using 117 ASPs, a Dutch research group (Bakker et al., 2003) found significant evidence for linkage at 7p13 and 15q15, with other non-significant but intriguing results including the 5p13 region. Finally, a genome-wide scan of families from a genetically isolated community in Colombia implicated regions on 8q12, 11q23, 4q13, 17p11, 12q23, and 8p23 (Arcos-Burgos et al., 2004).

The above findings are striking in their lack of overlap with one another, with the exception of 17p11 and 5p13, and with regions in which candidate genes for ADHD are known to reside. Although fine mapping and replication with larger samples may reveal greater overlap in the above samples, Suarez, Hampe, and van Eerdewegh (1994) have shown how the low power of genome scans to find genes of small effect could lead to an inconsistent pattern of replication. Additionally, differences in sample characteristics (e.g., proportion of DSM-IV subtypes, ethnicity, comorbidity, sex ratio and socioeconomic status) may also account for divergent findings.

Multifactorial models of ADHD. The above data from candidate gene and linkage studies suggest that ADHD is influenced by multiple genes of small effect, rather than a single major gene. Additionally, the fact that correlations between MZ twins are less than 1.0 indicates that non-genetic influences are also operational. Thus, the pattern of inheritance of ADHD can be considered multifactorial or 'complex.' Within this framework, there are several ways these genetic and nongenetic factors could combine to influence the phenotype. One possibility is that there are multiple independent pathways to ADHD, each of which contains genes that are necessary and sufficient to cause a subset of ADHD cases. A second possibility is a polygenic model in which multiple genes increase risk a small amount and no gene is necessary or sufficient to cause ADHD. Such models have implications for endophenotype selection and will be discussed more extensively later.

Summary. Molecular genetic studies of ADHD have yielded inconsistent results, some of which have been resolved systematically with meta-analysis. These findings suggest the presence of genes of small effect and/or heterogeneity that, in turn, highlight the need for large samples or the targeting of phenotypes on which genes exert a large effect. Heritable endophenotypes linked to the biological basis of ADHD may therefore be useful targets because the genes they share with ADHD may have a greater effect on the endophenotype than on the disorder itself and may therefore be easier to detect.

Criteria for an endophenotype

Several researchers have proposed criteria for useful endophenotypes with regard to schizophrenia and psychiatric conditions in general (Almasy & Blangero, 2001; Gottesman & Gould, 2003; Leboyer et al., 1998; Skuse, 2001). Recently, researchers have begun to discuss these criteria with regard to ADHD (Faraone, 2003; Faraone, submitted; Waldman, submitted). While there is no universally agreed-upon definition of a promising endophenotype, proposals share several key elements.

First, a useful endophenotype should co-occur with the condition of interest. Some have argued that an endophenotype should be disease-specific (Skuse, 2001); yet, since the endophenotype may be associated with a common gene variant that has a moderate causal influence on multiple disorders, we agree with others (Almasy & Blangero, 2001; Bellivier et al., 1998; Garber & Hollon, 1991; Leboyer et al., 1998) that specificity is useful but not a requirement. Similarly, some have argued that the endophenotype should be universal within the disease condition (see Faraone, 2003). However, the probable etiologic heterogeneity of ADHD suggests that it is unlikely that any endophenotype will be present in all individuals with ADHD. Indeed, endophenotypes may be particularly helpful for elucidating risk mechanisms in genetically heterogeneous

disorders (Freedman et al., 1999). We therefore contend that universality is also not a necessary criterion.

Second, the endophenotype should be a trait that can be measured reliably. Although it has been argued that the endophenotype should have temporal stability and occur before the onset of the illness (Bellivier et al., 1998; Skuse, 2001), the possibility that gene expression varies with development or that a deficit may improve with treatment suggests that this criterion should not be a rigid requirement. Yet, endophenotypes should be stable over relatively short periods of time (i.e., more trait-like than state-like) and be held to other standards for reliability.

Third, endophenotypes should show evidence of heritability. Familial transmission provides useful data that should be followed up with twin or adoption studies to disentangle genetic and shared environmental influences. Fourth, an endophenotype should show familial overlap with the disorder in question, and twin analyses should reveal that the same genetic factors influence both susceptibility to ADHD and performance on measures of the endophenotype. As discussed above, the endophenotype should appear in individuals who carry genes for a condition but do not express the disorder itself, i.e., the unaffected relatives of affected individuals (Gottesman & Gould, 2003). Because unaffected relatives may carry fewer genes for the condition than individuals with the full disorder, it is possible, though, that the endophenotype may appear to a lesser extent in these individuals than in those affected with the disorder.

Below, we use the four criteria discussed above to assess the suitability of deficits based on clinical and experimental measures of executive functions as endophenotypes for ADHD. An additional criterion for an endophenotype is that it should be grounded in neuroscience. While we agree that such grounding is valuable, researchers may disagree as to how to judge this criterion (for a thorough review of this issue see Castellanos & Tannock, 2002). Although neurocognitive measures are only one way to index the frontal-striatal impairments observed in ADHD, we focus on them because they are more cost-effective and easier to implement than electrophysiological and neuroimaging studies and are therefore of significant interest to the field (Faraone, 2003).

Criterion #1: Association with ADHD

Over time, evidence has accumulated to support the hypothesis that the symptoms of ADHD are related to impairment in the frontal cortex and the subcortical (striatal) regions that project to it (Satterfield & Dawson, 1971). The success of stimulant medications and animal models of hyperactivity implicate dopamine pathways that are consistent with these neuroanatomical regions (e.g., Gainetdinov et al., 1999; Giros, Jaber, Jones, Wightman, & Caron, 1996; Shaywitz, Klopper, & Gordon, 1978). Additionally, there are similarities between adult patients with frontal lesions and children with ADHD (Mattes, 1980), and both structural and functional neuroimaging studies have documented abnormalities in frontal-subcortical circuits that regulate attention, inhibition and motor intentional behavior. These include the dorsolateral prefrontal cortex, the anterior cingulate cortex, the caudate nucleus and the globus pallidus (Castellanos & Tannock, 2002; Giedd, Blumenthal, Molloy, & Castellanos, 2001; Seidman & Valera, 2002). Recent neuroimaging studies further suggest smaller lobules of the cerebellar vermis in ADHD subjects compared with controls (e.g., Berquin et al., 1998). Such areas have a high concentration of dopamine transporters (Anderson, Polcari, Lowen, Renshaw, & Teicher, 2002) and are connected to cortical loops that include the prefrontal cortex via the pons and other midbrain structures (Middleton & Strick, 2002).

Also consistent with this hypothesis is a large literature revealing that individuals with ADHD exhibit relatively poor performance on clinical neuropsychological tests presumed to assess functions associated with frontal systems (Barkley, 1997a; Pennington & Ozonoff, 1996; Tannock, 1998). These functions are deemed 'executive' due to their involvement in higher-order cognitive processes including self-regulation and goal-directed behavior (Loring, 1999). It is widely agreed that executive functions include multiple component operations including working memory, response inhibition, set shifting, abstraction, planning, organization, fluency and aspects of attention (Pennington & Ozonoff, 1996), although there is not universal consensus on the hierarchy or structure of the components (see Lyon & Krasnegor, 1996, for several proposals). In the current paper, we use the term 'executive functions (EF)' for ease of explication to refer to this general class of abilities.

Group differences in ADHD vs. non-ADHD subjects. Reviews of the literature (Pennington & Ozonoff, 1996; Sergeant, Geurts, & Oosterlaan, 2002; Willcutt et al., in press a) concur that the majority of studies find group differences between individuals with ADHD and non-ADHD controls on measures of EF. Although studies have primarily examined pre-adolescent boys, EF impairments have been documented in females (e.g., Castellanos et al., 2000; Hinshaw, Carte, Sarni, Treuting, & Zupan, 2002), adolescents (e.g., Clark, Prior, & Kinsella, 2000; Fischer, Barkley, Edelbrock, & Smallish, 1990) and adults (see Seidman et al., 2004) with ADHD. Moreover, deficits appear to be robust to statistical correction for group differences in IQ and comorbid psychiatric or learning disorders (e.g., Klorman et al., 1999; Nigg, Hinshaw, Carte, & Treuting, 1998; Seidman et al., 1995; Willcutt et al., 2001).

Some researchers have hypothesized that specific aspects of EF are more strongly associated with ADHD than others. To date, inhibitory control has been the most widely discussed EF deficit in ADHD (Barkley, 1997a), with numerous studies supporting relatively poor performance on neuropsychological measures of inhibition in boys and, more recently, girls with ADHD compared with controls (e.g., Bayliss & Roodenrys, 2000; Nigg, 1999; Oosterlaan, 1996; Schachar, Tannock, Marriott, & Logan, 1995). Moreover, two studies suggest that the development of inhibitory capacity may precede other aspects of EF (Klenberg, Korkman, & Lahti-Nuuttila, 2001; Sonuga-Barke, Dalen, Daley, & Remington, 2002), supporting Barkley's (1997a) hypothesis of the developmental primacy of inhibitory control.

In a review of these data, Nigg (2001) argued for further specification of the construct of inhibition as a way of clarifying the deficits in ADHD, concluding that there is more consistent evidence for an inhibitory deficit when the deficit involves suppression of a pre-potent motor response (e.g., on the Stop or basic Go/No-go tests), but variable evidence when inhibition refers to suppression of a conflicting, secondary response (e.g., interference control on Stroop or flanker tests). This conclusion is supported by recent meta-analyses (Mourik, Oosterlaan, & Sergeant, 2005; Oosterlaan, Logan, & Sergeant, 1998; Willcutt et al., in press a) suggesting higher effect sizes for response inhibition compared with interference control in ADHD.

Working memory is also of interest to ADHD researchers. Pennington and colleagues (Pennington, Bennetto, McAleer, & Roberts, 1996; Roberts & Pennington, 1996) have made theoretically compelling arguments that intact working memory is essential to successful inhibitory control. Only a limited number of studies have specifically examined working memory in ADHD. Although some have found such a deficit in ADHD samples (e.g., Dowson et al., 2004; McInnis et al., 2003) others have not (e.g., Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004) or have found that the ADHD deficit appeared to be explained by comorbid reading difficulties (Willcutt et al., 2001). Yet, Castellanos and Tannock (2002) point out that spatial working memory is a particularly interesting candidate core deficit because of evidence from animal, neuroimaging and electrophysiological studies. Moreover, data from an extended meta-analysis by Willcutt et al. (in press b) revealed moderate effect sizes for deficits in verbal and spatial working memory in ADHD (Cohen's $d = .55$ and .63 respectively), comparable to the effect size for response inhibition.

Although other components of EF have received less theoretical attention, Willcutt and colleagues' meta-analysis illustrates that deficits in ADHD samples are also found on measures of processing speed (Trails B), planning (Tower tests), organization (Rey Osterreith), set shifting (Wisconsin Card Sorting Test; WCST) and Continuous Performance Test (CPT) omissions and commissions (Cohen's *d* ranging from .43 to .69).

Neurocognitive heterogeneity in ADHD. While the above findings underscore the association of ADHD with various aspects of EF, careful examination of the literature also suggests neurocognitive variability across and within studies of ADHD. Variability *between* studies has been noted in reviews of the literature (Barkley, Grodzinsky, & DuPaul, 1992; Pennington & Ozonoff, 1996; Sergeant et al., 2002). More recently, researchers have noted the variability *within* ADHD samples. This variability is evident in studies that have examined whether measures of EF can be used as diagnostic tools for ADHD. Data on male (Doyle, Biederman, Seidman, Weber, & Faraone, 2000) and female (Hinshaw et al., 2002) youth as well as adults (Lovejoy et al., 1999) have found that abnormal scores on EF measures are predictive of ADHD; however, normal scores on a particular EF measure (or a combination of measures (Doyle et al., 2000)) cannot rule out the disorder. This pattern is due to the fact that not every person with ADHD is impaired on every test and that some individuals with ADHD perform within the normal range on all or most measures.

Despite the apparent strength of the response inhibition weakness in ADHD, slightly less than half of the individuals in several well-characterized ADHD samples show impairment on one of the most well-studied measures of this construct, the Stop Signal Reaction Time (SSRT) from the Stop Test (Crosbie & Schachar, 2001; Nigg, Blaskey, Stawikcki, & Sachek, 2004; Nigg, Willcutt, Doyle, & Sonuga-Barke, in press). In a review of data across different ADHD research centers (Nigg et al., in press), no other neurocognitive measure was impaired in more than 50% of youth with Combined-Type ADHD. Percent of subjects with ADHD that surpassed the 90th percentile of controls on the Stroop Color Word test, Trails B and CPT commissions ranged from 44% to 16%, and aggregating tests still only captured a subsample of cases (Nigg et al., in press).

Perhaps due to the frequency with which group differences are found between ADHD and control samples, the neuropsychological variability within ADHD has not been extensively acknowledged or studied, with some exceptions (Nigg et al., in press; Sonuga-Barke et al., 2002). Yet, cognitive heterogeneity in a disorder that, as a whole, is strongly associated with neuropsychological deficits has also been seen in the literature on schizophrenia (e.g., Goldstein & Shemansky, 1995; Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000; Palmer et al., 1997). Moreover, neurocognitive heterogeneity is consistent with the phenotypic and potential genetic heterogeneity of ADHD and with the ADHD neuroimaging literature (Seidman, Valera, & Makris,

submitted). Because selection of EF measures as endophenotypes for ADHD will be most effective if the sources of neurocognitive variability are better understood, we digress briefly to discuss this issue in more detail.

A) What factors moderate the variability of EF findings across and within ADHD samples?

The literature raises several possible factors that may be associated with variability of performance on EF measures in ADHD.

Family history. A handful of studies suggest an association between a family history of ADHD and impairment on EF measures. Crosbie and Schachar (2001) found that ADHD children with poor inhibition on the Stop Test had a higher rate of familial ADHD (48%) compared with the normal-inhibition ADHD group (19%) and controls (8%). Using a different study design, Seidman et al. (1995) found that ADHD youth with a positive family history of ADHD exhibited significantly worse performance on measures of interference control and abstract problem solving, with the latter finding replicated in an extended sample (Seidman, Biederman, Faraone, Weber, & Ouellette, 1997). These reports echo studies of schizophrenia (Faraone et al., 2000c) in which relatives from families with more than one member with the disorder had greater impairment on measures that may tap attention and working memory than relatives of families with one affected member. What is not yet clear in ADHD is whether familial and non-familial cases represent unique etiologies or whether familial cases manifest more severe deficits because they carry a greater number of susceptibility genes for the disorder. Thus, whether these groups show qualitative or quantitative differences should be a goal for future studies.

Comorbid disorders. The presence of an additional learning or psychiatric disorder may modify the neuropsychological profile of ADHD youth. Several studies (Lazar & Frank, 1998; Rucklidge & Tannock, 2002; Seidman, Biederman, Monuteaux, Doyle, & Faraone, 2001; Willcutt et al., 2001) have shown that individuals with ADHD who have comorbid learning disabilities may have more severe deficits on tests of EF than individuals with ADHD alone. Although limited in number, studies of ADHD youth with comorbid anxiety disorders suggest that this subgroup shows less severe deficits on response inhibition than ADHD children without anxiety (Manassis, Tannock, & Barbosa, 2000) but more severe deficits on working memory tasks (Pliszka, 1989; Tannock, Ickowicz, & Schachar, 1995). Comorbidity between ADHD and conduct disorder (CD) and juvenile bipolar disorder (BPD) are of particular interest with regard to the genetic basis of ADHD. Family studies suggest that ADHD + CD and ADHD + BPD are distinct familial subtypes of ADHD (i.e., the disorders travel together in relatives) and that the risk of ADHD to relatives for these comorbid conditions is considerably higher than to relatives of probands with ADHD alone (Doyle & Faraone, 2002; Faraone et al., 2000b). However, impairments on SSRT response inhibition did not differentiate ADHD + CD from ADHD alone in a recent meta-analysis (Oosterlaan et al., 1998). To date, no studies have compared the neuropsychological profiles of youth who have ADHD plus BPD to ADHD alone.

DSM-IV subtypes. Several studies have found evidence for greater neurocognitive impairments in individuals with ADHD Combined-Type (ADHD-C) versus Inattentive-Type (ADHD-I) (Hinshaw et al., 2002; Houghton et al., 1999; Klorman et al., 1999; Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). In Nigg and colleagues' study, the finding (for more impaired response inhibition) was limited to boys but not girls with ADHD-C. Yet, girls with ADHD-C versus girls with ADHD-I showed more impulsive errors in Hinshaw and colleagues' study. Despite these findings, in Willcutt et al.'s extended meta-analysis (in press b), no significant differences emerged between ADHD-C and ADHD-I on any EF measure, although gender specific effects were not examined. In contrast to these variable findings, the Hyperactive/Impulsive subtype of ADHD has failed to show EF deficits in the small number of studies that have addressed this issue (Bedard et al., 2003; Chhabildas, Pennington, & Willcutt, 2001; Schmitz et al., 2002). This lack of association between deficits and hyperactive/impulsive symptoms may also explain why Kuntsi, Oosterlaan, and Stevenson (2001a) did not find response inhibition deficits in a small sample of twins with extreme hyperactivity.

