The adrenergic receptor α -2A gene (*ADRA2A*) and neuropsychological executive functions as putative endophenotypes for childhood ADHD

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There is resurgent interest in the psychiatric literature in endophenotypes, variables thought to more strongly reflect the effects of candidate genes than do manifest disorders. In a sample of 176 children with attention deficit hyperactivity disorder (ADHD) and 52 of their siblings, we examined the validity of several putative endophenotypes for ADHD that represent commonly used clinical measures of multiple cognitive/neuropsychological domains of executive functions (EFs). We review their distributional normality, their relations to ADHD symptoms in probands and unaffected siblings relative to nonADHD controls, and their correlation in siblings. We also tested the EF measures' associations with the *ADRA2A* gene and whether they *mediated* or *moderated* the associations between ADHD and *ADRA2A*. Several EF measures showed association with *ADRA2A*, as well as moderation, but not mediation, of its association with ADHD. Implications of the results for evaluating the validity and utility of putative endophenotype measures and for finding candidate gene effects on ADHD are discussed.

Attention deficit hyperactivity disorder (ADHD) is among the most common psychiatric disorders of childhood and adolescence, with prevalence estimated at about 5% (American Psychiatric Association [APA], 1994), and is accompanied by considerable impairment and cost to children, families, and communities (Hinshaw, 2002; Rappley, 2005). Although its specific causes remain unknown, numerous studies have demonstrated a familial basis for the disorder, and twin and adoption studies suggest strongly that this familiarity is due mainly to genetic influences (Faraone et al., 2005; Waldman & Rhee, 2002), with heritabilities ranging from 60% to 80% across studies (Waldman & Rhee, 2002). The results of these quantitative genetic studies have led to a proliferation of molecular genetic research over the past decade. These include a small number of genome scans (Arcos-Burgos et al., 2004; Bakker et al., 2003;

Ogdie et al., 2003), along with a large number of candidate gene studies. Most candidate gene studies have focused on genes in the dopaminergic, serotonergic, and noradrenergic neurotransmitter systems, as well as on a handful of genes involved in brain and nervous system development (for recent reviews, see Faraone et al., 2005; Waldman & Gizer, in press). These studies have yielded mixed results, with both successful and failed replication attempts of the initial positive findings for each of the candidate genes examined, a situation that is similar to that for genetic association studies of other psychiatric disorders and almost all medical diseases (Ioannidis, Ntzani, Trikalinos, & Contopoulos-Ioannidis, 2001; Lohmueller, Pearce, Pike, Lander, & Hirschhorn, 2003).

Such mixed findings have called into question whether categorical diagnoses are the most meaningful phenotypes for genetic analysis, given that the majority of psychiatric diagnoses represent the imposition of rather arbitrary thresholds on continuous symptom dimensions. Several researchers (e.g., Plomin, DeFries, McClearn, & McGuffin, 2000) have advocated the analysis of associations between candidate genes and continuous dimensions of psychopathology, rather than diagnoses. Doing so may vary in appropriateness for different forms of psychopathology (Haslam, 2003; Waldman & Lilienfeld, 2001). Nonetheless, some behavioral genetic evidence suggests

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that ADHD may be one condition that represents an extreme on a continuum (Levy, Hay, McLaughlin, Wood, & Waldman, 1997). Therefore, in this article, we examine association with both the diagnosis of ADHD and its underlying symptom dimensions. This notion of dimensional indices of genetic risk has been extended further via psychiatric geneticists' heightened interest in shifting the phenotypic focus from manifest disorders to endophenotypes, or variables that are thought to more strongly and directly reflect the effects of genes that influence risk for psychopathology than do manifest disorders (Almasy & Blangero, 2001; Doyle et al., 2005; Gottesman & Gould, 2003; Waldman, 2005). Putative endophenotypes could include biological measures that represent the immediate products of risk-inducing genes, psychophysiological indices of nervous system function, and cognitive/neuropsychological constructs thought to reflect brain mechanisms that underlie a disorder.

Neuropsychological executive functions (EFs) are among the most often proposed endophenotypes for ADHD (Barkley, 1997; Nigg, 2001), although their value in this respect warrants further investigation (Doyle et al., 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). EF is often criticized as an underspecified construct (Pennington & Ozonoff, 1996); it is derived from the clinical neuropsychology literature, where it connotes the strategic or relatively deliberate regulation of response to context and the maintenance of behavior in relation to goals held in working memory (Pennington & Ozonoff, 1996). Despite continued issues in the definition of this construct, tractable models of EF are emerging (Lyon & Krasnegor, 1996; Posner & DiGirolamo, 1998), with a developmental focus (Diamond, Prevot, Callender, & Druin, 1997; Zelazo, Carter, Resnick, & Frye, 1997; Zelazo, Muller, Frye, & Marcovitch, 2003) and anchored in the neural sciences (where the terminology typically refers to *cognitive control*; Monsell & Driver, 1998; Nigg & Casey, 2005). These neural models all emphasize anterior networks in the brain and associated cortical-subcortical-thalamic neural circuits (Casey, Tottenham, & Fossella, 2002). For example, Posner and DiGirolamo (1998) have expanded on an earlier theory from Norman and Shallice (1986) by describing an executive control module that involves the anterior cingulate (a region of the frontal cortex) during active suppression of a competing response (e.g., during the Stroop task), but not during automatic or rote responding. Imaging and lesion data indicate that the frontal-to-subcortical circuits involved in various kinds of executive or cognitive control operations also include those connecting to the dorsolateral prefrontal cortex (PFC), as well as to the orbital PFC (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Casey et al., 2002). Activation patterns of these specific circuits may vary somewhat with task components (Casey et al., 2002).