B) What explains normal range performance?

Although the above factors may explain some neuropsychological variation within ADHD samples, they do not account for the many individuals with ADHD across each subtype who do not exhibit EF deficits. Explanations for this sub-sample of individuals have implications for the relationship between ADHD and EF and thus for endophenotype selection.

EF measures may not always capture frontal system impairments. One possibility is that EF measures are imperfect indicators of impairment in the frontal-subcortical circuits of interest in ADHD due to measurement issues or to a compensatory mechanism that allows some individuals to use alternative cognitive resources to solve 'frontal' tasks. Because reliable and valid measurement of EFs is crucial to their use as endophenotypes, we

will address this issue below (Criterion #2 – Measurement). With regard to compensatory mechanisms, the consequences of an early functional or structural insult to a frontal-subcortical pathway may be heterogeneous, depending on numerous genetic and environmental risk and protective factors interacting with the neural weakness. As a result, some children may be able to recruit other cognitive resources to solve tasks that would normally engage frontal circuits, although it is likely that such compensatory mechanisms would be vulnerable to disruption. Such a possibility may explain why some youth with ADHD perform well on executive measures in a structured testing situation but have real-world difficulties with organization, problem-solving, and the like when multiple potential distractors are present (Bernstein & Waber, 1990). Although compensatory mechanisms have not been studied extensively with regard to ADHD, studies of schizophrenia (Callicott et al., 2003) and obsessive-compulsive disorder (Deckersbach et al., 2002; Rauch, Savage, Alpert, Fischman, & Jenike, 1997) provide evidence for this phenomenon. Further work integrating neuroimaging paradigms and neurocognitive testing in ADHD is needed to explore whether compensatory mechanisms account for normal range performance in some subjects with ADHD.

EF deficits may not be the underlying deficit in ADHD. A second possibility is that EFs may not be the core deficit in ADHD. Instead, the overlap between ADHD and EF deficits could result from referral bias, assortative mating in parents or an alternative deficit that causes variably impaired performance in some or all cases on measures of EF either directly or via ADHD symptoms.

Referral bias. That ADHD and EF could co-occur as a result of referral bias was considered by Pennington and Ozonoff (1996), given that the only study in their review that did not show ADHD versus control differences on EF tests assessed a population sample. In this case, the overlap between the two conditions in clinic patients, who represent the majority of subjects in neuropsychological studies of ADHD, could be due to individuals exhibiting both impairments being more likely to be referred for treatment. This hypothesis is consistent with studies (Biederman et al., 2004; Clark et al., 2000; Nigg, Quamma, Greenberg, & Kusche, 1999) that show greater functional impairment in youth with disruptive disorders who also show EF deficits. Yet, in Wilcutt et al.'s extended meta-analysis (in press), the mean effect size for EF measures in community samples ($d = .49 \pm .06$) was only slightly lower than clinic-referred studies ($d = .56 \pm .04$). Thus, while referral bias may exist, it is unlikely to be the sole cause of the comorbidity of ADHD and EF deficits.

Assortative mating. Because both EF deficits and ADHD are associated with academic impairment and potentially with educational/occupational attainment and related social networks, adults with ADHD may be likely to meet and have children with adults with EF impairments. In turn, children of these individuals would exhibit both conditions if each were separately familial. Evidence for this non-random mating between individuals with ADHD and those with EF deficits has not been investigated extensively, although Nigg and colleagues (2004) found evidence for assortative mating based on IQ, as expected, but not for EF measures.

Alternative causal process. The above possibilities would explain the comorbidity between ADHD and EF deficits if EF deficits were not the core (i.e., necessary and sufficient) deficit leading to ADHD. Although a full discussion of alternative core processes is outside the scope of the current paper, state regulation impairments and delay aversion are two such mechanisms to consider as underlying at least some ADHD cases.

State regulation impairments. Briefly, Sergeant and colleagues (Sergeant, 2000; van der Meere, Gunning, & Stemerdink, 1996) have proposed a 'cognitive-energetic model' of ADHD, based on the work of Sanders (1983). Among the interesting contributions of this model is the idea that basic computational mechanisms for information processing are largely intact in ADHD but that impairments occur at a secondary level of state factors (arousal, activation and effort) that control how cognitive resources are allocated. In this model, a failure of inhibition (or other EFs) could, in part, result from a failure of *activation* of the inhibitory mechanism rather than a deficit in the mechanism itself. Although cortical arousal involves dopamine circuits, it also involves a complex interplay of several other neurotransmitter systems including norepinephrine, acetylcholine and serotonin. This model offers an explanation for the variability across and within ADHD samples and broadens the candidate pathophysiological mechanisms involved in ADHD.

Consistent with this theory are 1) increased reaction time (RT) variability in ADHD samples across a variety of computerized measures (Castellanos & Tannock, 2002), suggesting that individuals with ADHD tend to respond inconsistently (both faster and slower) compared to controls; and 2) evidence that the rate of presentation of stimuli affects ADHD subjects differently than controls (e.g., slow rates lead to poor performance, potentially due to under-arousal (Scheres, Oosterlaan, & Sergeant, 2001)). Kuntsi and colleagues (Kuntsi, Stevenson, Oosterlaan, & Sonuga-Barke, 2001b) note that Oosterlan et al. (1998) found slower baseline AND stop signal RT in ADHD youth versus controls, with ADHD youth just as likely to trigger the inhibitory process. In Kuntsi's own study (2001), RT variability

was a better discriminator between hyperactive and control youth than inhibition or working memory measures. Despite this intriguing evidence, in Nigg et al.'s study of heterogeneity (in press), only half of ADHD subjects showed significant RT variability compared with controls. As discussed by Sergeant (in press), better measures are needed to fully document the contribution of state-regulation factors in ADHD.

Shortened delay gradients. A second alternative mechanism that could underlie ADHD involves altered reinforcement and extinction processes. Sagvolden and colleagues (Johansen, Aase, Meyer, & Sagvolden, 2002; Sagvolden, Aase, Zeiner, & Berger, 1998) have posited that dysfunction in the mesolimbic-cortical branch of the dopamine system produces a shorter 'delay gradient' in individuals with ADHD. Oversimplified, one of the key elements of this model is that the impact of a reinforcer, via dopamine release in the nucleus accumbens, will only occur if the delay between the reinforcer and behavior is short. If frequent, proximal and potent reinforcers are lacking or distal, goal-directed behavior is disrupted and inattention and motor impulsivity occur. These and other researchers (Sonuga-Barke, 2002) have elaborated on this model, suggesting that some individuals with ADHD are characterized by delay-aversion, i.e., motivation to avoid delay.

Several studies have found impairments in ADHD youth as compared with controls on tasks designed to assess delay aversion (e.g., Kuntsi et al., 2001a; Sonuga-Barke, 2002). Yet, when Solanto et al. (2001) compared performance on the Stop Test and a delay aversion task in ADHD, measures were not highly correlated but together identified the majority of ADHD cases in a discriminant function analysis. This finding was replicated in pre-schoolers (Sonuga-Barke et al., 2002). Based on these data, Sonuga-Barke (2002) has proposed a dual pathway model of ADHD involving 1) an inhibitory deficit related to prefrontal regions and projections from the basal ganglia and striatum (involving the mesocortical branch of the DA system) and 2) an 'altered reward/reinforcement and extinction' deficit related to the nucleus accumbens and ventral-striatal network (involving the mesolimbic branch of the DA system). Whether the specific predictions of this model are borne out will require further empirical study. Yet, the model is important in that it is the first to formally posit multiple neurocognitive pathways to ADHD.

Summary and conclusions – Criterion #1. Numerous studies have documented impairments in youth with ADHD on measures of EF, with compelling data highlighting measures of response inhibition and working memory. This literature suggests that such measures fulfill Criterion #1 for an ADHD endophenotype. Nonetheless, effect sizes are modest, and data indicate substantial variability within and across ADHD samples. Thus far, such variability has only received limited attention in the field. Studies suggest several potential moderators of test performance, including a family history of ADHD, comorbidity and DSM-IV subtypes/symptom dimensions. Additionally, a substantial percentage of youth with ADHD may perform within the normal range on measures of EF upon formal testing. This normal range performance may reflect quantitative differences in severity of impairment, the use of compensatory neurocognitive mechanisms in some individuals, and/or the possibility that additional mechanisms underlie the neurocognitive impairments in some ADHD cases.

Presuming ADHD and EFs show some familial overlap (see Criterion #4), increased attention to neurocognitive heterogeneity offers the possibility of providing greater power for gene-finding, particularly if discrete neurocognitive subtypes exist within ADHD or if there is a strong association between specific genes and performance on individual measures. Yet, neurocognitive heterogeneity does not automatically reflect genetic heterogeneity, but could also result from pleiotropic effects of a core set of genes, genotypic variation outside of these genes or moderating factors such as development, environment, co-occurring conditions moderating performance and measurement issues (e.g., differential reliability of measures). In order to begin to address these possibilities, we recommend that ADHD endophenotype researchers move beyond the search for a single, core cognitive deficit in ADHD to ask 'How much neurocognitive heterogeneity exists in ADHD?' and 'What genetic and environmental risk factors account for this heterogeneity?'

Criterion #2: Measurement issues in the assessment of executive functions

It is widely agreed that greater attention to the psychometric properties of EF measures is needed (Denckla, 1996; Nigg, 2001; Pennington et al., 1996; Sergeant et al., 2002). Before measures of EF can be used as endophenotypes (or to assess neurocognitive heterogeneity in ADHD), we must confirm that tests are measuring what they are intended to measure in a reliable and valid way. For ease of discussion, we have organized our review in terms of reliability, sensitivity, validity (construct and discriminant) and developmental factors, although these issues are interrelated.

Reliability. The utility of any measure is constrained by its reliability. Although the long-term stability of executive deficits has not been addressed in ADHD, impaired neuropsychological functioning on a battery that included executive measures was

documented in a four-year follow-up of patients with schizophrenia (Faraone et al., 1999). Published clinical measures generally provide evidence of reasonable test–retest reliability in their manuals (e.g., Delis, Kaplan, & Kraemer, 2001; Wechsler, 2003). Yet, few objective studies have formally assessed the reliability of EF measures. Response inhibition variables on the Stop Test have previously been judged to be reliable (Kindlon, Mezzacappa, & Earls, 1995; Logan, Schachar, & Tannock, 1997); however, Kuntsi and colleagues (2001b) found a low test–retest reliability (intraclass correlation = .11) over several weeks on the SSRT calculated based on a different algorithm. These authors also assessed measures of working memory (delayed response alternation [DRA], sentence span and counting span), dual task performance, which involves the allocation of cognitive resources to tracking and memory tasks that are performed simultaneously. High test–retest reliability (i.e., intra-class correlations >.7) was found for the DRA and the delay aversion measure. Moderate reliability (intra-class correlations between .69 and .5) was found for sentence span and counting span.

Although these data are reassuring overall, additional studies underscore the complexity of the reliability issue. Pennington et al. (1996) found that the Wisconsin Card Sort Test (WCST) showed ceiling effects and poor reliability in a school-based sample but better test–retest reliability for impaired scores. State variables may impact performance on measures of EF, as well. For example, shorter sleep duration can affect verbal executive tasks (Harrison & Horne, 1998). Randazzo, Muehlbach, Schweitzer, and Walsh (1998) found that abstract thinking was influenced by even one night of sleep restriction, and Steenari et al. (2003) found that objectively measured sleep problems in children were associated with incorrect responses on a working memory measure. Thus, it is conceivable that some of the variability observed in the ADHD literature reviewed above could be due to limited reliability or state variables. Assessing neurocognitive deficits that are stable over time and cataloguing reliability at different levels of performance would provide increased control over error variance.

Sensitivity. Because many commonly used clinical neuropsychological tests of EF were adapted from the field of adult neuropsychology to measure the effects of a significant cerebral insult (Pennington & Ozonoff, 1996), such tests may not capture subtle cognitive impairments occurring within the context of development. Since individuals with EF deficits are highly responsive to external structure (Goldberg & Podell, 1995), the structured testing situation may also mask less severe impairments. Such a phenomenon has been documented by Draeger and colleagues (Draeger, Prior, & Sanson, 1986) who found that performance on a CPT task deteriorated significantly in ADHD but not control children when the examiner left the room. Additionally, normal range performance may represent a relative deficit for individuals with above average intellectual ability (Kremen et al., 2000). Because of their potentially greater sensitivity, measures from the cognitive or developmental sciences may provide a useful supplement to clinical measures (MacDonald & Carter, 2002; Nigg, 2000). Computerized measures can produce a fine-grained continuous variable reflecting the faster or slower speed of a response, tapping small inter-subject differences in processing, and identifying both higher and lower than average performance.

While limited sensitivity may account, at least in part, for normal range performance in ADHD subjects, the fact that variability is found on measures such as the Stop Test further indicates that the heterogeneity within ADHD samples is real. Thus, even with limited sensitivity, clinical measures of EF may be useful for selecting individuals whose deficits lay on the more severe end of the continuum since, in linkage studies, a high rate of false positive findings would be a greater liability than false negatives (Faraone et al., 1995). Still, measures with good sensitivity should be prioritized as candidate endophenotypes, because low sensitivity may limit our ability to detect subtle deficits in individuals for quantitative trait analyses as well as in unaffected relatives to provide support for the familial overlap of different measures with ADHD.

Construct validity. Because of the 'molar' nature of many clinical neuropsychological measures (Pennington & Ozonoff, 1996), deficits in other domains may impact EF test scores such that impaired results that are not due to an EF deficit per se. For example, poor Organization scores (Bernstein & Waber, 1996) on the ROCF could result from visual spatial deficits rather than organization problems. Neuropsychologists (Denckla, 1996; Pennington & Ozonoff, 1996; Sergeant et al., 2002) have advocated the use of control measures to parse out the executive component of tasks. Such procedures are often used clinically as part of the process approach to neuropsychology (White & Rose, 1997) but are not regularly incorporated into research designs with traditional neuropsychological tasks. With the publication of new tests that provide control tasks (e.g., Delis Kaplan Executive Function System (Delis et al., 2001); WISC-PI (Kaplan, Fein, Kramer, Delis, & Moris)) and intra-subject discrepancy scores, researchers can more easily incorporate control tasks into their batteries.

Measures derived from experimental cognitive psychology may also be useful for targeting specific processes. In relation to schizophrenia, MacDonald and Carter (2002) have argued that experimental tasks tap more precise functions and can limit the

use of alternative strategies for solving a task. Due to the lack of normative data and standardization across research labs, experimental tasks must be used cautiously and clearly described in publications. For example, researchers at the 5th Annual ADHD Molecular Genetics Conference (Faraone, submitted) found the use of different versions of unpublished tasks across sites to be a major challenge to collaboration and replication. Additionally, as discussed above, the same task can have highly variable reliability if different scoring algorithms are used (Kuntsi et al., 2001b; Logan et al., 1997).

Also related to construct validity is whether functional impairment on measures of EF is confounded by lower intelligence or concurrent mental disorders. The mean full scale IQ score of groups with DSM-IV ADHD typically falls .75–1.0 standard deviations below the mean of non-ADHD comparisons (e.g., Chhabildas et al., 2001; Hinshaw et al., 2002; Lahey et al., 1998), and the majority of children with ADHD meet criteria for at least one comorbid diagnosis (e.g., Angold, Costello, & Erkanli, 1999; Willcutt, Pennington, Chhabildas, Friedman, & Alexander, 1999). Based on these data, some researchers argue that intelligence and symptoms of comorbid psychopathology should be controlled in statistical analyses to parse out the effects of these correlated variables (e.g., Lahey et al., 1998; Werry, Reeves, & Elkind, 1987). Yet, others (e.g., Barkley, 1997b) have pointed out that the same deficits that underlie poor performance on EF measures may cause a child to perform poorly on standardized tests of intelligence. Indeed, theoretical models of intelligence often include executive control as one component (e.g., Lyon & Krasnegor, 1996). Moreover, executive deficits could account developmentally for IQ weakness in ADHD, either directly via the functionality of problem-solving skills or indirectly by interfering with academic success and the quantity of learned information. As a result, partialling of IQ in EF studies is debated and handled differently across studies. Additionally, evidence that ADHD and learning disabilities as well as CD and BPD share familial risk factors (Doyle & Faraone, 2002; Loo et al., 2004; Willcutt et al., 2002) raises the possibility that controlling for these variables would mistakenly remove a portion of the variance that is associated with ADHD. Although these issues have not been resolved, as discussed above, EF deficits in ADHD versus control samples are generally robust to correction for IQ and comorbid disorders.

Discriminant validity. EF deficits are found in a variety of disorders other than ADHD including autism, schizophrenia, phenylketonuria and, arguably, conduct disorder (Pennington & Ozonoff, 1996; Sergeant et al., 2002). In a recent review, Sergeant et al. (2002) suggest that discriminant validity may still emerge at the task level with 1) better control of ADHD symptoms when examining deficits in other disorders as well as 2) the inclusion of psychiatric comparison groups. However, discriminant validity need not be demonstrated at the task level for EF measures to be useful endophenotypes. Pennington and Ozonoff (1996) have argued that discriminant validity may also emerge at the neurobiological level. In this case, endophenotypes could be used to identify susceptibility genes, and subsequent exploration of the impact of risk alleles on neurobiological processes may in turn reveal differences between disorders in terms of severity of the core problem (e.g., the extent of dopamine depletion in the prefrontal cortex [PFC]), differences in the timing of a deficit, different impairments within the PFC, impairments in different regions that connect to the PFC, impairments in the PFC plus additional differing regions (Pennington & Ozonoff, 1996). Alternatively, the use of endophenotypes may enable detection of risk alleles common to several neurodevelopmental disorders of childhood that combine with unique variants to produce each specific disorder. This possibility is underscored by the fact that regions of interest from both the Dutch and US linkage studies of ADHD overlap with regions of interest in linkage studies of autism (Bakker et al., 2003; Smalley et al., 2002).

Developmental changes in executive functions. Finally, data on normative developmental changes from childhood into adulthood are sparse for many tasks, particularly experimental measures. In one study that examined performance on the Stop Test across the lifespan (Bedard et al., 2002), inhibitory control and a pure measure of reaction time improved throughout childhood, but performance on the pure reaction time measure began to decline at age 30 whereas a decline in inhibitory control was not seen until age 60. A study by Klenberg et al. (2001) suggests that, consistent with Barkley's theories, components of EFs on the NEPSY battery mature at different ages. More generally, it is fairly clear that different forms of executive control mature at different rates if one considers task output modality (motor versus language, for example (Dempster, 1992)). Such studies suggests the need to use large, non-clinical samples to better understand what is 'normal' on measures of EF across a wide range of ages. On a practical level, tasks that remain valid across a wide range of development will be useful endophenotype candidates in that they can be administered to relatives of all ages in family studies. Yet, effective developmental assessment may require changing tasks as well as norms. As Denckla (1996) points out, tasks sensitive to EF processes at a young age may be too simplistic or automated to tap executive processes in older individuals. Thus, attention to developmental sensitivity of particular tasks and to task modality may improve precision of

measurement, and researchers must consider the benefits of assessing similar functions with related tasks at different ages (see Diamond, Prevor, Callender, & Druin, 1997, for an example).

Summary and conclusions – Criterion #2. The psychometric properties of EF measures have not been documented extensively, but available data suggests that reliability, sensitivity and construct validity of EF tasks should not be taken for granted. Better cataloguing and assessment of reliability at different levels of performance would provide increased control over error variance. The possibility that state variables and non-EF factors may influence performance supports the use of strategies to reduce the effects of error on a single test. Computerized experimental measures offer the potential for assessment of the full range of ability, via measurement of reaction time rather than only accuracy, and for more precise targeting of a specific component of EF compared with clinical measures. Yet, such measures also have limitations at the present time in terms of standardization across labs and normative data. Clinical measures that exhibit limited sensitivity may still be useful to select homogenous subgroups of individuals who show more significant levels of impairment.

Criterion #3: Genetics of executive functions

For neurocognitive measures to be useful endophenotypes for ADHD, they should themselves show evidence of heritability and association with specific genes. There is a significant literature suggesting that general cognitive functioning (IQ) is highly heritable (Plomin, 1999). Yet, few twin and candidate gene studies have examined measures of EF.

Twin studies. Table 1 shows published twin studies that have examined measures of EF as well as aspects of attention relevant to ADHD. The most salient features of this literature are the small sample sizes and limited number of measures that have been examined. Yet, considered together, these studies provide preliminary evidence that such measures show genetic influence. The intraclass correlation between MZ twins is higher than for DZ twins for most measures. Heritabilities range from zero to 88%, with the majority of studies showing at least some genetic influence based on formal model-fitting analyses or estimates using intraclass correlations (Falconer & MacKay, 1996). Because of sample sizes, specific estimates of heritability should be interpreted cautiously, and non-significant studies (e.g., Campana, Macciardi, Gambini, & Scarone, 1996) may have lacked adequate statistical power to detect small to moderate levels of heritability.

Although additional studies with large samples are needed, these preliminary data suggest that measures may have lower heritability than ADHD, which has been estimated to range from .7 to .9 (Thapar et al., 1999; Waldman & Rhee, 2002). Given the measurement issues discussed above, it is possible that error or low reliability may be contributing to their lower heritabilities. Furthermore, measures that are not normally distributed (e.g., a count of commission errors) may not be amenable to quantitative genetic analyses, even after data transformation procedures. Yet, even if such measures are less heritable than ADHD, they may still be more useful for finding genes than the disorder itself if a smaller number of genes contribute to the EF measures than contribute to the overall ADHD diagnosis. For example, since the magnitude of effect for a single gene depends on the number of genes involved (Faraone et al., 2000b; Risch, 1990a), an endophenotype with three genes contributing to a heritability of .5 would be more powerful than a behavioral phenotype with 20 genes contributing to a heritability of .8.

Candidate gene studies of EF tasks. A small number of published studies have examined the association between specific genes and measures of attention and EF in non-ADHD samples. The Valine (Val) allele of the gene for the Catechol-O-methyltransferase (COMT) enzyme leads to a four-fold increase in the degradation of dopamine compared to the Methionine (Met) allele. Several studies have demonstrated an association between the Val allele and increased perseverative errors on the WCST. Egan and colleagues (Egan et al., 2001) found a dose–response relationship between the Val allele and perseverative errors in both schizophrenic and control patients, with this genotype explaining 4.1% of the variance in this measure. The association between the Val allele and perseverative errors has been replicated in other samples of controls and patients with schizophrenia (Joober et al., 2002; Malhotra et al., 2002). Additionally, using fMRI, Egan et al. (2001) found that an increased number of Val alleles was associated with greater activation (lower physiologic efficiency) of the dorsolateral PFC and the anterior cingulate during a working memory test.

A study using the attention network task (ANT), a computerized measure based on Posner's model of attention, has also yielded interesting findings for four genes of interest in ADHD (DRD4, DAT, COMT and MAOA; Fossella et al., 2002). In this study, the executive attention (Conflict) scale, which includes aspects of cued reaction time and flanker tasks and showed evidence of heritability in a twin study, also showed the most robust associations with specific genes; however, results were contrary to expectation. For DRD4, less efficient performance was associated with having the 4-repeat allele of the Exon III VNTR. This polymorphism contributed 3.9% of the overall

Table 1 Twin studies of neuropsychological measures of attention and executive functions

Study	Ns (pairs) MZ/DZ	Measures	Key variable	Twin intraclass correlations rMZ	rDZ	Heritability (h^2)
Goodman & Stevenson, 1989	102/111	Wechsler	FFD (attention and working memory)	.60	.44	.32[a]
		'E' scan	'E' scan (attentiveness)	.54	.33	.42[a]
Bartfai, Pedersen, Asarnow, & Schalling, 1991	10 MZA 10 MZT	SPAN	SPAN (visual attention/ target identification)	.53	−.06	.71[b]
Pennington et al., 1996	20/30	WCST	Perseverative Errors	.49	.21	.56[a]
			Total Errors	.60	.16	.88[a]
Myles-Worsley & Coon, 1997	59/33	SPAN	Accuracy (visual attention/ target identification)	.19	.31	Models not fit to data.
		SSAT	Baseline accuracy (average identification accuracy)	.44	.01	Model parameter did not differ significantly from 0.
			P/N ratio (selective attention)	.51	.20	.41[b]
		degraded stimulus CPT	d' (discrimination between target and non-target)	.26	.08	.28[b] (Model parameter did not differ significantly from 0).
			Beta (decision criteria)	.37	−.14	Models not fit to data.
Fan, Wu, Fossella, & Posner, 2001	26/26	ANT	Alerting (maintenance of an alert state)	.47	.38	.18[b]
			Orienting (visual orienting)	.10	.40	.00[b]
			Conflict (executive control)	.73	.28	.72[b]
Holmes et al., 2002	20/20	MFFT	# correct (attention)	.79	−.42	Heritability not calculated; Authors conclude MFFT # incorrect may be genetically influenced.
			# incorrect (impulse control)	.73	−.08	
			mean RT (speed of information processing)	.80	.31	
		CPT-IP	Matches (attention)	−.18	.53	
			False alarms (impulse control)	−.10	.38	
Campana et al., 1996	15/9	WCST	Categories Completed	.02	−.06	Heritabilities based on intrapair correlations did not differ significantly from zero.
			Total Errors	.33	−.03	
			Perseverative Errors	.17	−.01	
Ando, Ono, & Wright, 2001	143/93	Revised Shah & Miyake (1996) spatial & verbal WM span	Verbal Executive (verbal WM)	.44	.23	.43[b]
			Spatial Executive (spatial WM)	.50	.22	.49[b]

Table 1 Continued

Study	Ns (pairs) MZ/DZ	Measures	Key variable	Twin intraclass correlations rMZ	rDZ	Heritability (h^2)
Swan & Carmelli, 2002	80/78	Wechsler	Digit Symbol (processing speed)	.73	.19	.68[b]
		Stroop	Color-Word Interference (naming/ processing speed/ interference control)	.55	.14	.50[b]
		Trail Making B	Seconds to completion (set shifting)	.42	.30	.50[b]
		COWA	Verbal Fluency (initiation & maintenance of word production set)	.51	.41	.34[b]
				Male/female	Male/female	
Stins, van Baal, Polderman, Verhulst & Boomsma, 2004	32 MZ male/ 22 DZ male	Stroop	Color (Color-naming/effortful semantic processing/processing speed)	.78/.60	.47/.38	.70[b]
			Color-Word (Word recognition/ color-naming/effortful semantic processing/processing speed/interference control)	.75/.70	.37/.68	.74[b]
	43 MZ female/ 16 DZ female	Flanker	Interference (Interference control)	.44/.55	.11/.32	.49[b]
			Overall Reaction Time (Reaction time)	.38/.35	−.01/.18	Models not fit to data.
			Flanker Effect (Interference control)	.12/.09	−.07 .52	Models not fit to data.

'E' scan = scattered letters test where subject crosses out the letter 'E'; FFD = Freedom From Distractibility; SPAN = Span of Apprehension Test; SSAT = Spontaneous Selective Attention Task; CPT = Continuous Performance Test; ANT = Attention Network Task; MFFT = Matching Familiar Figures Test; WCST = Wisconsin Card Sort Test; WM = Working memory; MZA = Monozygotic twins reared apart; MZT = Monozygotic twins reared together; DZT = Dyzygotic twins reared together; COWA = Controlled Oral Word Association; [a] = based on intraclass correlation; [b] = based on biometrical model-fitting.

variation in this scale. This finding was unexpected because the 7-repeat allele is associated with a blunted response to dopamine and has been the high-risk allele in most studies of ADHD (Faraone, Doyle, Mick, & Biederman, 2001). Two DRD4 polymorphisms from the region 5' to the gene transcription start site were also examined. Although the120 base pair repeat upstream of the start codon did not show a significant relationship to test performance, a dose–response pattern was observed regarding a C/T single nucleotide polymorphism (SNP). Here, the C/C genotype was associated with worse performance compared to the T/T genotype. Again, this relationship was the opposite of what might be hypothesized because transcription of the DRD4 gene from the T allele is reduced by 40% compared with the C allele (Barr et al., 2001).

Fosella et al. (2002) also found that two MAOA polymorphisms (the 3-repeat allele of the MAOA promoter repeat polymorphism [MAO-LPR], which has been associated with lower transcription induction, and a silent C to T change in exon 14 [C1460T]) showed an association with worse performance on the executive attention scale. Performance on the Alerting scale of the ANT was also associated with the MAOA- LPR (3 repeat). The DAT1 (10 repeat allele) and COMT (Met allele) showed trends towards associations with worse performance but these relationships did not reach statistical significance; however, the presence of the COMT Met allele plus the MAOA LPR 3 repeat allele was associated with worse performance on the executive attention scale. Consistent with the DRD4 finding, association with MAOA-LPR and the trends for DAT1 and COMT also fit the pattern of alleles associated with higher levels of synaptic dopamine or dopamine signaling relating to worse test performance. Also interesting was that, similar to the findings for COMT and the WCST above, genes only contributed a small amount of variance (<5%) to the scales with which they were associated.

Finally, Auerbach, Benjamin, Faroy, Geller, and Ebstein (2001) examined the relation between DRD4 and cognitive functions relevant to ADHD in healthy one-year-old infants. Those with the exon III VNTR 7-repeat allele showed lower sustained attention (shorter duration of looking and shorter latencies to first look away) than those without this allele. Additionally, the shortest attention was found in infants who had the DRD4-7 allele and were homozygous for the short allele of the serotonin transporter gene promoter (5-HTTLPR).

Summary and conclusions – Criterion #3. Twin studies examining the heritability of EF measures are few in number, and most are characterized by small sample sizes. Thus, this literature does not provide a definitive resource for selecting the most heritable measures for endophenotype studies. Even so, studies allow for some preliminary conclusions – namely, that such measures may be genetically influenced but may be less heritable than ADHD. Given evidence reviewed above, measurement error may account for at least some of this reduced heritability. A possibility that has not been explored is whether extreme EF deficits are more strongly heritable than individual differences across the distribution.

Even if the heritability of the endophenotype is lower than for ADHD as a whole, however, endophenotypes can still be useful for molecular genetic studies if the magnitude of the effect of a given gene on a particular endophenotype is larger than it is for the disorder. Studies suggest an association between the COMT Val allele and perseverative errors on the WCST, and other studies suggest a role of DRD4, MAOA and 5HTT in aspects of attention. Yet, none of these studies have documented a gene contributing large amounts of variance to test performance. Additionally, a handful of studies provide evidence of multiple genes contributing to some measures. Because the most useful endophenotype measures will be those that are genetically simple rather than complex, the extent of genetic complexity of neurocognitive measures requires further investigation.

Criterion #4: Familial/genetic overlap of executive functions and ADHD

Family studies. Neurocognitive deficits in relatives have been documented in siblings and parents of probands with other disorders that are associated with EF deficits, such as schizophrenia (e.g., Cornblatt & Malhotra, 2001; Faraone et al., 1999) and autism (e.g., Piven et al., 1997; Hughes et al., 1999]. To date, the data in ADHD samples have been less robust. Two studies failed to find neurocognitive deficits in parents of ADHD youth on measures of attention and EF (Asarnow et al., 2002; Murphy & Barkley, 1996). Although Murphy and Barkley acknowledge the small size of the groups in their study, Asarnow and colleagues assessed nearly 200 parents and thus had substantial power to detect differences, and impairments were found in parents of patients with schizophrenia.

The above studies did not distinguish between parents who did and did not have ADHD themselves. This distinction is useful because neurocognitive deficits in unaffected relatives would suggest that impairments are part of the underlying liability to ADHD, whereas the presence of such deficits in affected relatives only suggests that they result from the disorder or from unique environmental influences. Studies that have distinguished between affected and unaffected relatives of ADHD probands have found variable results, but the general pattern suggests some evidence of subtle deficits in unaffected relatives, despite greater deficits in affected

relatives. Seidman, Biederman, Monuteaux et al. (2000) compared affected and unaffected siblings of males with ADHD to unaffected siblings of male controls on the Stroop, WCST, an auditory CPT, measures of verbal learning, the ROCF and a letter cancellation test. Unaffected siblings did not differ from control siblings on individual measures, although the combined neuropsychological battery was nearly able to significantly differentiate between these groups ($p = .06$). The siblings of ADHD probands who themselves had ADHD showed impairments on the Stroop, the WCST and a measure of verbal learning.

Evidence of subtle impairments in unaffected relatives comes from Slaats-Willemse, Swaab-Barneveld, de Sonneville, van der Meulen, and Buitelaar (2003) on measures of inhibition in multiplex families. They assessed 25 youth with at least one other relative with ADHD, their 25 unaffected siblings and 48 age- and IQ-matched normal controls. Measures included the Stroop Interference subtest, false alarms on the Go–No-Go test and commission errors from a visual CPT. On the three tasks, unaffected siblings had intermediate scores between the ADHD and control groups, although the differences between unaffected relatives and controls fell short of statistical significance.

In a larger study, Nigg et al. (2004) assessed the variability of reaction time on EF and related measures (Stop Test, Trails B, Stroop and Tower of London) in over 350 relatives of ADHD probands. Significant proband–relative correlations indicated that measures were familial, but the magnitude of these correlations was modest (.03 to .19). Impairments were found on RT variability for mothers, the SSRT for mothers of female probands, and Trails B for relatives of probands with ADHD-C, and the latter two findings withstood correction for relatives' ADHD.