Factor-analytic and conceptual models suggest that the clinical and cognitive measures relevant to this broad executive or regulatory domain likely reflect multiple component operations, although debate continues as to

whether a common factor may underlie part of the variance that is common across many of these measures. Thus, both imaging studies (Casey et al., 2002) and statistical analyses of phenotypic measures (Miyake, Friedman, Emerson, Witzki, & Howerter, 2000) suggest that EFs reflect distinct, yet related, component processes. Consequently, numerous conceptual models of how to fractionate the EF domain have been suggested (Lyon & Krasnegor, 1996). Here, we worked from a basic five-component model suggested by Pennington (1997) that specifies response inhibition, set shifting, working memory, planning, and interference control (see Nigg, 2000; Pennington & Ozonoff, 1996; Willcutt et al., 2005). Several of these abilities have been extensively discussed as potential ADHD endophenotypes (see Barkley, 1997; Willcutt et al., 2005), giving this model some appeal for our purposes. These abilities are theorized to involve operations in a series of parallel frontal-striatal neural loops involved in higher order regulation of cognition, affect, and behavior (Nigg & Casey, 2005), as has been alluded to above. Neuropsychological measures that conceptually reflect these component abilities have shown varying but generally replicated associations with ADHD both in our sample (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002) and in meta-analytic investigations (Willcutt et al., 2005). Because they are so widely used in research and clinical practice, we emphasized these clinical neuropsychological measures in our battery, supplemented by key chronometric measures.

In addition, we considered two output control domains that are outside this particular executive framework but whose involvement in ADHD has been suggested. Response *variability* is viewed as an important potential marker of ADHD. It may reflect problems in timing and motor control (Castellanos & Tannock, 2002) or arousal regulation (Sergeant, Oosterlaan, & van der Meere, 1999). Importantly, it already has shown familiarity (Kuntsi & Stevenson, 2001). Output *speed* is often viewed as an index of effort or activation (Sergeant et al., 1999). It was included in the form of raw decision reaction time and in the form of naming speed (Carte, Nigg, & Hinshaw, 1996) in order to broaden the battery.

Various criteria for the selection of endophenotypes have been proposed, but only recently have there been attempts to comprehensively systematize criteria for their validity and utility (Doyle et al., 2005; Gottesman & Gould, 2003; Waldman, 2005). In this study, we examine the validity of several EF measures as endophenotypes for ADHD and investigate their utility by testing their association with a candidate gene, the $\alpha 2$ noradrenergic receptor gene (i.e., *ADRA2A*), that we have previously reported is associated with ADHD (Park et al., 2005). We also use these analyses to illustrate a comprehensive approach for assessing the validity and utility of putative endophenotypes (Waldman, 2005).

This report will be organized in relation to five criteria for the validity of endophenotypes outlined by Waldman (2005). We will review whether deficits on these measures (1) were normally distributed, (2) were related to ADHD

symptoms in the population, as we have reported previously for these measures with this sample (Nigg, 1999; Nigg et al., 2002), (3) were greater in affected probands than in their unaffected siblings and (4) in unaffected siblings than in controls (also reported on in detail for this sample, along with data on parent EF scores, in Nigg, Blaskey, Stawicki, & Sachek, 2004), and (5) were correlated in siblings. In this report, we will reanalyze those data for the portion of our sample that was genotyped for single nucleotide polymorphisms (SNPs) in *ADRA2A* (described below). SNPs refer to a single nucleotide base change (e.g., C → A) at a particular chromosomal location. We then will provide new analyses evaluating the utility of the EF measures—specifically, (6) whether EF measures show association with the *ADRA2A* SNPs, as well as (7) whether they *mediate* or *moderate* the associations between ADHD and *ADRA2A*. To our knowledge, these are among the first data to be reported with regard to the last two questions.

The α -2A noradrenergic receptor gene (i.e., *ADRA2A*) represents an interesting candidate gene for ADHD for several reasons. First, an extensive theoretical and empirical literature suggests that noradrenergic neurotransmitters may be centrally involved in ADHD (e.g., Biederman & Spencer, 1999; Pliszka, McCracken, & Maas, 1996). Second, noradrenergic activity supports at least some of the cognitive abilities that are thought to be deficient in ADHD, such as working memory and other EFs, in rodents, nonhuman primates, and humans (Arnsten, 1998). Third, it appears that noradrenergic activity relevant to EFs is particularly pronounced in the PFC (Arnsten, Steere, & Hunt, 1996), an area of the brain related to EFs (Nigg & Casey, 2005; Pennington & Ozonoff, 1996) that is smaller in ADHD children than in age-matched controls (Castellanos & Tannock, 2002). Fourth, methylphenidate, a common psychostimulant used to successfully control symptoms of ADHD, is thought to facilitate norepinephrine activity in the rat brain, and pharmacological agents, such as guanfacine and clonidine, that act primarily on the noradrenergic system have been shown to facilitate working memory in rodents, nonhuman primates, and humans (Arnsten, 2000). Consistent with this is the evidence for Atomoxetine as a therapeutic agent for ADHD, given its role in blocking the norepinephrine transporter (Spencer et al., 2002). Fifth, it also has been suggested that stimulation of the Alpha2 class of adrenergic receptors facilitates the activating effects of norepinephrine on at least some of the EFs subsumed by the PFC (Arnsten et al., 1996), but not on other tasks that are subsumed primarily by other cortical or subcortical regions. In contrast, stimulation of the Alpha1 class of adrenergic receptors likely plays an inhibitory role in such PFC-mediated functions (Arnsten, 2000). Although there is some suggestion that the 2A adrenergic receptor is more strongly and centrally involved than is the 2C receptor in noradrenergic activity in the PFC relevant to EFs (Arnsten, 2000), future research comparing the three Alpha2 class receptors is needed to draw strong conclusions

regarding potential differences among the receptors' functions. Here, we will focus further on the α -2A gene.