The above three studies suggest that deficits in unaffected relatives may be subtle, with positive or near-positive findings emerging when strategies are employed to maximize power to detect impairments. For example, in Seidman et al.'s study (2000), combining information across tests may have aggregated subtle impairments into a more robust measure of neuropsychological integrity. In Slaats-Willemse et al.'s paper (2003), assessing multiplex families, who theoretically possess more susceptibility genes for ADHD than families with one affected individual, may have facilitated the detection of cognitive impairments associated with the genetic underpinnings of the disorder. Nigg et al.'s study (2004) suggests a stronger association of deficits with relatives of females and/or ADHD-C. Recently, Doyle et al. (in press) tested these ways of maximizing power to detect deficits in a large sample of relatives of female ADHD probands. Overall results were similar to the Seidman et al. (2000) study based on parallel methodology in relatives of boys. The battery as a whole distinguished between unaffected relatives and controls, and greater impairments were seen in affected versus unaffected relatives; however, limiting analyses to multiplex families improved detection of impairments in unaffected relatives. In these individuals, impairments emerged on measures of EF, processing speed and mathematics skills, i.e., on Wechsler Oral Arithmetic subtest, the Stroop Color, Color-Word and Interference subtests and the WRAT-R Arithmetic test. No robust differences emerged between relatives of probands with ADHD-C and ADHD-I, with the exception of clear impairments for relatives of ADHD-I but not ADHD-C on a measure of processing speed (Wechsler Digit Symbol/Coding).

In sum, when EF impairments in relatives of ADHD youth are found, they are of low magnitude, more notable in affected compared with unaffected relatives, typically observed on only a minority of measures, and as yet not well-replicated. Yet, despite the lack of robust findings, the fact that several studies find some evidence of deficits in unaffected relatives provides support for partial familial overlap of ADHD and EF on some measures.

Adoption studies. Two published adoption studies have examined laboratory measures in the biological and adoptive relatives of ADHD probands, although the majority of measures were related to aspects of attention and reaction time rather than aspects of EF per se. In one study, biological parents of ADHD children performed more poorly on measures of visual attention and reaction time than did adoptive relatives of ADHD children (Alberts-Corush, Firestone, & Goodman, 1986), but no differences between biological and adoptive parents were found on an impulsivity measure from a maze test. In the second study, Nigg, Swanson, and Hinshaw (1997) found that biological parents of ADHD boys showed hemispheric asymmetry on a visual-spatial orienting task, consistent with a deficit in alerting, compared with adoptive parents of ADHD boys and parents of control boys. This pattern of response may be relevant to broad conceptions of EF that include vigilance and arousal regulation (e.g., Barkley, 1997a), although others would view the alerting network as essentially a separate network from the executive frontal-striatal loops (Berger & Posner, 2000) and potentially supporting alternative endophenotypes for ADHD.

Twin studies. Thus far, three twin studies have assessed the genetic overlap of ADHD and measures of neurocognitive functioning. The first examined whether ADHD shares genetic variance with parent-ratings of EF (Coolidge, Thede, & Young, 2000). The 8-item scale showed a heritability of .77 and a phenotypic correlation of .83 with ADHD, the majority of which ($r = .79$) was due to genetic factors. Although these findings are intriguing, it is

possible that shared method variance rather than an actual genetic relationship is contributing to the high genetic correlation of these phenotypes, given that parents were reporting on both ADHD and EF symptoms. More data on the construct validity of such self-report scales of EF is also needed.

Two studies used population-based twin samples to assess the relation between ADHD symptoms and performance on a battery of neuropsychological tests (Chhabildas, Willcutt, & Pennington, submitted; Kuntsi & Stevenson, 2001). Using the correlation of the two phenotypes in MZ versus DZ twins, twin studies allow estimation of bivariate heritability (h_g^2). This statistic ranges from zero to 1 and indicates the extent to which variability in one trait is attributable to the same genetic influences that impact another trait. Kuntsi and colleagues examined the bivariate heritability of extreme hyperactivity and measures of working memory, delay aversion and reaction time – all of which had shown group differences between hyperactive and control children. The SSRT was not assessed in this study because the mean score of the hyperactive group on this measure did not differ significantly from controls. A composite measure of cognitive tasks that best discriminated between hyperactive and control youth was also examined. This score incorporated reaction time measures (standard deviation and mean), omission errors, delay aversion and verbal IQ. Results showed genetic overlap between extreme hyperactivity and RT variability ($h_g^2 = .64$), which may tap state regulation, and of the composite discriminant score ($h_g^2 = .80$). Bivariate heritability estimates were relatively high for commission errors ($h_g^2 = .60$); however, these were not statistically significant due to high standard errors and the small sample size. Delay aversion did not show any evidence of genetic overlap with extreme hyperactivity ($h_g^2 = -.06$).

The second twin study examined a larger sample of twins selected for DSM-IV ADHD (Chhabildas et al., submitted) and measures of inhibition (SSRT and CPT commission errors), working memory (sentence and counting span), vigilance (CPT omission errors), perseverative errors (WCST), and processing speed (WISC-R Coding and Trailmaking). Estimates of bivariate heritability were somewhat lower than those obtained by Kuntsi and Stevenson (2001; $h_g^2 = .20–.38$), but were significant for all neurocognitive variables with the exception of perseverative errors. Higher bivariate heritabilities were obtained for inattentive compared with hyperactive/impulsive symptoms. Similar to Kuntsi and Stevenson (2001), the strongest evidence of bivariate heritability ($h_g^2 = .52$) was obtained for a discriminant function score that included measures of processing speed, vigilance, working memory, and inhibition.

In sum, twin studies suggest that ADHD and EF share genetic influences but, like family studies, indicate that the genetic overlap between ADHD and EF is not substantial.

Candidate gene studies of EF deficits in ADHD samples. Thus far, a handful of studies have examined the relationship between ADHD, neuropsychological dysfunction and specific genes. Langley and colleagues (2004) found that the DRD4 Exon III 7-repeat allele was associated with incorrect responses on the Matching Familiar Figures Test (MFFT) and faster reaction time for incorrect responses on the MFFT and the Stop Task. No differences between those with and without the 7-repeat allele were found on the Go–No-Go Test, SSRT or the CPT- Identical Pairs version (CPT-IP), and ADHD youth showed greater impairments than controls regardless of whether they had the 7-repeat allele.

Two other studies found associations with DRD4, but with impaired performance in subjects *without* the 7 repeat allele. Swanson et al. (2000) examined a battery of computerized attention tasks in subjects with ADHD-C. Contrary to expectation given the association of the 7-repeat allele with the ADHD diagnosis in this sample, the group with the 7-repeat allele showed normal speed and variability of test responses. Slow and variable responses were found in the group without this allele. Manor et al. (2002) documented similar findings regarding the relation of DRD4 to a continuous performance test generally associated with attention or vigilance rather than EF per se (the Test of Variables of Attention; TOVA) in ADHD subjects from the Israeli population. In this sample, however, ADHD was associated with the short alleles of DRD4 (2–5 repeats) versus the long alleles (6–8 repeats) in family-based and case–control association analyses. Consistent with the short alleles as the risk alleles in this group, individuals with shorter repeats had more commission errors and longer reaction times.

Results of these latter two studies are consistent with Fossella et al.'s study of healthy adults (2002) in finding DRD4 Exon III VNTR short alleles associated with worse performance. Manor and colleagues (2002) suggest that either that the exon III polymorphism is in linkage disequilibrium with the true risk allele or that there is allelic heterogeneity, with multiple alleles of this gene potentially associated with disease status. Given the functional significance of the Exon III polymorphism (Asghari et al., 1995; Van Tol et al., 1992), the latter possibility may be more likely. Fossella and colleagues (2002) raise the intriguing explanation that both higher and lower than average levels of synaptic dopamine may produce neurocognitive impairments. This hypothesis is consistent with results of clinical trials (Tannock, Schachar, & Logan, 1995) documenting an inverted 'U' shaped response curve across low to high doses of methylphenidate, a medication that influences dopamine availability in the synapse.

A handful of other studies have assessed the association of other genes with cognitive performance in ADHD. Manor et al., (2004) found that the 148

base pair allele of the DRD5 polymorphism was associated with greater errors of omission and commission, response time and variability of response time on the TOVA (a visual CPT). Other recent studies have not found significant associations. For instance, in 124 children with ADHD, Mills et al. (2004) found no association between COMT and performance on the Wechsler Arithmetic and Digit Span (forwards and backwards) subtests, the MFFT, the CPT-IP and the Stop Signal and Go–No-Go Tests. Another recent study (Taerk et al., 2004) did not find an association between COMT genotypes and the WCST, Tower of London and the Self-Ordered Pointing Task in a similarly large ADHD sample. These findings are not surprising since studies of COMT have not yielded conclusive association with the ADHD diagnosis (see Faraone et al., in press). Recently, Adams et al. (2004) found no evidence for association of the gene for a glutamate receptor (GRIN2A) with ADHD in 183 families or with the SSRT or Digit Span (forwards and backwards) in a subset of these individuals. Because at least one family of glutamate receptors may modulate the effects of dopamine and serotonin (Miyamoto et al., 2001) and the gene for GRIN2A is located within the region of interest on16p13 found in the UCLA linkage sample, further studies of this gene are warranted.

Summary and conclusions – Criterion #4. Family studies suggest that EF impairments may, in part, be associated with the ADHD diagnosis itself; however, deficits of low magnitude in unaffected relatives leave open the possibility that performance on EF measures is an index of the genetic liability to ADHD. The small number of twin and adoption studies that have addressed this issue provide further evidence that ADHD and EF may share some genetic influences. Yet, these studies also indicate that either a significant proportion of the genetic influences on ADHD differ from the genetic influences on EF measures or else some factor (e.g., heterogeneity/reliability) is limiting the detection of the extent of the shared genetic influences.

Both family and twin studies also suggest that familial/genetic overlap is most robust for scores based on multiple neurocognitive measures, raising the possibility that this strategy is useful for reducing error variance. However, the concept of aggregating across EF measures requires consideration as it can be at odds with the aim of identifying endophenotypes that will help to disassemble complex phenotypes into more precise components with a simple genetic structure. Although aggregation presumably reduces error, it is not clear whether the aggregated measures were useful in the above studies due to tapping a general, latent EF trait with better reliability, whether the composite is tapping into multiple endophenotypes or even whether the finding suggests that the inherited cognitive deficit in ADHD is general rather than specific.

Given these unresolved issues, it is not surprising that the small number of molecular genetic studies of ADHD and neurocognitive measures have been inconclusive. Three studies found an association between DRD4 and test performance; however, only one found this association to be with the 7-repeat allele, while two studies suggest that the short alleles of DRD4 were associated with an aberrant pattern of responses. Findings raise the possibility that both high and low levels of synaptic dopamine could be associated with neurocognitive deficits. One study found an association between DRD5 and performance on a CPT, and two studies did not find associations between COMT and GRIN2A and EF measures.

Impressions and recommendations for future studies

The literature provides clear evidence that neural mechanisms are disrupted in the ADHD brain and that these disruptions can be observed on EF measures broadly conceived. If a single EF deficit were identified in ADHD samples, particularly one that was heritable, able to be reliably measured and showed substantial familial or genetic overlap with the disorder, such a deficit would be an obvious candidate for use in molecular genetic studies. However, our review shows that the choice of neurocognitive endophenotypes for ADHD is not straightforward. Although impairments within the general class of EFs are associated with the ADHD diagnosis, the variability of deficits has made a definitive neurocognitive model of ADHD difficult to discern. Given that measures of EF show preliminary evidence of heritability and at least some familial/genetic overlap with ADHD, such deficits are potentially useful as ADHD endophenotypes. Yet, measures of EF appear less heritable than ADHD, and extant studies do not show individual genes accounting for more than 5% of the variance in neurocognitive tests. Additionally, the overlap between ADHD and EF in family and twin studies is partial rather than substantial. While these issues do not negate the utility of EF measures as endophenotypes for ADHD, they constitute a challenge for how subsequent research should progress.

Understanding neuropsychological variability in the context of multifactorial models of ADHD. Addressing neurocognitive heterogeneity in ADHD has the potential to yield homogenous subgroups that show greater evidence of familial overlap with aspects of EF. However, heterogeneity at the neurocognitive level does not necessarily reflect genetic heterogeneity. Drawing on Tsuang and Faraone's discussion of the link between phenotypic and etiological heterogeneity with regard to schizophrenia (Tsuang & Faraone, 1995)

and bipolar disorder (Faraone & Tsuang, 2003), neurocognitive variability could represent several scenarios. A single etiological class of risk factors is the most parsimonious possible multifactorial model. In this model, cases arise from a single pool of genetic and environmental influences, each with a small effect, that act together to produce the diagnostic phenotype. The specific factors that any person has do not themselves matter, only that the total number of factors exceeds a certain threshold. Etiological homogeneity is feasible if the number of potential risk genes approximates the actual threshold (Tsuang & Faraone, 1995). For example, if 8 out of 10 risk factors are required for ADHD, cases will predominantly share etiological factors. In this model, if one or more EF deficits lie in the causal pathway leading to the behavioral symptoms of ADHD, the variability of performance on neurocognitive tests may represent the pleiotropic effects of the core set of genes, along with the influence of various factors such as measurement issues, development, environment, co-occurring conditions moderating performance and genotypic variation outside the core set of genes that influence cognition and/or ADHD. In the context of such a model, studying EF impairments in ADHD would be useful for indexing the core set of genes for the condition, particularly if such impairments tap phenotypes that are less genetically complex than ADHD as a whole. Strategies to improve the utility of the neurocognitive measures would include reducing the impact of noise (e.g., measurement error, hypothesized environmental risk factors, etc.).

A second possibility is true neurocognitive subtypes within ADHD, e.g., as conceptualized in Sonuga-Barke's dual-pathway model (Sonuga-Barke, 2002). In this scenario, different ADHD cases may arise from unique neurocognitive deficits, each of which reflects a unique pool of genetic risk factors. If this model were borne out, teasing apart neurocognitive heterogeneity would facilitate gene-finding by increasing the homogeneity of phenotypes to be examined. Identification of subtypes would be particularly straightforward if, for example, specific neurocognitive deficits were linked to phenotypic features of ADHD (e.g., symptom dimensions).

A third possibility lies between these models. In this scenario, ADHD cases may arise from a single pool of genetic and environmental factors, with the pool of risk factors much larger than the threshold and the risk factors potentially but not necessarily overlapping. For example, if 9 of 20 risk factors were required to develop ADHD, there could be neurocognitive heterogeneity due to the specific risk factors present in a given case. In this case, strategies outlined for the two models above would still be useful, especially if there were a direct relation between particular genes and specific neurocognitive impairments. If not, the same neurocognitive deficits could be associated with different genes in different samples. This possibility is reasonable because the PFC is one of the most widely interconnected regions in the brain (Goldberg & Seidman, 1991). Here, careful attention to sample characteristics and the use of genetically simple measures that could maximally differentiate impairments could be useful research strategies, but a pattern of heterogeneous findings may result across different studies. In this case, as others have suggested (Gottesman & Gould, 2003; Pennington & Ozonoff, 1996), after associations with the endophenotype are made, 'bottom up' research strategies to trace gene products may be necessary for resolution of pathophysiological models. Additionally, interdisciplinary collaborations using neuroimaging and/or psychophysiological measures that could differentiate deficits may be important additions to neurocognitive measures if such models are operating with regard to ADHD.

Research strategies. Although, at present, it is difficult to differentiate between the above multifactorial models, a range of research strategies, some of which have been discussed, can help ADHD molecular genetic research move forward. Table 2 summarizes these recommendations, along with the key findings from Criteria #1–4 reviewed above.

Further cognitive analysis of ADHD. The literature we have reviewed suggests that examination of neurocognitive heterogeneity is important for establishing more precise neurodevelopmental models of ADHD as well as the success of endophenotypic studies. We have argued for greater attention to moderators of variability of neurocognitive performance within ADHD samples such as family history, comorbidity and inattentive versus hyperactive/impulsive symptoms to determine whether qualitative or quantitative differences exist on these dimensions within ADHD samples. Such examinations offer the possibility of more homogenous neurocognitive subgroups to be used in molecular genetic studies. This line of research also has clinical implications in terms of the potential identification of individuals who respond differently to academic, pharmacologic or behavioral interventions. Examining features that differentiate the neurocognitive deficits in ADHD from those in other disorders (Pennington & Ozonoff, 1996; Sergeant et al., 2002) may also help to delineate one or more neurocognitive profiles that are unique to ADHD (e.g., like an MMPI code type). Constructs such as state-regulation factors (Sergeant et al., 2002) and delay aversion (Sonuga-Barke et al., 2002) that may assist in understanding neurocognitive heterogeneity should be regularly incorporated, along with carefully chosen measures of EF, into studies assessing familial/genetic overlap of neuropsychological impairments and ADHD.