The *ADRA2A* gene has been investigated most frequently among the adrenergic receptor genes in their association with ADHD. Initial studies attempting to link this gene to ADHD yielded inconsistent results when the association between ADHD and an SNP (i.e., rs1800544) was examined in the 5' promoter region of *ADRA2A* (Comings et al., 1999; Comings, Gonzalez, Cheng Li, & MacMurray, 2003; Roman et al., 2003; Xu et al., 2001). The 5' promoter refers to the untranslated region of the gene that precedes the part of the gene that codes for proteins. Although it is not involved in coding for proteins, the 5' promoter contains elements that regulate the function of the gene and is often regarded as playing the role of an "on-off switch" in the activation of a gene. In contrast to the previous studies, in our study (Park et al., 2005) we found a positive association by taking a haplotype approach. Whereas SNPs refer to a single nucleotide base change at a particular chromosomal location, haplotypes refer to a series of DNA polymorphisms that are in close contiguity on a chromosomal strand in a particular genomic region (e.g., within a candidate gene). In our previous study (Park et al., 2005), we examined haplotypes and within-family tests of association and linkage (i.e., using both conventional and quantitative TDTs) between ADHD subtypes and symptom dimensions and *ADRA2A* SNPs. Linkage refers to the cosegregation among family members of the presence or absence of the target disorder with specific alleles of one or more DNA markers. We found statistical trends for association and linkage between the 5' promoter SNP and ADHD, as well as significant association and linkage with both the inattentive and the hyperactive-impulsive symptom dimensions. For each of these analyses, the allele associated with the disorder was the same as that found in the aforementioned studies. In addition, a second SNP in the 3' UTR of *ADRA2A* also was associated with ADHD and the combined subtype, as well as with both the inattentive and the hyperactive-impulsive symptom dimensions. The 3' UTR refers to the untranslated region of the gene that follows the part of the gene that codes for proteins. Although it is not involved in coding for proteins, the 3' UTR may contain elements that regulate the function of the gene. In all, given its important role in the PFC and cognitive control operations and its likely association with ADHD, *ADRA2A* is a logical candidate gene for which to evaluate the validity and utility of putative endophenotypes, such as measures of EFs.

METHOD

Participants

Probands were $n = 166$ children who belonged to the ADHD combined type (*ADHD-C*, $n = 98$, or 59%) or the ADHD inattentive type (*ADHD-PI*, $n = 38$, or 23%), with the remaining ADHD probands (i.e., 18%) meeting criteria for ADHD hyperactive-impulsive type or subtype NOS. Given that ADHD subtype differences were not the focus of this study, they will not be treated further in this article.

Seventy-two non-ADHD controls and 52 siblings were also assessed as described below, and 9 of the latter (i.e., 17%) also met our operational criteria for ADHD. This sample was nearly the same as that reported by Nigg et al. (2004) and Park et al. (2005), with only a slight variation in number due to missing genotype data. The sibling sample here is the same as that reported in Nigg et al. (2004).

To maximize generalizability, a generally but not exclusively community-based recruitment strategy was followed. Families with a child in the first through the sixth grade were recruited from mass-mailed invitation letters and public advertisements, with a small percentage (10%) recruited from a local pediatric clinic specializing in ADHD referrals and from a local support group for parents of children with ADHD. To the extent possible, control families were matched on sex, age, and recruitment source (a neighboring general pediatric clinic or the same local school districts). A multistage screening process was used to select the children, which will be described next.

Diagnostic assignment of index children. Index children were considered as possible ADHD-C or ADHD-PI if they either (1) passed prescreen cutoffs on *both* parent and teacher versions of common ADHD rating instruments (Child Behavior Checklist or Teacher Report Form [Achenbach, 1991], Behavior Assessment Scale for Children [Reynolds & Kamphaus, 1992], Conners [1997] Rating Scale, or a DSM-IV symptoms checklist [Swanson et al.'s, 2000, SNAP-IV or the ADHD Rating Scale, depending on year of the study]), or (2) were diagnosed as ADHD (any type) by a physician or psychologist in the community who utilized teacher and parent ratings to arrive at the diagnosis. Children were considered as possible controls if they were below cutoffs on all parent and teacher scales and were never diagnosed with ADHD.

Child diagnosis then was confirmed using a parent-structured diagnostic interview (the DISC-IV; Shaffer, Fisher, & Lucas, 1997), supplemented by an "or" algorithm following the DSM-IV field trials validity data (Lahey et al., 1994). Prior versions of the DISC have exhibited acceptable reliability and validity. The "or" algorithm was implemented as follows. If children met age of onset, duration, impairment, and cross-situational criteria, diagnostic assignment was determined by counting a symptom as present if it was endorsed by the parent (on the DISC-IV) or the teacher (as "sometimes" or "often" present) on the symptom checklist.

Control children were negative for ADHD (all types) on the basis of the above criteria, with four or fewer symptoms in either domain by the "or" algorithm. Families were excluded from all groups if the target child yielded five symptoms of inattention or overactivity, on the basis of the field trial data indicating that these borderline cases might have ADHD-C or ADHD-PI (Lahey et al., 1994; $n = 20$ excluded). Key proband comorbid disorders were also assessed. Oppositional defiant disorder or conduct disorder was assigned on the basis of DISC-IV algorithms. We excluded reading disorder (RD) at screen in most years, but $n = 8$ children were allowed in with RD in the final year of the study. RD was assigned if (1) the absolute level of average Wechsler (1992) Individual Achievement Test Reading and Spelling scores were less than or equal to a standard score of 85 and (2) Full Scale IQ minus reading/spelling average was at least 15 points. IQ was estimated with a reliable and valid five-test short form of the Wechsler (1991) Intelligence Scale for Children, 3rd edition (WISC-III; Sattler, 1999).

Diagnostic assignment of siblings. For a subset of families, one sibling was assessed. We selected the sibling nearest in age to the target child, providing that the sibling was old enough to complete the neuropsychological measures (at least 6 years of age). We were unable to obtain teacher ratings for most of the siblings, so we will rely here on parent ADHD rating scale scores. We sought primarily to avoid false negatives in estimating ADHD status for siblings. Therefore, we used the 80th percentile as our rule-in for ADHD, a cut point that provides excellent negative predictive power (Power et al., 1998). We thus expected this cut point to slightly overselect

ADHD in siblings in order to enable us to rule out ADHD as an explanation for unaffected siblings' cognitive performance.

Exclusion criteria. Families and children were excluded from all groups if the target child had mental retardation, autistic disorder, Tourette syndrome, a current major depressive episode, bipolar disorder, or a physical or neurological handicap ascertained by parent report. Siblings with any of those conditions were excluded as well. All the children were native English speakers, had normal hearing and normal or corrected-to-normal vision, and had a valid Full Scale IQ > 75 (APA, 1994).

Procedure and Measures

All evaluations were conducted at Michigan State University in a standardized sequence. Test administrators and diagnostic interviewers were carefully trained, followed practiced scripts in providing test instructions, had their test administration procedures checked via videotape in a periodic quality control procedure, and were blind to child diagnostic status and study hypotheses. Although test-retest reliability is not available for all of the versions of the tests used here, they will be presented below where available. Recent data indicate that test-retest reliabilities are acceptable, although not excellent, for clinical executive function measures that are very similar to those utilized here, including tasks related to the Stroop, Trails, and Tower tests (Delis, Kaplan, & Kramer, 2001). EF measures were selected with the intent of capturing a range of component EFs hypothesized to be relevant to ADHD. As such, they are expected to reflect, to varying degrees, activity in the prefrontal regions in which the *ADRA2A* is expressed, as follows.

Response inhibition. Response inhibition, or suppression of a prepotent motor response, is postulated to require activation of a circuit linking the basal ganglia and the orbitofrontal cortex (Casey et al., 2002) and is often suggested as an ADHD endophenotype (Barkley, 1997; Crosbie & Schachar, 2001; Holmes et al., 2002). Performance in adults involves the right inferior frontal cortex and basal ganglia (Aron et al., 2003). Response inhibition was operationalized with the tracking version of the *stop task* using the same procedures as those in Logan, Schachar, and Tannock (1997) and Nigg (1999). The stop task is a computerized choice reaction time (RT) task. Following two blocks of 32 practice trials, four blocks of 64 trials were administered. In the tracking version of this task, stop signal RT, the index of inhibitory control, is estimated by subtracting mean stop signal latency from mean go RT (Logan et al., 1997). Simulation data have shown the estimated stop signal RT to be reliable with four blocks of trials and robust to violations of the statistical and theoretical assumptions underlying the task (Band, van der Molen, & Logan, 2003). Cronbach's α was found to be $> .88$ for both the stop signal and the go RTs.

Set shifting. The ability to rapidly alternate mental set was operationalized with the Trailmaking Test Forms A and B from the Halstead-Reitan Neuropsychological Battery (Reitan, 1979). Trailmaking A requires the subjects to connect circles containing a series of numbers in order (e.g., 1–15) and served as an index of simple motor speed, whereas Trailmaking B requires the subjects to trace a path between alternating letters and numbers, as rapidly as they can without making errors. Individuals who have sustained frontal lobe damage show deficits in their performance on the Trailmaking Test (Stuss et al., 2001). We will report on time to completion of Forms A and B herein and have used the inverse of completion time in analyses, since it has better distributional properties. We also computed a Trails B – A score in an effort to isolate the EF component of these tasks and used this in analyses as well. Studies evaluating the psychometric properties of Trails A and B have reported estimates of test-retest reliability that ranged from .50 to .89 (Spren & Strauss, 1998).

Planning/working memory. The term *planning* here entails both reasoning and working memory, with particular demands on visual working memory, thus placing demands on the PFC in adults

and children (Levin et al., 1994). It was operationalized with the Tower of London task (Krikorian, Bartok, & Gay, 1994). This task activates the PFC and associated neural regions (Newman, Carpenter, Varma, & Just, 2003). Participants viewed boards having three wooden pegs of unequal heights on which three wooden balls of different colors were to be moved one at a time, from a standard start position, to match pictured positions. The 12 problems increased in difficulty from two to five moves, with a possible total score of 36 points based on the number of trials needed to solve each problem. Prior studies suggest that it differentiates ADHD-C and control groups (Klorman et al., 1999; Nigg et al., 2002) and that it shows moderate test-retest reliability (.51; Delis et al., 2001). The outcome variable was the total score (range, 0–36).

Interference control. Interference control refers to the ability to monitor response conflict and suppress a competing response in order to carry out a primary response. It entails activation of the anterior cingulate and the dorsolateral PFC (Cabeza & Nyberg, 1997). It was operationalized with the Stroop Color–Word Interference Test (Golden, 1978). The Stroop is a widely used neuropsychological measure (MacLeod, 1991). Dorsolateral frontal lobe activity has been found to be increased during the incongruent color–word condition (Banich et al., 2000). The paper-and-pencil version of the task was administered, with 45 sec per trial. To evaluate interference control apart from naming speed, we created a residual score by regressing color–word naming on color and word naming. Versions of color naming, word naming, and color–word interference tasks very similar to those used here have been found to show adequate reliability (.77–.90; Delis et al., 2001).

Response variability. Variability in output speed on fast tasks is a candidate endophenotype emphasized in a recent neuroscience model of ADHD (Castellanos & Tannock, 2002), due to its ramifications for timing and motor control; it also has ramifications for models of arousal and output regulation (Posner & Peterson, 1990). Response variability was assessed by the within-subjects RT standard deviation on the go trials on the Logan stop task described above.

Response and naming speed. These measures provide one commonly cited index of effort or activation (Posner & Peterson, 1990; Sergeant et al., 1999), although naming speed also entails retrieval processes. We assessed output speed as (1) mean RT on the go trials on the Logan stop task, (2) naming speed (Carte et al., 1996) as indexed by the standardized Stroop word and color naming scores, and (3) motor speed as time to complete Trails A.