Table 2 Summary of findings: measures of executive functions (EF) and criteria for a useful endophenotype for ADHD

Criterion	Evidence	Unresolved issues	Directions for future studies
# 1 – Association with ADHD	Robust – Extensive literature has documented associations between ADHD & impairments on measures of EF. Compelling associations with response inhibition & working memory.	– No single 'core' neurocognitive deficit (i.e., necessary & sufficient) for ADHD has been identified – Neurocognitive heterogeneity appears to exist but has not been extensively explored – Not clear whether heterogeneity reflects quantitative or qualitative neurocognitive differences within ADHD	1. Continue cognitive analysis of ADHD: a) attend to moderators of neurocognitive heterogeneity (e.g., family history, persistence, comorbidity, symptom dimensions (DSM-IV subtype); b) incorporate promising non-EF constructs (e.g., state regulation factors, delay aversion) into family & twin studies with EF measures c) directly compare theoretical models; d) compare individuals with ADHD to those with other conditions associated with EF deficits 2. Use empirical strategies such as measures/constructs that maximize relative risk, statistical programs/methods that do not require a priori specification of cutoffs or subgroups to identify best phenotypes for molecular genetic studies (e.g., PBAT for family-based association studies, ordered subset analysis for linkage studies)
# 2 – Good psychometric properties	Not well studied. Some evidence of test–retest &/or internal consistency reliability.	– Reliability may differ across different levels of ability – Clinical measures may tap multiple functions & have limited sensitivity – Experimental measures may be more sensitive & specific but lack standardization & normative data	1. Conduct new studies to derive normative data across the lifespan & reliability across ability levels for measures for which such data are unavailable (particularly for promising measures from experimental cognitive neuroscience) 2. Implement control tasks &/or experimental measures to try to isolate deficits 3. Use data aggregation strategies to reduce error variance (e.g., measures that are stable over time; combine measures conceptually or via factor analysis)
# 3 – Heritability & association with relevant genes in normal/ population samples	Not well studied. Available data suggest measures may be less heritable than ADHD. Measures unlikely to be influenced by a single gene. Replicated association between COMT & WCST perseverative errors.	– Few measures already examined, often with small sample sizes – Inadequate data for conclusions about which measures are most heritable – Measures may themselves be complex phenotypes	1. Conduct large population-based twin study to examine heritability of a range of EF measures (particularly for promising measures from field of experimental cognitive neuroscience) 2. Conduct large study to examine association with individual genes & complexity of neurocognitive measures
# 4 – Familial/ genetic overlap with ADHD & association with specific genes in ADHD samples	Not well studied. Twin & adoption studies suggest family/genetic overlap between several measures of EF, attention & pure reaction time with ADHD; however, overlap is partial rather than substantial and discrepancies exist across studies. Association between DRD4 & measures of impulsivity & response speed, but risk alleles vary across study.	– Limited number of studies – Not clear whether impairments associated with disease status	1. Conduct large family &/or twin studies of ADHD & EF that collect molecular genetic data. Include measures from cognitive neuroscience and measures of state-regulation and delay aversion, attending to psychometric issues & examining whether stratifying samples by family history, persistence, comorbidity & symptom type (DSM-IV subtype) will better identify deficits in unaffected relatives of ADHD probands. If not, use empirical strategies to select cognitive phenotypes for analysis. Collaboration across sites may be needed to obtain large samples.

ADHD = Attention-deficit/hyperactivity disorder; EF = Executive functions; WCST = Wisconsin Card Sorting Test.

Direct assessment of statistical power. In both new and existing studies, empirical methods to increase the statistical power of molecular genetic studies may also facilitate the selection of neurocognitive measures that are useful for gene-finding. To date, none of the available endophenotype studies of ADHD have directly addressed statistical power. This issue is paramount, given that performance on many neurocognitive measures may not be mediated by a single gene. Risch (1990b) has demonstrated that the statistical power of a linkage study increases with the magnitude of risk ratios, which are computed by dividing the affection rate among each relative type by the rate of affection in the population. Following Risch's usage, we refer to these ratios as 'lambdas' (λ). Risch also showed that power depends only on λ and on no other genetic parameters. Low λ values may be due to a variety of factors, such as oligogenic transmission, genetic heterogeneity, phenocopies and low penetrance.

Given his mathematical analysis, Risch (1990b) suggested that defining disease status in a manner that increases λ would increase the power of linkage studies. Faraone et al. (1995) showed how this could be applied empirically in endophenotype definitions for molecular genetic studies of schizophrenia. The potential value of endophenotypes for ADHD is seen in the fact that λ values for the transmission of ADHD in family studies are consistently low, ranging from 2 to 3 for the risk to siblings and 2 to 8 for the risk to parents (Faraone et al., 2000b). If, as we suspect, more than one gene causes ADHD, then the λ for any single gene must be low. For example, if three genes of equal effect combine additively to cause ADHD, then to attain an empirical λ of 5, the λ for each gene would be about 1.7. If an ADHD endophenotype had a higher λ value, it could prove to be a useful tool for finding ADHD susceptibility genes. Because neurocognitive measures appear to have lower heritability than ADHD, higher λ values would likely occur as the result of reduced complexity of the endophenotype compared with ADHD. These facts highlight the need for identification of endophenotypic measures that show reduced complexity as phenotypes.

Maximizing lambda within the range of EF measures that are impaired in ADHD could allow selection of measures for further study without fully resolving the core neurocognitive deficits in ADHD. A study of neurocognitive performance of probands with schizophrenia, their siblings and controls provides an example of this strategy (Egan et al., 2001). In this sample, relative risk was elevated for Trails B and the California Verbal Learning Test compared to risk for the diagnosis. Thus, the use of these measures would provide increased power over the diagnosis in further genetic analyses in that sample, regardless of the underlying neurocognitive substrate of the disorder or the underlying trait that the measures were tapping. In turn, results of genetic analyses would inform theory as well as the design of further studies. Selecting measures that maximize relative risk in this way is consistent with the overall purpose of the endophenotype concept (i.e., to use biologically-based measures to maximize power to find genes for ADHD). Although this strategy emphasizes empirical over theoretical methods, it is still grounded in the theory that led to the initial selection of measures to be examined.

Reduction of error variance. Another way to maximize power is to reduce error variance. Several strategies for doing so have been discussed above. Selection of measures that reliably and validly assess individuals along the full range of performance would allow for quantitative trait analyses and could capitalize on designs using discordant relative pairs. Analyses on these relatives are based on the expectation that such relatives should share a given allele *less* often than is expected by chance. Compared with most other sibling selection strategies, discordant sibling pair designs provide more statistical power for linkage analyses (Dolan & Boomsma, 1998; Risch & Zhang, 1995) and may also provide information useful for association mapping (Boehnke & Langefeld, 1998). Because data on reliability and validity across age and ability level are limited for many neurocognitive measures, researchers at the 5th annual ADHD Molecular Genetics Conference agreed that a large-scale study addressing such issues would be useful to the field (Faraone, submitted).

Rice and Todorov (1994) also recommend the use of longitudinal or repeated measures designs for diagnostic assessment to reduce measurement errors in genetic studies. This strategy could be applied to neurocognitive measures of ADHD by incorporating information about stability across time into the endophenotype definition. Additional strategies to reduce error include the use of control tasks, experimental measures (with potentially more precise and sensitive targeting of functions than multifactorial clinical measures) and data aggregation strategies aimed at reducing the error associated with a single test.

This latter strategy appears promising given that aggregated measures from neurocognitive batteries in twin and family studies have shown greater familial overlap with ADHD than individual measures (Chhabildas et al., submitted; Doyle, Biederman, Seidman, Reske-Nielsen, & Faraone, in press; Kuntsi & Stevenson, 2001; Seidman et al., 2000). Yet, as we have discussed, the use of composite measures is slightly at odds with the aim of selecting endophenotypes that are genetically simple component parts of complex phenotypes unless aggregation strategies aim to tap specific rather than broad constructs. The literature on other disorders illustrates that such measures can be created both conceptually and empirically. For example, Grigorenko and colleagues found differential probability of linkage for conceptually derived scales of specific dyslexia-related phenotypes that aggregated information from at least

two relevant measures (Grigorenko, Wood, Meyer, & Pauls, 2000). Factor analysis can also capture multiple neurocognitive deficits, were they to exist, based on empirical grounds (i.e., a weighted linear combination of scores) if a priori hypotheses have not been fully articulated. Krabbendam, Marcelis, Delespaul, Jolles, and van Os (2001) showed how this is possible using a battery of measures in patients with schizophrenia. Similarly, Leckman et al., (2003) have used factor analysis to identify dimensions of OCD symptoms, some of which are associated with an increased familial risk for the disorder.

Selection of measures with highest heritability or for which a given gene contributes a significant amount of variance. Neurocognitive measures that are highly heritable as well as measures to which a given gene contributes a significant amount of variance will be the most powerful tools for genetic studies of ADHD. As we have reviewed, the relevant literature is growing but does not yet provide a definitive guide for comparing measures with regard to these criteria. Large twin studies that better document the heritability of such measures would therefore be of value to the field but may require collaborations across research groups to achieve adequate sample sizes. In the absence of twin data, family studies can be used to test if a putative endophenotype is familial and to calculate upper limits of heritability. If twin studies continue to show that measures are less heritable than ADHD per se, the value of such measures in endophenotype studies will come from their more direct association (as compared to the disorder as a whole) with individual genes. Because many measures may, themselves, be complex phenotypes, paradigms from experimental cognitive neuroscience that tap precise functions may be the most promising to pursue in future heritability and reliability studies.

Adoption of data analytic strategies in molecular genetic studies to accommodate heterogeneity and/or select genetically powerful phenotypes. Finally, given *a priori* hypotheses about subgroups of neurocognitive deficits in ADHD, covariates can be incorporated into family-based association studies (e.g., into logistic regression extensions of the transmission disequilibrium test (TDT; Waldman, Robinson, & Rowe, 1999). In linkage analysis, subgroups of interest can also be examined. However, because multifactorial genetic models of ADHD may render *a priori* delineation of subgroups or target phenotypes difficult, empirically driven analytic strategies that can assist with selection of the most genetically powerful phenotypes may be particularly beneficial tools for researchers. For example, Lange and colleagues (2003) have developed a two-stage testing strategy to test null hypotheses regarding the association of a set of quantitative phenotypes with a given marker without the need to adjust for multiple comparisons in the subsequent family-based test. This strategy uses a program that includes several features that allow for the 'planning of family based association tests' (PBAT; Lange, DeMeo, Silverman, Weiss, & Laird, 2004). In the first stage, the association of several phenotypes and the marker locus is tested using a population-based statistic grounded in generalized estimating equations that model the quantitative phenotypes as a function of genotypes of interest. The phenotype with the strongest genetic component (i.e., with the smallest *p*-value) can then be tested for association with the marker in a subsequent family-based association test (FBAT) test. The nominal significance level of the subsequent test is not biased because offspring genotypes from informative families (i.e., families with at least one heterozygous parent) that are used in calculating the FBAT statistic are not used in the first-stage population-based statistic. If more than one of the quantitative phenotypes is associated with the marker in the first stage or based on expectation, a multivariate extension of the procedure could be implemented (Lange et al., 2003). Lange and colleagues have illustrated this strategy using the phenotype of childhood asthma. Such a strategy is useful at the present time for researchers desiring to avoid the pitfalls of multiple testing but faced with the dilemma that multivariate models of ADHD and neurocognitive heterogeneity may not translate into a single candidate neurocognitive measure to target.

Linkage analyses are also amenable to empirical strategies for phenotype selection. For example, Hauser et al., (2004) developed a strategy called ordered subset analysis (OSA) to identify subsets of families, based on their score on a covariate, that provide the greatest evidence for linkage rather than meet *a priori* assumptions about how a subset should be selected. This strategy has been applied successfully to a fine mapping analysis in autism (Shao et al., 2003). In this study, a significantly higher LOD score for a region on Chromosome 15 was found in families where relatives shared high scores on the 'insistence on sameness (IS)' factor from an autism interview. This method provides yet another means by which to use neurocognitive impairments to assist in identifying chromosomal regions of interest in ADHD by reducing heterogeneity when the delineation of specific subgroups is premature.

Conclusions

A great deal of work still lies ahead regarding understanding the relationship between genetic and neurobiological factors in ADHD, but the potential impact of such work is vast from a public health perspective. ADHD is estimated to affect about 8% of the population around the world (Faraone, Sergeant, Gillberg, & Biederman, 2003). The societal cost of the condition is significant, given its association with

academic underachievement, substance abuse, conduct problems, underemployment (Barkley, Fischer, Edelbrock, & Smallish, 1990; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993), increased health care utilization (Leibson, Katusic, Barbaresi, Ransom, & O'Brien, 2001) and accidents, including driving-related problems (Barkley, Murphy, & Kwasnik, 1996; Woodward, Fergusson, & Horwood, 2000). Specification of genetic and environmental risk factors and their associated pathophysiological risk mechanisms will help characterize early predictors of persistence and morbidity that, in turn, will pave the way for more refined treatment and primary prevention strategies. The data reviewed above suggest that neurocognitive endophenotypes for ADHD offer potential to move this line of research forward; however, such studies will not be a quick fix for the field. Rather, careful consideration must be given to issues of heterogeneity and measurement to maximally reduce the complexity of the endophenotypes themselves and take advantage of their potential to target a more homogenous piece of the etiological puzzle of ADHD.

Acknowledgements

This work was supported in part by grants K08-MH-66072 to Dr. Doyle, R21-MH066191 to Dr. Faraone, R01 MH59105 to Dr. Nigg, and K01-MH01818 to Dr. Waldman.

Correspondence to

Alysa E. Doyle, Massachusetts General Hospital, YAW 6900, 55 Fruit Street, Boston, MA 02114,USA; Email: doylea@helix.mgh.harvard.edu

References

Adams, J., Crosbie, J., Wigg, K., Ickowicz, A., Pathare, T., Roberts, W., Malone, M., Schachar, R., Tannock, R., Kennedy, J.L., & Barr, C.L. (2004). Glutamate receptor, ionotropic, N-methyl D-aspartate 2A (GRIN2A) gene as a positional candidate for attention-deficit/hyperactivity disorder in the 16p13 region. *Molecular Psychiatry*, *9*, 494–499.

Alberts-Corush, J., Firestone, P., & Goodman, J.T. (1986). Attention and impulsivity characteristics of the biological and adoptive parents of hyperactive and normal control children. *American Journal of Orthopsychiatry*, *56*, 413–423.

Almasy, L., & Blangero, J. (2001). Endophenotypes as quantitative risk factors for psychiatric disease: Rationale and study design. *American Journal of Medical Genetics*, *105*, 42–44.

American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd edn; DSM-III). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th edn; DSM-IV). Washington, DC: American Psychiatric Association.

Anderson, C.M., Polcari, A., Lowen, S.B., Renshaw, P.F., & Teicher, M.H. (2002). Effects of methylphenidate on functional magnetic resonance relaxometry of the cerebellar vermis in boys with ADHD. *American Journal of Psychiatry*, *159*, 1322–1328.

Ando, J., Ono, Y., & Wright, M.J. (2001). Genetic structure of spatial and working memory. *Behavioral Genetics*, *31*, 615–624.

Angold, A., Costello, J., & Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology and Psychiatry*, *40*, 57–87.

Arcos-Burgos, M., Castellanos, F.X., Konecki, D., Lopera, F., Pineda, D., Palacio, J.D., Rappoport, J.L., Berg, K., Bailey-Wilson, J., & Muenke, M. (2004). Pedigree disequilibrium test (PDT) replicates association and linkage between DRD4 and ADHD in multigenerational and extended pedigrees from a genetic isolate. *Molecular Psychiatry*, *9*, 252–259.

Arnsten, A.F.T. (2001). Dopaminergic and noradrenergic influences on cognitive functions mediated by prefrontal cortex. In M.V. Solanto & F.X. Castellanos (Eds.), *Basic and clinical neuroscience* (pp. 185–208). New York: Oxford University Press.

Asarnow, R.F., Nuechterlein, K.H., Subotnik, K.L., Fogelson, D.L., Torquato, R.D., Payne, D.L., Asamen, J., Mintz, J., & Guthrie, D. (2002). Neurocognitive Impairments in nonpsychotic parents of children with schizophrenia and attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *59*, 1053–1060.

Asghari, V., Sanyal, S., Buchwaldt, S., Paterson, A., Jovanic, V., & Van Tol, H.H.M. (1995). Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *Journal of Neurochemistry*, *65*, 1157–1165.

Auerbach, J.G., Benjamin, J., Faroy, M., Geller, V., & Ebstein, R. (2001). DRD4 related to infant attention and information processing: A developmental link to ADHD? *Psychiatric Genetics*, *11*, 31–35.