DNA analysis. DNA was collected by buccal brush. The promoter SNP, rs1800544 (*MspI*/RFLP), was typed by a modified amplification of the region, using deaza dGTP as described. Briefly, polymerase chain reaction (PCR) was performed in 20 μ l containing 40 ng of genomic DNA, 62.5 μ M each of dATP, dTTP, dCTP, 31.25 μ M of dGTP, 31.25 μ M of deaza dGTP, 1 μ M of each primer, 1.5 mM of $MgCl_2$, 1X PCR buffer, and 0.5 units of Taq DNA polymerase. For the 5' UTR SNP, rs1800545 (*HhaI* RFLP), PCR amplification was performed using primer sets, 5'-CCAAGTTATCAGGCCACCGA-3' and 5'-TGCTCCTGGCGGAACATGAA-3' in 20- μ l volume containing 40 ng of genomic DNA, 200 μ M of dNTPs, 1 μ M of each primer, 1.5 mM of $MgCl_2$, 1X PCR buffer, 2 μ l of DMSO, and 0.5 units of Taq DNA polymerase. Amplification included an initial denaturing step at 94°C for 3 min, followed by 35 cycles consisting of 30 sec at 94°C, 30 sec at 60°C, and 45 sec at 72°C, and the final extension step for 5 min at 72°C. After amplification, 10 units of *HhaI* restriction enzyme were added, and digestion was performed at 37°C for 2 h. The region for the 3' UTR SNP, rs553668 (*DraI* RFLP), was amplified in 20 μ l containing 40 ng of genomic DNA, 200 μ M of dNTPs, 1 μ M of each primer, 1.5 mM of $MgCl_2$, 1X PCR buffer, and 0.5 units of Taq DNA polymerase (primer sets: 5'-TACAAGGGCATGGCTCACAA-3' and 5'-CCAAGGCCAGGATTTCACAA-3'), using the same cycling parameters as above. Digestion of the PCR product was performed with 10 units of *DraI* restriction enzyme at 37°C for 2 h. All restriction fragments were detected using 3% agarose gel stained with ethidium bromide.

RESULTS

Tests of the Validity of Executive Functions as Putative Endophenotype Measures

Tests of distributional normality. Although not a prerequisite for validity or utility, endophenotype measures will be more tractable for subsequent analyses if they exhibit good psychometric properties, including normal distributions with the absence of skewness and kurtosis. Unfortunately, none of the EF measures examined as putative endophenotypes in this study were normally distributed, as indicated by the Shapiro–Wilk test of normality, which was significant (i.e., $p < .05$) for all of the EF measures. In addition, with the lone exception of the Stroop word condition, all of the EF measures exhibited significant skewness and kurtosis (i.e., $p < .05$), as indicated by the skewness and kurtosis values exceeding twice their standard errors. Although these findings do not prevent meaningful analyses of endophenotype measures, they suggest caution in their interpretation.

Relation of EF measures to ADHD symptoms in the population. We have provided a comprehensive analysis of the relation of these measures to ADHD symptoms in ADHD and control children and in their relatives in Nigg et al. (2002; Nigg et al., 2004). Here, we will provide a reanalysis of these data for the subsample with genotype data available for *ADRA2A*. Given that this is not a general population sample but, rather, a sample of ADHD probands and controls and their siblings, we examined this relation in two distinct subsamples, using Pearson correlations between the endophenotype measures and the ADHD symptoms. These included ADHD probands and nonADHD controls, and the unaffected and affected siblings of the ADHD probands. With only a few exceptions (i.e., stop signal RT variability [SSSD], go RT, and all the indices from the Stroop test of interference), the correlations were very similar across the two subpopulations and correlations were not systematically higher or lower in either subpopulation. Most of the correlations were modest in magnitude and were between .15 and .25 for almost all of the EF measures (see Table 1). The only exceptions for which correlations were lower were go RT, Trails B – A, and the Stroop interference index.

Endophenotype deficit differences between ADHD probands and their unaffected siblings and between siblings and nondisordered controls. Waldman (2005) suggested that valid endophenotypes should show deficits that are greater in ADHD probands than in their unaffected siblings and greater in those siblings than in nondisordered controls if the endophenotype, in fact, represents an index of the genetic liability underlying the disorder. In Nigg et al. (2004), we looked at sibling (and parent) performance after controlling for sibling ADHD, to show that EF deficits in siblings were not entirely explained by their having ADHD. Here, we provided a more complete test of Waldman's hypothesis by using a set of univariate ANOVAs that incorporated two a priori, orthogonal polynomial contrasts. The first of these contrasts fit a linear trend to the EF measure group means in such a way that

ADHD probands were greater (in the disordered direction) than their unaffected siblings, who were greater, in turn, than the nondisordered controls. The second contrast tested a quadratic trend that captured the deviation of the unaffected siblings' EF measure group means from being intermediate to those of the ADHD probands and the nondisordered controls. In cases of heterogeneity of variance across the three groups (as assessed by significance of the Levene test), robust tests of these contrasts were conducted.

The first contrast was significant for almost all of the EF measures, with only two measures (i.e., go RT and the Stroop interference index) showing a statistical trend for significance and small effect sizes (i.e., $\eta^2 \leq .01$) and p values for the remaining measures ranging from .018 to $< .001$ and low-to-moderate effect sizes ranging from $\eta^2 = .02$ to .09 (see Table 1). This suggests that the ADHD probands showed greater deficits than did their unaffected siblings, who showed greater deficits, in turn, than did the nondisordered controls for all of the EF measures. Somewhat similar results emerged for the second contrast, which was nonsignificant for most of the EF measures, suggesting that the unaffected siblings were, indeed, intermediate between the ADHD probands and the nondisordered controls in their EF function. Exceptions to these results were the Stroop word and color conditions, whereas marginally significant deviations were noted for the Trails A and B indices and the Stroop interference index.

Sibling correlations to assess the familiarity of putative endophenotype measures. Correlations of EF measures between first-degree relatives and children with ADHD were reported in Nigg et al. (2004) and will be recapitulated here. Although these correlations demonstrate familiarity, they are indeterminate as to whether this familial basis reflects genetic or shared environmental influences. Nonetheless, sibling correlations are consistent with genetic influences' underlying the putative endophenotype measures, although it remains for future twin and/or adoption studies to disentangle their underlying genetic and environmental influences.

Sibling correlations for the EF measures spanned a considerable range, with one measure (go RT) exhibiting a negative sibling correlation and another measure (the Stroop interference index) exhibiting a sibling correlation of zero (see Table 1). Sibling correlations for the remaining EF measures were of modest to moderate magnitude, ranging from a low of .09 (for Trails B – A) to a high of .41 (for stop signal RT). These results are similar to those reported in Nigg et al. (2004), although it is worth noting that there, we reported RT on Trails B to show substantial familiarity in a larger sample of relatives that included parents as well as siblings. Although these sibling correlations may reflect shared environmental influences to some extent, most are consistent with moderate heritabilities for the putative endophenotype measures.

Tests of the Utility of Putative Endophenotype Measures

Associations of ADHD diagnoses and symptom dimensions with ADRA2A SNPs and haplotypes. We

next conducted a series of analyses directed at examining the utility of the EF measures as endophenotypes in candidate gene analyses of association and linkage with ADRA2A. As a prelude to these analyses, we repeated the within-family analyses of association and linkage between the ADHD diagnoses and symptom dimensions and the ADRA2A SNPs and haplotypes that were reported in Park et al. (2005), which did not include the siblings. We used an extension of the Transmission Disequilibrium Test (TDT; Spielman, McGinnis, & Ewens, 1993) to conduct these analyses. The TDT is a within-family test of association and linkage that contrasts the number of transmitted and nontransmitted alleles from heterozygous parents (i.e., parents with one high-risk and one low-risk allele at a DNA marker) to their affected children. The TDT is commonly used for statistical genetic analyses, given its test of both association and linkage, its ability to include both probands and their siblings in analyses, and its robustness to potential biases due to the possibility of population stratification. Population stratification refers to the possibility of observing an association between the disorder and the gene of interest, in the absence of any causal effects of the gene, because the sample comprises subsamples of individuals, typically of different ethnic backgrounds, who differ in both rates of the disorder and allele frequencies for the marker or haplotype in the gene being analyzed. The program we used to conduct these analyses was FBAT (Rabinowitz & Laird, 2000), which extends the conventional TDT by accommodating multiple categorical and continuous traits, analyses of haplotypes composed of multiple SNPs, missing parental genotypic data, and ambiguous phase of haplotypes (i.e., ambiguity in determining which alleles of the multiple SNPs composing the haplotypes are contiguous on a chromosomal strand). A recent simulation study (Kistner & Weinberg, 2004) showed that in a variety of analytic scenarios, FBAT was among the most powerful of the available analytic methods that extend the TDT.

As is shown in Table 2, both the *MspI* and *DraI* SNPs were significantly associated and linked with the diagnosis of ADHD (with moderate effect sizes ranging from $\eta^2 = .13$ to .17), as well as with the inattentive and hyperactive-impulsive symptom dimensions (with low to moderate effect sizes ranging from $\eta^2 = .05$ to .13). It is worth noting that the effects of ADRA2A appeared to be stronger on the hyperactive-impulsive ($\eta^2 = .10$ –.13) than on the inattentive ($\eta^2 = .05$ –.06) symptom dimension and that a dominant model (in which either one or two copies of a particular allele confer risk for disorder) provided a somewhat better fit than did an additive model (in which risk for disorder increases monotonically from zero to one to two copies of a particular allele) for the symptom dimensions. In contrast to these results, associations with the *HhaI* SNP were nonsignificant and low in magnitude ($\eta^2 \leq .02$).

Analyses of association and linkage between the ADHD phenotypes and the three common haplotypes (i.e., frequency $\geq .02$) composed of these SNPs revealed a protective haplotype (comprising the “1” allele for each of the

three SNPs) and a high-risk haplotype (comprising the “2” allele for the *MspI* and *DraI* SNPs and the “1” allele for the *HhaI* SNP). The protective haplotype was the most frequent (haplotype frequency estimated = .71) and was negatively associated and linked with the ADHD diagnosis ($p = .004$, $\eta^2 = .16$) and the hyperactive-impulsive symptom dimension ($p = .031$) under an additive, but not a dominant, model. This haplotype was not associated or linked with the inattentive symptom dimension ($p = .110$ or $.222$, $\eta^2 = .007$) under either a dominant or an additive model. The high-risk haplotype was less frequent (haplotype frequency estimated = .17) and was positively associated and linked with the ADHD diagnosis ($p = .001$, $\eta^2 = .27$) and both the hyperactive-impulsive ($p = .0008$ or $.005$, $\eta^2 = .17$) and the inattentive ($p = .013$ or $.055$, $\eta^2 = .09$) symptom dimensions under both dominant and additive models. The least frequent of the common haplotypes (comprising the “2” allele for the *MspI* and *HhaI* SNPs and the “1” allele for the *DraI* SNP; haplotype frequency estimated = .10) was not associated or linked with the ADHD diagnosis ($p = .270$, $\eta^2 = .02$) or with either the hyperactive-impulsive ($p = .302$ or $.493$, $\eta^2 = .006$) or the inattentive ($p = .292$ or $.442$, $\eta^2 = .007$) symptom dimension under either the dominant or the additive model. These results are quite similar to those presented previously from this sample, using a different analytic method (Park et al., 2005), and are shown here as a point of reference for the analyses of association between the three *ADRA2A* SNPs and each of the EF measure indices to follow below.