Bakker, S., van der Meulen, E., Buitelaar, J., Sandkuijl, L., Pauls, D., Monsuur, A., Van't Slot, Minderaa, R.B., Gunning, W.B., Pearson, P.L., & Sinke, R.J. (2003). A whole-genome scan in 164 Dutch sib pairs with attention-deficit/hyperactivity disorder: Suggestive evidence for linkage on chromosomes 7p and 15q. *American Journal of Human Genetics*, *72*, 1251–1260.

Barkley, R. (1997a). *ADHD and the nature of self-control*. New York: Guilford.

Barkley, R. (1997b). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin*, *121*, 65–94.

Barkley, R., Murphy, K., & Kwasnik, D. (1996). Motor vehicle driving competencies and risks in teens and young adults with attention deficit hyperactivity disorder. *Pediatrics*, *98*, 1089–1095.

Barkley, R.A. (2000). Genetics of childhood disorders: XVII. ADHD, Part 1: The executive functions and ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*, *39*, 1064–1068.

Barkley, R.A., Fischer, M., Edelbrock, C.S., & Smallish, L. (1990). The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *29*, 546–557.

Barkley, R.A., Grodzinsky, G., & DuPaul, G.J. (1992). Frontal lobe functions in attention deficit disorder with and without hyperactivity: A review and research report. *Journal of Abnormal Child Psychology*, *20*, 163–188.

Barr, C.L., Feng, Y., Wigg, K.G., Schachar, R., Tannock, R., Roberts, W., Malone, M., & Kennedy, J.L. (2001). 5'-untranslated region of the dopamine D4 receptor gene and attention-deficit hyperactivity disorder. *American Journal of Medical Genetics*, *105*, 84–90.

Bartfai, A., Pedersen, N.L., Asarnow, R.F., & Schalling, D. (1991). Genetic factors for the span of apprehension test: A study of normal twins. *Psychiatry Research*, *38*, 115–124.

Bayliss, D.M., & Roodenrys, S. (2000). Executive processing and attention deficit hyperactivity disorder: An application of the supervisory attentional system. *Developmental Neuropsychology*, *17*, 161–180.

Bedard, A.C., Ickowicz, A., Logan, G.D., Hogg-Johnson, S., Schachar, R., & Tannock, R. (2003). Selective inhibition in children with attention-deficit hyperactivity disorder off and on stimulant medication. *Journal of Abnormal Child Psychology*, *31*, 315–327.

Bedard, A.C., Nichols, S., Barbosa, J.A., Schachar, R., Logan, G.D., & Tannock, R. (2002). The development of selective inhibitory control across the life span. *Developmental Neuropsychology*, *21*, 93–111.

Bellivier, F., Henry, C., Szoke, A., Schurhoff, F., Nosten-Bertrand, M., Feingold, J., Launay, J.M., Leboyer, M., & Laplance, J.M. (1998). Serotonin transporter gene polymorphisms in patients with unipolar or bipolar depression. *Neuroscience Letters*, *255*, 143–146.

Berger, A., & Posner, M.I. (2000). Pathologies of brain attentional networks. *Neuroscience and Biobehavioral Reviews*, *24*, 3–5.

Bernstein, J., & Waber, D. (1990). Developmental neuropsychological assessment: The systemic approach. In A. Boulton, G. Baker, & M. Hiscock (Eds.), *Neuromethods: Neuropsychology* (pp. 311–371). Clifton, NJ: Humana Press.

Bernstein, J.H., & Waber, D.P. (1996). *Developmental scoring system for the Rey-Osterreith Complex Figure [manual]*. Odessa, FL: Psychological Assessment Resources, Inc.

Berquin, P.C., Giedd, J.N., Jacobsen, L.K., Hamburger, S.D., Krain, A.L., Rapoport, J.L., & Castellanos, F.X. (1998). Cerebellum in attention-deficit hyperactivity disorder: A morphometric MRI study. *Neurology*, *50*, 1087–1093.

Biederman, J. (1997). *Treatment of ADHD with an emphasis on stimulant medication*. Paper given at The Evaluation and Treatment of ADHD in Pediatrics, Boston, MA, October 28.

Biederman, J., Monuteaux, M., Seidman, L., Doyle, A.E., Mick, E., Wilens, T., Fererro, F., Morgan, C., & Faraone, S.V. (2004). Impact of executive function deficits and ADHD on academic outcomes in children. *Journal of Consulting and Clinical Psychology*, *72*, 757–766.

Biederman, J., Newcorn, J., & Sprich, S. (1991). Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. *American Journal of Psychiatry*, *148*, 564–577.

Boehnke, M., & Langefeld, C.D. (1998). Genetic association mapping based on discordant sib pairs: The discordant-alleles test. *American Journal of Human Genetics*, *62*, 950–961.

Booth, J.R., Burman, D.D., Meyer, JR., Lei, Z., Trommer, B.L., Davenport, N.D., Li, W., Parrish, T.B., Gitelman, T.R., & Mesulum, M. (2005). Larger deficits in brain networks for response inhibition than for visual selective attention in attention deficit hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry*, *46*, 94–111.

Borecki, I.B., Rao, D.C., Yaouanq, J., & Lalouel, J.M. (1990). Serum ferritin as a marker of affection for genetic hemochromatosis. *Human Heredity*, *40*, 159–166.

Callicott, J.H., Egan, M.F., Mattay, V.S., Bertolino, A., Bone, A.D., Verchinksi, B., & Weinberger, D.R. (2003). Abnormal FMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *American Journal of Psychiatry*, *160*, 709–719.

Campana, A., Macciardi, F., Gambini, O., & Scarone, S. (1996). The Wisconsin Card Sorting Test (WCST) performance in normal subjects: A twin study. *Neuropsychobiology*, *34*, 14–17.

Castellanos, F.X., Marvasti, F.F., Ducharme, J.L., Walter, J.M., Israel, M.E., Krain, A., Pavlovsky, C., & Hommer, D.W. (2000). Executive function oculomotor tasks in girls with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*, *39*, 644–650.

Castellanos, F.X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. *Nature Reviews Neuroscience*, *3*, 617–628.

Chhabildas, N., Pennington, B.F., & Willcutt, E.G. (2001). A comparison of the neuropsychological profiles of the DSM-IV Subtypes of ADHD. *Journal of Abnormal Child Psychology*, *29*, 529–540.

Chhabildas, N., Willcutt, E.G., & Pennington, B.F. (submitted). A twin study of the validity of the executive function theory of ADHD.

Clark, C., Geffen, G., & Geffen, L. (1989). Catecholamines and the covert orientation of attention in humans. *Neuropsychologia*, *27*, 131–139.

Clark, C., Prior, M., & Kinsella, G.J. (2000). Do executive function deficits differentiate between adolescents with ADHD and oppositional defiant/conduct disorder? A neuropsychological study using the Six Elements Test and Hayling Sentence Completion Test. *Journal of Abnormal Child Psychology*, *28*, 403–414.

Coolidge, F.L., Thede, L.L., & Young, S.E. (2000). Heritability and the comorbidity of attention deficit hyperactivity disorder with behavioral disorders and executive function deficits: A preliminary investigation. *Developmental Neuropsychology*, *17*, 273–287.

Cornblatt, B.A., & Malhotra, A.K. (2001). Impaired attention as an endophenotype for molecular genetic studies of schizophrenia. *American Journal of Medical Genetics*, *105*, 11–15.

Crosbie, J., & Schachar, R. (2001). Deficient inhibition as a marker for familial ADHD. *American Journal of Psychiatry*, *158*, 1884–1890.

de Villiers, A.S., Russell, V.A., Sagvolden, T., Searson, A., Jaffer, A., & Taljaard, J.J. (1995). Alpha 2-adrenoceptor mediated inhibition of [3H]dopamine release from nucleus accumbens slices and monoamine levels in a rat model for attention-deficit hyperactivity disorder. *Neurochemical Research*, *20*, 427–433.

Deckersbach, T., Savage, C., Curran, T., Bohne, A., Wilhelm, S., Baer, L., Jenike, M.A., & Rauch, S.L. (2002). A study of parallel implicit and explicit information processing in patients with obsessive-compulsive disorder. *American Journal of Psychiatry*, *159*, 1780–1782.

Delis, D., Kaplan, E., & Kraemer, J.H. (2001). *Delis–Kaplan executive function system (D-KEFS)*: The Psychological Corporation.

Dempster, F.N. (1992). The rise and fall of the inhibitory mechanism: Towards a unified theory of cognitive development and aging. *Development Review*, *12*, 45–75.

Denckla, M.B. (1996). A theory and model of executive function: A neuropsychological perspective. In G.R. Lyon & N.A. Krasnegor (Eds.), *Attention, memory and executive function* (ch. 15*)*. Baltimore: Paul H. Brooks.

Diamond, A., Prevor, M.B., Callender, G., & Druin, D.P. (1997). Prefrontal cortex cognitive deficits in children treated early and continuously for PKU. *Monographs of Social Research and Child Development*, *62*, 1–208.

Dolan, C.V., & Boomsma, D.I. (1998). Optimal selection of sib pairs from random samples for linkage analysis of a QTL using the EDAC test. *Behavior Genetics*, *28*, 197–206.

Dowson, J.H., McLean, A., Bazanis, E., Toone, B., Young, S., Robbins, T.W., & Sahakian, B.J. (2004). Impaired spatial working memory in adults with attention-deficit/hyperactivity disorder: Comparisons with performance in adults with borderline personality disorder and in control subjects. *Acta Psychiatrica Scandinavica*, *110*, 45–54.

Doyle, A.E., Biederman, J., Seidman, L., Reske-Nielsen, J., & Faraone, S.V. (in press). Neuropsychological functioning in relatives of girls with and without ADHD. *Psychological Medicine*.

Doyle, A.E., Biederman, J., Seidman, L., Weber, W., & Faraone, S. (2000). Diagnostic efficiency of neuropsychological test scores for discriminating boys with and without attention deficit hyperactivity disorder. *Journal of Consulting and Clinical Psychology*, *68*, 477–488.

Doyle, A.E., & Faraone, S. (2002). Familial links between ADHD, conduct disorder and bipolar disorder. *Current Psychiatry Reports*, *4*, 146–152.

Draeger, S., Prior, M., & Sanson, A. (1986). Visual and auditory attention performance in hyperactive children: Competence or compliance. *Journal of Abnormal Child Psychology*, *14*, 411–424.

Durston, S., Tottenham, N.T., Thomas, K.M., Davidson, M.C., Eigsti, I.M., Yang, Y., Ulug, A.M., & Casey, B.J. (2003). Differential patterns of striatal activation in young children with and without ADHD. *Biological Psychiatry*, *53*, 871–878.

Egan, M.F., Goldberg, T.E., Gscheidle, T., Weirich, M., Rawlings, R., Hyde, T.M., Bigelow, L., & Weinberger, D.R. (2001). Relative risk for cognitive impairments in siblings of patients with schizophrenia. *Biological Psychiatry*, *50*, 98–107.

Falconer, D.S., & MacKay, T.F.C. (1996). *Introduction to quantitative genetics*. Essex, England: Longman Group LTD.

Fan, J., Wu, Y., Fossella, J.A., & Posner, M.I. (2001). Assessing the heritability of attentional networks. *BioMed Central Neuroscience*, *2*, 14.

Faraone, S.V. (1999). A family based association study of the DAT and DRD4 genes in ADHD. In *World Congress of Psychiatric Genetics*. Monterrey, CA.

Faraone, S.V. (2000). Genetics of childhood disorders: XX. ADHD, Part 4: Is ADHD genetically heterogeneous? *Journal of the American Academy of Child and Adolescent Psychiatry*, *39*, 1455–1457.

Faraone, S.V. (2002). Report from the third international meeting of the Attention-Deficit Hyperactivity Disorder Molecular Genetics Network. *American Journal of Medical Genetics*, *114*, 272–276.

Faraone, S.V. (2003). Report from the fourth international meeting of the attention deficit hyperactivity disorder molecular genetics network. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, *121B*, 55–59.

Faraone, S.V. (submitted). Report from the 5th international meeting of the attention deficit hyperactivity disorder molecular genetics network.

Faraone, S.V., Biederman, J., Feighner, J.A., & Monuteaux, M.C. (2000a). Assessing symptoms of attention deficit hyperactivity disorder in children and adults: Which is more valid? *Journal of Consulting and Clinical Psychology*, *68*, 830–842.

Faraone, S.V., Biederman, J., & Monuteaux, M.C. (2000b). Toward guidelines for pedigree selection in genetic studies of attention deficit hyperactivity disorder. *Genetic Epidemiology*, *18*, 1–16.

Faraone, S.V., Doyle, A.E., Mick, E., & Biederman, J. (2001). Meta-analysis of the association between the 7-repeat allele of the dopamine d(4) receptor gene and attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *158*, 1052–1057.

Faraone, S.V., Kremen, W., Lyons, M., Pepple, J., Seidman, L., & Tsuang, M. (1995). Diagnostic accuracy and linkage analysis: How useful are schizophrenia spectrum phenotypes? *American Journal of Psychiatry*, *152*, 1286–1290.

Faraone, S.V., Perlis, R.H., Doyle, A.E., Smoller, J.W., Goralnick, J., Holmgren, M.A., et al. (in press). Molecular genetics of attention deficit hyperactivity disorder. *Biological Psychiatry*.

Faraone, S.V., Seidman, L.J., Kremen, W.S., Toomey, R., Pepple, J.R., & Tsuang, M.T. (1999). Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: A 4-year follow-up study. *Journal of Abnormal Psychology*, *108*, 176–181.

Faraone, S.V., Seidman, L.J., Kremen, W.S., Toomey, R., Pepple, J.R., & Tsuang, M.T. (2000c). Neuropsychologic functioning among the nonpsychotic relat-

ives of schizophrenic patients: The effect of genetic loading. *Biological Psychiatry*, *48*, 120–126.

Faraone, S.V., Sergeant, J.A., Gillberg, C., & Biederman, J. (2003). The worldwide prevalence of ADHD: Is it an American condition? *World Psychiatry*, *2*, 104–113.

Faraone, S.V., & Tsuang, M.T. (2003). Heterogeneity and the genetics of bipolar disorder. *American Journal of Human Genetics*, *123C*, 1–9.

Fischer, M., Barkley, R.A., Edelbrock, C.S., & Smallish, L. (1990). The adolescent outcome of hyperactive children diagnosed by research criteria: II. Academic, attentional, and neuropsychological status. *Journal of Consulting and Clinical Psychology*, *58*, 580–588.

Fisher, S.E., Francks, C., McCracken, J.T., McGough, J.J., Marlow, A.J., MacPhie, I.L., Newbury, D.F., Crawford, L.R., Palmer, C.G., Woodward, J.A., Del'Homme, M., Cantwell, D.P., Nelson, S.F., Monaco, A.P., & Smalley, S.L. (2002). A genomewide scan for loci involved in attention-deficit/hyperactivity disorder. *American Journal of Medical Genetics*, *70*, 1183–1196.

Fossella, J.A., Sommer, T., Fan, J., Wu, Y., Swanson, J.M., & Pfaff, D.W. (2002). Assessing the molecular genetics of attention networks. *BMC Neuroscience*, *4*, 14.

Freedman, R., Adler, L.E., & Leonard, S. (1999). Alternative phenotypes for the complex genetics of schizophrenia. *Biological Psychiatry*, *45*, 551–558.

Freedman, R., Coon, H., Myles-Worsley, M., Orr-Urtreger, A., Olingy, A., Davis, A., Polmeropoulos, M., Holik, J., Hopkins, J., Hoff, M., Rosenthal, J., Waldo, M.C., Reimherr, F., Wender, P., Yaw, J., Young, D.A., Breese, C.R., Adams, C., Patterson, D., Adler, L.E., Kruglyak, L., Leonard, S., & Byerley, W. (1997). Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proceedings of the National Academy of Sciences*, *94*, 587–592.

Freedman, R., Leonard, S., Gault, J., Hopkins, J., Cloninger, C., Kaufmann, C., Tsuang, M.T., Faraone, S.F., Malaspina, D., Svrakic, D.M., Sanders, A., & Gejman, P. (2001). Linkage disequilibrium for schizophrenia at the chromosome 15q13-14 locus of the alpha7-nicotinic acetylcholine receptor subunit gene (CHRNA7). *American Journal of Medical Genetics*, *105*, 20–22.

Gainetdinov, R.R., Wetsel, W.C., Jones, S.R., Levin, E.D., Jaber, M., & Caron, M.G. (1999). Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. *Science, 283*, 397–402.

Garber, J.E., & Hollon, S.D. (1991). What can specificity designs say about causality in psychopathology research? *Psychological Bulletin*, *110*, 129–136.

Geurts, H.M., Verte, S., Oosterlaan, J., Roeyers, H., & Sergeant, J.A. (2004). How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? *Journal of Child Psychology and Psychiatry, 45,* 836–854.

Giedd, J., Blumenthal, J., Molloy, E., & Castellanos, F. (2001). Brain imaging of attention deficit/hyperactivity disorder. *Annals of the New York Academy of Sciences*, *931*, 33–49.