Associations of the putative endophenotype measures with the *ADRA2A* SNPs. We next conducted robust tests of association and linkage between the three SNPs in *ADRA2A* and each of the EF measure indices, using FBAT (shown in Table 3). The *MspI* polymorphism (which, as will be recalled, was associated with ADHD) was associated and linked with performance on the Tower of London task, variability in RTs on the stop signal task, and RTs for both Trails A and B ($p = .033$ to $.002$, $\eta^2 = .05$ – $.10$). The *HhaI* polymorphism (not associated with ADHD) was not significantly associated or linked with any of the EF measures, likely due to its relatively low minor allele frequency (.12), but there were statistical trends for association with RTs for both Trails A and B and the Stroop word, color, and color–word conditions ($p = .095$ – $.065$, $\eta^2 = .04$ – $.05$). The *DraI* polymorphism (which was related to ADHD above) was associated and linked with RTs for both Trails A and B, as well as for the Trails B – A index ($p = .061$ – $.003$, $\eta^2 = .04$ – $.06$). These results are fairly consistent in suggesting association and linkage across the three SNPs, particularly with the Trails RT measures. Somewhat less consistent results appeared with response variability on the stop signal task, the Tower of London task, and the output speed indices from the Stroop test. It is worth noting that the associated EF measures are indicators of working memory and

response readiness or arousal, functions that are posited to involve noradrenergic mechanisms.

Mediation and moderation of associations of ADHD with the *ADRA2A* SNPs via the putative endophenotype measures. We next conducted a series of logistic regression analyses to test whether and the extent to which the putative endophenotype measures mediated and/or moderated association and linkage between the diagnosis of ADHD and the three *ADRA2A* SNPs. In these logistic regression analyses, ADHD diagnostic status was the dichotomous outcome variable (i.e., 1 = diagnosis present, 0 = diagnosis absent), and genotype for a given SNP (i.e., “11,” “12,” or “22”) was the categorical explanatory variable. *Mediation* refers to the extent to which a putative endophenotype explains part or all of the association between an *ADRA2A* SNP and ADHD and is indicated when the association between the SNP and ADHD is weakened or eliminated with the inclusion of the putative endophenotype in the logistic regression equation. In contrast, *moderation* refers to the extent to which a putative endophenotype strengthens or weakens the association between an *ADRA2A* SNP and ADHD and is indicated by a significant interaction between the SNP and the putative endophenotype in predicting ADHD diagnostic status. Specifically, we predicted that the association between the *ADRA2A* SNPs and ADHD would be stronger in the presence of deficits on the EF measures. Given that these regression analyses represent between-family, rather than within-family, analyses of association, they are not robust to the potentially biasing effects of population stratification. We thus included a categorical variable that indicated ethnic background in the first step of the regression equations, in order to control for any ethnic group differences in ADHD diagnostic status or genotype before testing for mediation and moderation.

As is shown in Table 3, none of the EF measures appeared to mediate any of the associations between ADHD diagnostic status and the three *ADRA2A* SNPs, since the inclusion of these measures resulted in almost no decrease in the significance or magnitude of the associations (the greatest such decrease accounted for only 1.2% of the variance). Indeed, in fully one third of these analyses, the magnitude of the association between ADHD diagnostic status and the *ADRA2A* SNP actually *increased* (indicating a suppression effect, denoted by S in Table 3), with the largest such increase accounting for 2.3% of the variance. These results suggest that, rather than accounting for all or even part of the associations between ADHD diagnostic status and the *ADRA2A* SNPs, inclusion of the putative endophenotype measures either had no impact on the associations or actually increased their magnitudes. The latter appeared to be true particularly for indices derived from the Stroop test.

In contrast to the results for the tests of mediation, several of the interactions that represent tests of moderation were significant or marginally so. The *MspI* SNP in-