Giros, B., Jaber, M., Jones, S.R., Wightman, R.M., & Caron, M.G. (1996). Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature*, *379*, 606–612.

Goldberg, E., & Podell, K. (1995). Later alligator in the frontal lobes. In H.H. Jasper, S. Riggio, & P.S. Goldman-Rakic (Eds.), *Epilepsy and the functional anatomy of the frontal lobes* (pp. 85–96). New York: Raven Press.

Goldberg, E., & Seidman, L.J. (1991). Higher cortical functions in normals and in schizophrenia: A selective review. In S.R. Steinhauer, J.H. Gruzelier, & J. Zubin (Eds.), *Handbook of schizophrenia (*volume 5*): Neuropsychology, psychophysiology and information processing*. Amsterdam: Elsevier Science.

Goldstein, G., & Shemansky, W.J. (1995). Influences on cognitive heterogeneity in schizophrenia. *Schizophrenia Research*, *18*, 59–69.

Goodman, R., & Stevenson, J. (1989). A twin study of hyperactivity: II. The aetiological role of genes, family relationships and perinatal adversity. *Journal of Child Psychology and Psychiatry*, *30*, 691–709.

Gottesman, I.I., & Gould, T.D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*, *160*, 636–645.

Grigorenko, E.L., Wood, F.B., Meyer, M.S., & Pauls, D.L. (2000). Chromosome 6p influences on different dyslexia-related cognitive processes: Further confirmation. *American Journal of Human Genetics*, *66*, 715–723.

Harrison, Y., & Horne, J.A. (1998). Sleep loss impairs short and novel language tasks having a prefrontal focus. *Journal of Sleep Research*, *7*, 95–100.

Hauser, E.R., Watanabe, R.M., Duren, W.L., Bass, M.P., Langefeld, C.D., & Boehnke, M. (2004). Ordered subset analysis in genetic linkage mapping of complex traits. *Genetic Epidemiology*, *27*, 53–63.

Hinshaw, S.P., Carte, E.T., Sarni, N., Treuting, J.J., & Zupan, B. (2002). Preadolescent girls with attention-deficit/hyperactivity disorder: II. Neuropsychological performance in relation to subtypes and individual classification. *Journal of Consulting and Clinical Psychology*, *70*, 1099–1111.

Holmes, J., Payton, A., Barret, J., Harrington, R., McGuffin, P., Owen, M., Ollier, W., Worthington, J., Gill, M., Kirley, A., Hawi, Z., Fitzgerald, M., Asherson, P., Curran, S., Mill, J., Gould, A., Taylor, E., Kent, L., Craddock, N., & Thapar, A. (2002). Association of DRD4 in children with ADHD and comorbid conduct problems. *American Journal of Medical Genetics*, *114*, 150–153.

Houghton, S., Douglas, G., West, J., Whiting, K., Wall, M., Langsford, S., Powell, L., & Carroll, A. (1999). Differential patterns of executive function in children with attention-deficit hyperactivity disorder according to gender and subtype. *Journal of Child Neurology*, *14*, 801–805.

Hughes, C., Plumet, M.H., & Leboyer, M. (1999). Towards a cognitive phenotype for autism: increased prevalence of executive dysfunction and superior spatial span amongst siblings of children with autism. *Journal of Child Psychology and Psychiatry*, *40*, 705–718.

Johansen, E., Aase, H., Meyer, A., & Sagvolden, T. (2002). Attention-deficit/hyperactivity disorder (ADHD) behaviour explained by dysfunctioning re-

inforcement and extinction processes. *Behavioral Brain Research*, *130*, 37–45.

Joober, R., Gauthier, J., Lal, S., Bloom, D., Lalonde, P., Rouleau, G., Benkelfat, C., & Labelle, A. (2002). Catechol-O-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. *Archives of General Psychiatry*, *59*, 662–663.

Kaplan, E., Fein, D., Kramer, J., Delis, D., & Moris, R. (1999). *WISC-III as a process instrument*. San Antonio, TX: The Psychological Corporation.

Kindlon, D., Mezzacappa, E., & Earls, F. (1995). Psychometric properties of impulsivity measures: Temporal stability, validity and factor structure. *Journal of Child Psychology and Psychiatry*, *36*, 645–661.

Klenberg, L., Korkman, M., & Lahti-Nuuttila, P. (2001). Differential development of attention and executive functions in 3- to 12-year-old Finnish children. *Developmental Neuropsychology*, *20*, 407–428.

Klorman, R., Hazel-Fernandez, L.A., Shaywitz, S.E., Fletcher, J.M., Marchione, K.E., Holahan, J.M., Stuebing, K.K., & Shaywitz, B.A. (1999). Executive functioning deficits in attention-deficit/hyperactivity disorder are independent of oppositional defiant or reading disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *38*, 1148–1155.

Krabbendam, L., Marcelis, M., Delespaul, P., Jolles, J., & van Os, J. (2001). Single or multiple familial cognitive risk factors in schizophrenia? *American Journal of Medical Genetics, 105,* 183–188.

Kremen, W.S., Seidman, L.J., Faraone, S.V., Toomey, R., & Tsuang, M.T. (2000). The paradox of normal neuropsychological function in schizophrenia. *Journal of Abnormal Psychology*, *109*, 743–752.

Kuntsi, J., Oosterlaan, J., & Stevenson, J. (2001a). Psychological mechanisms in hyperactivity: I. Response inhibition deficit, working memory impairment, delay aversion, or something else? *Journal of Child Psychology and Psychiatry*, *42*, 199–210.

Kuntsi, J., & Stevenson, J. (2001). Psychological mechanisms in hyperactivity: II The role of genetic factors. *Journal of Child Psychology and Psychiatry*, *42*, 211–219.

Kuntsi, J., Stevenson, J., Oosterlaan, J., & Sonuga-Barke, E. (2001b). Test–retest reliability of new delay aversion task and executive function. *British Journal of Developmental Psychology*, *19*, 339–348.

Lahey, B., Pelham, W., Stein, M., Loney, J., Trapani, C., Nugent, K., Kipp, H., Schmidt, E., Lee, S., Cale, M., Gold, E., Hartung, C., Willcutt, E., & Bauman, B. (1998). Validity of DSM-IV attention-deficit/hyperactivity disorder for younger children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *37*, 695–702.

Lange, C., DeMeo, D., Silverman, E.K., Weiss, S.T., & Laird, N.M. (2004). PBAT: Tools for family-based association studies. *American Journal of Human Genetics*, *74*, 367–369.

Lange, C., Lyon, H., DeMeo, D., Raby, B., Silverman, E.K., & Weiss, S.T. (2003). A new powerful nonparametric two-stage approach for testing multiple phenotypes in family-based association studies. *Human Heredity*, *56*, 10–17.

Langley, K., Marshall, L., van den Bree, M., Thomas, H., Owen, M., O'Donovan, M., & Thapar, A. (2004). Association of the dopamine D4 receptor gene 7-repeat allele with neuropsychological test performance of children with ADHD. *American Journal of Psychiatry*, *161*, 133–138.

Lazar, J.W., & Frank, Y. (1998). Frontal systems dysfunction in children with attention- deficit/hyperactivity disorder and learning disabilities. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *10*, 160–167.

Leboyer, M., Bellivier, F., Nosten-Bertrand, M., Jouvent, R., Pauls, D., & Mallet, J. (1998). Psychiatric genetics: Search for phenotypes. *Trends of Neuroscience*, *21*, 102–105.

Leckman, J.F., Pauls, D.L., Zhang, H., Rosario-Campos, M.C., Katsovich, L., Kidd, K.K., Pakastis, A.J., Alsobrook, J.P., Robertson, M.M., McMahon, W.M., Walkup, J.T., van der Wetering, B.J., King, R.A., & Cohen, D.J. (2003). Obsessive-compulsive symptom dimensions in affected sibling pairs diagnosed with Gilles de la Tourette syndrome. *American Journal of Medical Genetics*, *116B*, 60–68.

Leibson, C.L., Katusic, S.K., Barbaresi, W.J., Ransom, J., & O'Brien, P.C. (2001). Use and costs of medical care for children and adolescents with and without attention-deficit/hyperactivity disorder. *Journal of the American Medical Association*, *285*, 60–66.

Logan, G.D., Schachar, R.J., & Tannock, R. (1997). Impulsivity and inhibitory control. *Psychological Science*, *8*, 60–64.

Loo, S.K., Fisher, S.E., Francks, C., Ogdie, M.N., MacPhie, I.L., Yang, M., McCracken, J.T., McGough, J.J., Nelson, S.F., Monaco, A.P., & Smalley, S.L. (2004). Genome-wide scan of reading ability in affected sibling pairs with attention-deficit/hyperactivity disorder: Unique and shared genetic effects. *Molecular Psychiatry*, *9*, 485–493.

Lopez, R.E. (1965). Hyperactivity in twins. *Canadian Psychiatric Association Journal*, *10*, 421–426.

Loring, D.W. (Ed.) (1999). *INS dictionary of neuropsychology*. New York: Oxford University Press.

Lovejoy, D.W., Ball, J.D., Keats, M., Stutts, M.L., Spain, E., Janda, L., & Janusz, J. (1999). Neuropsychological performance of adults with attention deficit hyperactivity disorder (ADHD): Diagnostic classification estimates for measures of frontal lobe/executive functioning. *Journal of the International Neuropsychological Society*, *5*, 222–233.

Lyon, G.R., & Krasnegor, N.A. (1996). *Attention, memory, and executive function*. Baltimore, MD: Paul H. Brookes Publishing Co.

MacDonald, A.W. III., & Carter, C.S. (2002). Cognitive experimental approaches to investigating impaired cognition in schizophrenia: A paradigm shift. *Journal of Clinical Neuropsychology*, *24*, 873–882.

Malhotra, A.K., Kestler, L.J., Mazzanti, C., Bates, J.A., Goldberg, T., & Goldman, D. (2002). A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *American Journal of Psychiatry*, *159*, 652–654.

Manassis, K., Tannock, R., & Barbosa, J. (2000). Dichotic listening and response inhibition in children with comorbid anxiety disorders and ADHD. *Journal*

of the American Academy of Child and Adolescent Psychiatry, *39*, 1152–1159.

Mannuzza, S., Klein, R.G., Bessler, A., Malloy, P., & LaPadula, M. (1993). Adult outcome of hyperactive boys: Educational achievement, occupational rank and psychiatric status. *Archives of General Psychiatry*, *50*, 565–576.

Manor, I., Corbex, M., Eisenberg, J., Gritsenkso, I., Bachner-Melman, R., Tyano, S., & Ebstein, R.P. (2004). Association of the dopamine D5 receptor with attention deficit hyperactivity disorder (ADHD) and scores on a continuous performance test (TOVA). *American Journal of Medical Genetics*, *127B*, 73–77.

Manor, I., Tyano, S., Eisenberg, J., Bachner-Melman, R., Kotler, M., & Ebstein, R.P. (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). *Molecular Psychiatry*, *7*, 790–794.

Mattes, J.A. (1980). The role of frontal lobe dysfunction in childhood hyperkinesis. *Comprehensive Psychiatry*, *21*, 358–369.

McCracken, J.T., Smalley, S.L., McGough, J.J., Crawford, L., Del'Homme, M., Cantor, R.M., Liu, A., & Nelson, S.F. (2000). Evidence for linkage of a tandem duplication polymorphism upstream of the dopamine D4 receptor gene (DRD4) with attention deficit hyperactivity disorder (ADHD). *Molecular Psychiatry*, *5*, 531–536.

McInnis, M.G., Dick, D.M., Willour, V.L., Avramopoulos, D., MacKinnon, D.F., Simpson, S.G., et al. (2003). Genome-wide scan and conditional analysis in bipolar disorder: Evidence for genomic interaction in the National Institute of Mental Health genetics initiative bipolar pedigrees. *Biological Psychiatry*, *54*, 1265–1273.

Middleton, F., & Strick, P. (2002). Basal-ganglia 'projections' to the prefrontal cortex of the primate. *Cerebral Cortex*, *12*, 926–935.

Mills, S., Langley, K., Van Den Bree, M., Street, E., Turic, D., Owen, M.J., O'Donovan, M.C., & Thapar, A. (2004). No evidence of association between Catechol-O-Methyltransferase (COMT) Val158Met genotype and performance on neuropsychological tasks in children with ADHD: A case–control study. *BMC Psychiatry*, *4*, 15.

Miyamoto, Y., Yamada, K., Noda, Y., Mori, H., Mishina, M., & Nabeshima, T. (2001). Hyperfunction of dopaminergic and serotonergic neuronal systems in mice lacking the NMDA receptor epsilon1 subunit. *Journal of Neuroscience*, *21*, 750–757.

Mourik, R., Oosterlaan, J., & Sergeant, J.A. (2005). The Stroop revisited: A meta-analysis of interference control in AD/HD. *Journal of Child Psychology and Psychiatry*, *46*, 150–165.

Murphy, K.R., & Barkley, R.A. (1996). Parents of children with attention-deficit/hyperactivity disorder: Psychological and attentional impairment. *American Journal of Orthopsychiatry*, *66*, 93–102.

Myles-Worsley, M., & Coon, H. (1997). Genetic and developmental factors in spontaneous selective attention: A study of normal twins. *Psychiatry Research*, *71*, 163–174.

Nigg, J.T. (1999). The ADHD response-inhibition deficit as measured by the stop task: Replication with DSM-IV combined type, extension, and qualification. *Journal of Abnormal Child Psychology*, *27*, 393–402.

Nigg, J. T. (2000). On inhibition/disinhibition in developmental psychopathology: Views from cognitive and personality psychology and a working inhibition taxonomy. *Psychological Bulletin*, *126*, 220–246.

Nigg, J.T. (2001). Is ADHD a disinhibitory disorder? *Psychological Bulletin*, *127*, 571–598.

Nigg, J.T., Blaskey, L., Stawikcki, J., & Sachek, J. (2004). Evaluating endophenotype model of ADHD neuropsychological deficit: Results for parents and siblings of children with DSM-IV ADHD combined and inattentive subtypes. *Journal of Abnormal Psychology*, *113*, 614–625.

Nigg, J.T., Blaskey, M.A., Huang-Pollock, C., & Rappley, M.D. (2002). Neuropsychological executive functions and DSM-IV ADHD subtypes. *Journal of the American Academy of Child and Adolescent Psychiatry*, *41*, 59–66.

Nigg, J.T., Hinshaw, S.P., Carte, E.T., & Treuting, J.J. (1998). Neuropsychological correlates of childhood attention-deficit/hyperactivity disorder: Explainable by comorbid disruptive behavior or reading problems? *Journal of Abnormal Psychology, 107,* 468–480.

Nigg, J.T., Quamma, J.P., Greenberg, M.T., & Kusche, C.A. (1999). A two-year longitudinal study of neuropsychological and cognitive performance in relation to behavioral problems and competencies in elementary school children. *Journal of Abnormal Child Psychology*, *27*, 51–63.

Nigg, J.T., Swanson, J.M., & Hinshaw, S.P. (1997). Covert visual spatial attention in boys with attention deficit hyperactivity disorder: Lateral effects, methylphenidate response and results for parents. *Neuropsychologia*, *35*, 165–176.

Nigg, J.T., Willcutt, E.G., Doyle, A.E., & Sonuga-Barke, E. (in press). Causal heterogeneity in ADHD: Do we need neuropsychological subtypes? *Biological Psychiatry*.

Ogdie, M., Macphie, I., Minassian, S., Yang, M., Fisher, S., Francks, C., Cantor, R.M., McCracken, J.T., McGough, J.J., Nelson, S.F., Monaco, A.P., & Smalley, S.L. (2003). A genomewide scan for attention-deficit/hyperactivity disorder in an extended sample: Suggestive linkage on 17p11. *American Journal of Human Genetics*, *72*, 1268–1279.

Oosterlaan, J. (1996). *Response inhibition in children with attention deficit hyperactivity and related disorders*. Switzerland: Ciba Geigy.

Oosterlaan, J., Logan, G., & Sergeant, J. (1998). Response inhibition in AD/HD, CD, comorbid AD/HD + CD, anxious, and control children: A meta-analysis of studies with the stop task. *Journal of Child Psychology and Psychiatry*, *39*, 411–425.

Palmer, B.W., Heaton, R.K., Paulsen, J.S., Kuck, J., Braff, D., Harris, M.J., Zisook, S., & Jeste, D.V. (1997). Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology*, *11*, 437–446.

Payton, A., Holmes, J., Barrett, J.H., Sham, P., Harrington, R., McGuffin, P., O'Donovan, M., Owen, M.,

Ollier, W., Worthington, J., & Thapar, A. (2001). Susceptibility genes for a trait measure of attention deficit hyperactivity disorder: A pilot study in a non-clinical sample of twins. *Psychiatry Research*, *105*, 273–278.

Pennington, B.F. (2002). *The development of psychopathology: Nature and nurture*. New York: Guilford Press.

Pennington, B.F., Bennetto, L., McAleer, O., & Roberts, R.J. (1996). Executive functions and working memory: Theoretical and measurement issues. In G.R. Lyon & N.A. Krasnegor (Eds.), *Attention, memory and executive function*. (ch. 18) Baltimore: Paul H. Brooks.

Pennington, B.F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry*, *37*, 51–87.

Piven, J., & Palmer, P. (1997). Cognitive deficits in parents from multiple-incidence autism families. *Journal of Child Psychology and Psychiatry*, *38*, 1011–1021.

Pliszka, S.R. (1989). Effect of anxiety on cognition, behavior, and stimulant response in ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*, *28*, 882–887.

Plomin, R. (1999). Genetics and general cognitive ability. *Nature*, *402*, C25–29.

Quist, J.F., & Kennedy, J.L. (2001). Genetics of childhood disorders: XXIII. ADHD, Part 7: The serotonin system. *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*, 253–256.

Randazzo, A.C., Muehlbach, M.J., Schweitzer, P.K., & Walsh, J.K. (1998). Cognitive function following acute sleep restriction in children ages 10–14. *Sleep*, *21*, 861–868.

Rasmussen, E., Neuman, R., Heath, A., Levy, F., Hay, D., & Todd, R. (2002). Replication of the latent class structure of Attention-Deficit/Hyperactivity Disorder (ADHD) subtypes in a sample of Australian twins. *Journal of Child Psychology and Psychiatry*, *43*, 1018–1028.

Rauch, S., Savage, C., Alpert, N., Fischman, A., & Jenike, M. (1997). The functional neuroanatomy of anxiety: A study of three disorders using positron emission tomography and symptom provocation. *Biological Psychiatry*, *42*, 446–452.

Rice, J., & Todorov, A. (1994). Stability of diagnosis: Application to phenotype definition. *Schizophrenia Bulletin*, *20*, 185–190.

Risch, N. (1990a). Linkage strategies for genetically complex traits. I. Multilocus models. *American Journal of Human Genetics*, *46*, 222–228.

Risch, N. (1990b). Linkage strategies for genetically complex traits. II. The power of affected relative pairs. *American Journal of Human Genetics*, *46*, 229–241.

Risch, N., & Zhang, H. (1995). Extreme discordant sib pairs for mapping quantitative trait loci in humans. *Science*, *268*, 1584–1589.

Roberts, R.J., & Pennington, B.F. (1996). An interactive framework for examining prefrontal cognitive processes. *Developmental Neuropsychology*, *12*, 105–126.

Rowe, D.C., Stever, C., Giedinghagen, L.N., Gard, J.M., Cleveland, H.H., Terris, S.T., Mohr, J.H., Sherman, S., Abramowitz, A., & Waldman, I.D. (1998). Dopamine DRD4 receptor polymorphism and attention deficit hyperactivity disorder. *Molecular Psychiatry*, *3*, 419–426.

Rucklidge, J.J., & Tannock, R. (2002). Neuropsychological profiles of adolescents with ADHD: Effects of reading difficulties and gender. *Journal of Child Psychology and Psychiatry*, *43*, 988–1003.

Russell, V., de Villiers, A., Sagvolden, T., Lamm, M., & Taljaard, J. (1995). Altered dopaminergic function in the prefrontal cortex, nucleus accumbens and caudate-putamen of an animal model of attention-deficit hyperactivity disorder – the spontaneously hypertensive rat. *Brain Research*, *676*, 343–351.

Sagvolden, T., Aase, H., Zeiner, P., & Berger, D. (1998). Altered reinforcement mechanisms in attention-deficit/hyperactivity disorder. *Behavioral Brain Research*, *94*, 61–71.

Sanders, A. (1983). Towards a model of stress and performance. *Acta Psychologica*, *53*, 61–97.

Satterfield, J.H., & Dawson, M.E. (1971). Electrodermal correlates of hyperactivity in children. *Psychophysiology*, *8*, 191–197.

Schachar, R., Tannock, R., Marriott, M., & Logan, G. (1995). Deficient inhibitory control in attention deficit hyperactivity disorder. *Journal of Abnormal Child Psychology*, *23*, 411–437.

Scheres, A., Oosterlaan, J., & Sergeant, J. (2001). Response execution and inhibition in children with AD/HD and other disruptive disorders: The role of behavioural activation. *Journal of Child Psychology and Psychiatry*, *42*, 347–357.

Schmitz, M., Cadore, L., Paczko, M., Kipper, L., Chaves, M., Rohde, L.A., Moura, C., & Knijnik, M. (2002). Neuropsychological performance in DSM-IV ADHD subtypes: An exploratory study with untreated adolescents. *Canadian Journal of Psychiatry*, *47*, 863–869.

Seidman, L., Biederman, J., Monuteaux, M., Weber, W., & Faraone, S.V. (2000). Neuropsychological functioning in nonreferred siblings of children with attention deficit hyperactivity disorder. *Journal of Abnormal Psychology*, *109*, 252–265.

Seidman, L., Doyle, A., Fried, R., Valera, E., Crum, K., & Matthews, L. (2004). Neuropsychological functioning in adults with attention-deficit/hyperactivity disorder. In T. Spencer (Ed.), *Adult ADHD, psychiatric clinics of North America* (vol. 27). (pp. 261–282). Elsevier Science.

Seidman, L., & Valera, E. (2002). The ADHD brain. In J. Biederman (Ed.), *ADHD: Current understanding of etiology, diagnosis, & neurobiology* (p. 44). Boston: Veritas Institute for Medical Education.

Seidman, L., Valera, E., & Makris, N. (submitted). Structural brain imaging of attention-deficit/hyperactivity disorder. *Biological Psychiatry*.

Seidman, L.J., Biederman, J., Faraone, S.V., Milberger, S., Norman, D., Seiverd, K., Benedict, K., Guite, J., Mick, E., & Kiley, K. (1995). Effects of family history and comorbidity on the neuropsychological performance of children with ADHD: Preliminary findings. *Journal of American Academy of Child and Adolescent Psychiatry*, *34*, 1015–1024.

Seidman, L.J., Biederman, J., Faraone, S.V., Weber, W., & Ouellette, C. (1997). Toward defining a neuropsychology of attention deficit-hyperactivity disorder: Performance of children and adolescents

from a large clinically referred sample. *Journal of Consulting and Clinical Psychology*, *65*, 150–160.

Seidman, L.J., Biederman, J., Monuteaux, M.C., Doyle, A.E., & Faraone, S.V. (2001). Learning disabilities and executive dysfunction in boys with attention deficit hyperactivity disorder. *Neuropsychology*, *15*, 544–556.

Sergeant, J.A. (2000). The cognitive-energetic model: An empirical approach to attention-deficit hyperactivity disorder. *Neuroscience Biobehavioral Reviews*, *24*, 7–12.

Sergeant, J.A. (in press). Modeling attention-deficit/hyperactivity disorder: A critical appraisal of the cognitive-energetic model.

Sergeant, J.A., Geurts, H., & Oosterlaan, J. (2002). How specific is a deficit of executive functioning for attention-deficit/hyperactivity disorder? *Behavioural Brain Research*, *130*, 3–28.

Shao, Y., Cuccaro, M., Hauser, E., Raiford, K., Menold, M., Wolpert, C., et al. (2003). Fine mapping of autistic disorder to chromosome 15q11-q13 by use of phenotypic subtypes. *American Journal of Human Genetics*, *72*, 539–548.

Shaywitz, B.A., Klopper, J.H., & Gordon, J.W. (1978). Methylphenidate in G-hydroxydopamine treated developing rat pups. *Child Neurology*, *35*, 463–467.

Shaywitz, S.E., Cohen, D.J., & Shaywitz, B.A. (1978). The biochemical basis of minimal brain dysfunction. *The Journal of Pediatrics*, *92*, 179–187.

Skuse, D.H. (2001). Endophenotypes and child psychiatry. *British Journal of Psychiatry*, *178*, 395–396.

Slaats-Willemse, D., Swaab-Barneveld, H., de Sonneville, L., van der Meulen, E., & Buitelaar, J. (2003). Deficient response inhibition as a cognitive endophenotype of ADHD. *Journal of American Academy of Child and Adolescent Psychiatry*, *42*, 1242–1248.

Smalley, S.L., Kustanovich, V., Minassian, S.L., Stone, J.L., Ogdie, M.N., McGough, J.J., McCracken, J.T., MacPhie, I.L., Francks, C., Fisher, S.E., Cantor, R.M., Monaco, A.P., & Nelson, S.F. (2002). Genetic linkage of attention-deficit/hyperactivity disorder on chromosome 16p13, in a region implicated in autism. *American Journal of Medical Genetics*, *71*, 959–963.

Smith, K.M., Daly, M., Fischer, M., Yiannoutsos, C.T., Bauer, L., Barkley, R., & Navia, B.A. (2003). Association of the dopamine beta hydroxylase gene with attention deficit hyperactivity disorder: Genetic analysis of the Milwaukee longitudinal study. *American Journal of Medical Genetics*, *119B*, 77–85.

Solanto, M., Abikoff, H., Sonuga-Barke, E., Schachar, R., Logan, G., Wigal, T., Hechtman, L., Hinshaw, S., & Turkel, E. (2001). The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: A supplement to the NIMH multimodal treatment study of AD/HD. *Journal of Abnormal Child Psychology*, *29*, 215–228.

Sonuga-Barke, E.J. (2002). Psychological heterogeneity in AD/HD – a dual pathway model of behaviour and cognition. *Behavioural Brain Research*, *130*, 29–36.

Sonuga-Barke, E.J., Dalen, L., Daley, D., & Remington, B. (2002). Are planning, working memory, and inhibition associated with individual differences in preschool ADHD symptoms? *Developmental Neuropsychology, 21,* 255–272.

Steenari, M.R., Vuontela, V., Paavonen, E.J., Carlson, S., Fjallberg, M., & Aronen, E. (2003). Working memory and sleep in 6- to 13-year-old schoolchildren. *Journal of American Academy of Child and Adolescent Psychiatry*, *42*, 85–92.

Stins, J.F., van Baal, G.C., Polderman, T.J., Verhulst, F.C., & Boomsma, D.I. (2004). Heritability of Stroop and flanker performance in 12-year-old children. *BMC Neuroscience*, *5*, 49.

Suarez, B.K., Hampe, C.L., & Van Eerdewegh, P. (1994). Problems of replicating linkage claims in psychiatry. In E.S. Gershon, C.R. Cloninger, & J.E. Barrett (Eds.), *Genetic approaches in mental disorders* (pp. 23–46). Washington, DC: American Psychiatric Press.

Swan, G.E., & Carmelli, D. (2002). Evidence for genetic mediation of executive control: A study of aging male twins. *Journal of Gerontology B Psychological Sciences and Social Sciences*, *57*, P133–143.

Swanson, J., Oosterlaan, J., Murias, M., Schuck, S., Flodman, P., Spence, M. A., Wasdell, M., Ding, Y., Chi, H.C., Smith, M., Mann, M., Carlson, C., Kennedy, J.L., Sergeant, J.A., 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. *Proceedings of the National Academy of Sciences of the United States of America*, *97*, 4754–4759.

Taerk, E., Grizenko, N., Ben Amor, L., Lageix, P., Mbekou, V., Deguzman, R., Torkaman-Zehi, A., Ter-Stepanian, M., Baron, C., & Joober, R. (2004). Catechol-O-Methyltransferase (COMT) Val108/158 Met polymorphism does not modulate executive function in children with ADHD. *BMC Medical Genetics*, *5*, 30.

Tannock, R. (1998). Attention deficit hyperactivity disorder: Advances in cognitive, neurobiological, and genetic research. *Journal of Child Psychology and Psychiatry*, *39*, 65–99.

Tannock, R., Ickowicz, A., & Schachar, R. (1995). Differential effects of methylphenidate on working memory in ADHD children with and without comorbid anxiety. *Journal of the American Academy of Child and Adolescent Psychiatry*, *34*, 886–896.

Tannock, R., Schachar, R., & Logan, G. (1995). Methylphenidate and cognitive flexibility: Dissociated dose effects in hyperactive children. *Journal of Abnormal Child Psychology*, *23*, 235–266.

Thapar, A., Holmes, J., Poulton, K., & Harrington, R. (1999). Genetic basis of attention deficit and hyperactivity. *British Journal of Psychiatry*, *174*, 105–111.

Todd, R.D. (2000). Genetics of attention deficit/hyperactivity disorder: Are we ready for molecular genetic studies? *American Journal of Medical Genetics (Neuropsychiatric Genetics), 96,* 241–243.

Todd, R.D., Neuman, R.J., Lobos, E.A., Jong, Y.J., Reich, W., & Heath, A.C. (2001). Lack of association of dopamine D4 receptor gene polymorphisms with ADHD subtypes in a population sample of twins. *American Journal of Medical Genetics*, *105*, 432–438.

Tsuang, M.T., & Faraone, S.V. (1995). The case for heterogeneity in the etiology of schizophrenia. *Schizophrenia Research*, *17*, 161–175.

van der Meere, J., Gunning, W., & Stemerdink, N. (1996). Changing a response set in normal development and in ADHD children with and without tics. *Journal of Abnormal Child Psychology*, *24*, 767–786.

Van Tol, H.H., Wu, C.M., Guan, H.C., Ohara, K., Bunzow, J.R., Civelli, O., Kennedy, J., Seeman, P., Niznik, H.B., & Jovanovik, B. (1992). Multiple dopamine D4 receptor variants in the human population. *Nature*, *358*, 149–152.

Waldman, I.D. (submitted). Statistical approaches to complex phenotypes: Evaluating neuropsychological endophenotypes for ADHD. *Biological Psychiatry*.

Waldman, I.D., & Rhee, S.H. (2002). Behavioral and molecular genetic studies. In S. Sanberg (Ed.), *Hyperactivity and attention disorders of childhood* (2nd edn. pp. 290–335). New York: Cambridge University Press.

Waldman, I.D., Robinson, B. F., & Rowe, D.C. (1999). A logistic regression based extension of the TDT for continuous and categorical traits. *Annals of Human Genetics*, *63*, 329–340.

Waldman, I.D., Rowe, D.C., Abramowitz, A., Kozel, S.T., Mohr, J.H., Sherman, S.L., Cleveland, H.H., Sanders, M.L., Gard, J.M., & Stever, C. (1998). Association and linkage of the dopamine transporter gene and attention-deficit hyperactivity disorder in children: Heterogeneity owing to diagnostic subtype and severity. *American Journal of Human Genetics*, *63*, 1767–1776.

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV)*. San Antonio, TX: The Psychological Corporation.

Werry, J.S., Reeves, J.C., & Elkind, G.S. (1987). Attention deficit, conduct, oppositional, and anxiety disorders in children: I. A review of research on differentiating characteristics. *Journal of the American Academy of Child and Adolescent Psychiatry*, *26*, 133–143.

White, R.F., & Rose, F.E. (1997). The Boston process approach: A brief history and current practice. In G. Goldstein & T.M. Incagnoli (Eds.), *Contemporary approaches to neuropsychological assessment: Critical issues in neuropsychology* (pp. 171–211). New York: Plenum Press.

Willcutt, E.G., Brodsky, K., Chhabildas, N., Shanahan, M., Yerys, B., Scott, A., & Pennington, B.F. (in press a). The neuropsychology of ADHD: Validity of the executive function hypothesis. In D. Gozal & D. Molfese (Eds.), *Attention deficit hyperactivity disorder from genes to practice*. Totowa, NJ: Humana Press.

Willcutt, E.G., Doyle, A.E., Nigg, J.T., Faraone, S.V., & Pennington, B.F. (in press b). Validity of the executive function theory of ADHD: A meta-analytic review. *Biological Psychiatry*.

Willcutt, E.G., Pennington, B.F., Boada, R., Ogline, J.S., Tunick, R.A., Chhabildas, N.A., & Olson, R.K. (2001). A comparison of the cognitive deficits in reading disability and attention-deficit/hyperactivity disorder. *Journal of Abnormal Psychology*, *110*, 157–172.

Willcutt, E.G., Pennington, B.F., Chhabildas, N.A., Friedman, M.C., & Alexander, J. (1999). Psychiatric comorbidity associated with DSM-IV ADHD in a nonreferred sample of twins. *Journal of the American Academy of Child and Adolescent Psychiatry*, *38*, 1355–1362.

Willcutt, E.G., Pennington, B.F., Smith, S.D., Cardon, L.R., Gayan, J., Knopik, V.S., Olson, R.K., & DeFries, J.C. (2002). Quantitative trait locus for reading disability on chromosome 6p is pleiotropic for attention-deficit/hyperactivity disorder. *American Journal of Medical Genetics*, *114*, 260–268.

Woodward, L.J., Fergusson, D.M., & Horwood, L.J. (2000). Driving outcomes of young people with attentional difficulties in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry*, *39*, 627–634.

Manuscript accepted 24 February 2005