Table 3
Evaluation of Utility of Endophenotype Criteria with *ADRA2A* SNPs

	Tower of London	SSRT	SSSD	GoRT	Trails A (Inverse)	Trails B (Inverse)	Trails B – A (Inverse)	Stroop Word	Stroop Color	Stroop Color–Word	Stroop Interference
Marker: <i>MspI</i> Associated with SNP (between)? Associated with SNP (within)? Mediates association with ADHD? Moderates association with ADHD?	$\eta^2 = .004$, $p = .630$	$\eta^2 = .01$, $p = .400$	$\eta^2 = .00$, $p = .933$	$\eta^2 = .00$, $p = .887$	$\eta^2 = .01$, $p = .097$	$\eta^2 = .01$, $p = .085$	$\eta^2 = .003$, $p = .209$	$\eta^2 = .01$, $p = .282$	$\eta^2 = .01$, $p = .333$	$\eta^2 = .005$, $p = .573$	$\eta^2 = .00$, $p = .989$
	$\eta^2 = .06$, $p = .019$	$\eta^2 = .00$, $p = .796$	$\eta^2 = .05$, $p = .033$	$\eta^2 = .00$, $p = .830$	$\eta^2 = .10$, $p = .002$	$\eta^2 = .08$, $p = .005$	$\eta^2 = .001$, $p = .701$	$\eta^2 = .00$, $p = .287$	$\eta^2 = .00$, $p = .405$	$\eta^2 = .00$, $p = .976$	$\eta^2 = .02$, $p = .118$
	No; $\Delta\eta^2 = .001$, $\Delta p = .007$	No; $\Delta\eta^2 = .005$, $\Delta p = -.183$	No; $\Delta\eta^2 = .007$, $\Delta p = .071$	No; $\Delta\eta^2 = .000$, $\Delta p = -.015$	No; $\Delta\eta^2 = .004$, $\Delta p = .163$	No; $\Delta\eta^2 = .002$, $\Delta p = .096$	No; $\Delta\eta^2 = .002$, $\Delta p = .093$	No, S; $\Delta\eta^2 = .008$, $\Delta p = -.175$	No, S; $\Delta\eta^2 = .013$, $\Delta p = -.253$	No, S; $\Delta\eta^2 = .012$, $\Delta p = -.229$	No, S; $\Delta\eta^2 = .017$, $\Delta p = -.299$
	No; $\Delta\eta^2 = .009$, $p = .520$	No; $\Delta\eta^2 = .002$, $p = .820$	No; $\Delta\eta^2 = .001$, $p = .900$	No; $\Delta\eta^2 = .005$, $p = .716$	Yes; $\Delta\eta^2 = .045$, $p = .036$	No; $\Delta\eta^2 = .023$, $p = .182$	No; $\Delta\eta^2 = .003$, $p = .849$	No; $\Delta\eta^2 = .006$, $p = .682$	No; $\Delta\eta^2 = .010$, $p = .534$	No; $\Delta\eta^2 = .019$, $p = .277$	No; $\Delta\eta^2 = .032$, $p = .128$
	$\eta^2 = .02$, $p = .066$	$\eta^2 = .02$, $p = .015$	$\eta^2 = .03$, $p = .032$	$\eta^2 = .02$, $p = .055$	$\eta^2 = .01$, $p = .463$	$\eta^2 = .01$, $p = .461$	$\eta^2 = .01$, $p = .639$	$\eta^2 = .00$, $p = .639$	$\eta^2 = .00$, $p = .665$	$\eta^2 = .02$, $p = .116$	$\eta^2 = .02$, $p = .087$
Marker: <i>HhaI</i> Associated with SNP (between)? Associated with SNP (within)? Mediates association with ADHD? Moderates association with ADHD?	$\eta^2 = .04$, $p = .140$	$\eta^2 = .00$, $p = .796$	$\eta^2 = .02$, $p = .383$	$\eta^2 = .00$, $p = .830$	$\eta^2 = .05$, $p = .065$	$\eta^2 = .05$, $p = .066$	$\eta^2 = .000$, $p = .929$	$\eta^2 = .04$, $p = .077$	$\eta^2 = .04$, $p = .095$	$\eta^2 = .05$, $p = .067$	$\eta^2 = .02$, $p = .171$
	No; $\Delta\eta^2 = .008$, $\Delta p = .112$	No; $\Delta\eta^2 = .012$, $\Delta p = .463$	No; $\Delta\eta^2 = .003$, $\Delta p = .048$	No; $\Delta\eta^2 = .001$, $\Delta p = .006$	No, S; $\Delta\eta^2 = .011$, $\Delta p = -.144$	No, S; $\Delta\eta^2 = .009$, $\Delta p = -.123$	No, S; $\Delta\eta^2 = .005$, $\Delta p = -.054$	No; $\Delta\eta^2 = .001$, $\Delta p = .041$	No; $\Delta\eta^2 = .001$, $\Delta p = .106$	No; $\Delta\eta^2 = .003$, $\Delta p = .122$	No; $\Delta\eta^2 = .001$, $\Delta p = .077$
	No; $\Delta\eta^2 = .001$, $p = .897$	Yes; $\Delta\eta^2 = .03$, $p = .074$	No; $\Delta\eta^2 = .025$, $p = .118$	Yes; $\Delta\eta^2 = .054$, $p = .013$	No; $\Delta\eta^2 = .005$, $p = .700$	No; $\Delta\eta^2 = .026$, $p = .135$	No; $\Delta\eta^2 = .015$, $p = .330$	No; $\Delta\eta^2 = .022$, $p = .222$	No; $\Delta\eta^2 = .014$, $p = .394$	Yes; $\Delta\eta^2 = .043$, $p = .056$	No; $\Delta\eta^2 = .030$, $p = .136$
	$\eta^2 = .001$, $p = .911$	$\eta^2 = .00$, $p = .888$	$\eta^2 = .00$, $p = .817$	$\eta^2 = .00$, $p = .851$	$\eta^2 = .00$, $p = .633$	$\eta^2 = .00$, $p = .928$	$\eta^2 = .004$, $p = .622$	$\eta^2 = .00$, $p = .717$	$\eta^2 = .00$, $p = .545$	$\eta^2 = .002$, $p = .787$	$\eta^2 = .00$, $p = .851$
	$\eta^2 = .03$, $p = .135$	$\eta^2 = .00$, $p = .796$	$\eta^2 = .03$, $p = .190$	$\eta^2 = .00$, $p = .830$	$\eta^2 = .06$, $p = .030$	$\eta^2 = .04$, $p = .061$	$\eta^2 = .05$, $p = .003$	$\eta^2 = .00$, $p = .991$	$\eta^2 = .00$, $p = .920$	$\eta^2 = .003$, $p = .841$	$\eta^2 = .00$, $p = .367$
Marker: <i>DraI</i> Associated with SNP (between)? Associated with SNP (within)? Mediates association with ADHD? Moderates association with ADHD?	No; $\Delta\eta^2 = .006$, $\Delta p = .002$	No; $\Delta\eta^2 = .005$, $\Delta p = .013$	No; $\Delta\eta^2 = .005$, $\Delta p = .013$	No; $\Delta\eta^2 = .002$, $\Delta p = -.003$	No; $\Delta\eta^2 = .001$, $\Delta p = .018$	No; $\Delta\eta^2 = .000$, $\Delta p = .010$	No; $\Delta\eta^2 = .002$, $\Delta p = .007$	No, S; $\Delta\eta^2 = .023$, $\Delta p = -.029$	No, S; $\Delta\eta^2 = .019$, $\Delta p = -.023$	No, S; $\Delta\eta^2 = .016$, $\Delta p = -.019$	No, S; $\Delta\eta^2 = .021$, $\Delta p = -.023$
	Yes; $\Delta\eta^2 = .046$, $p = .028$	No; $\Delta\eta^2 = .003$, $p = .796$	No; $\Delta\eta^2 = .004$, $p = .701$	No; $\Delta\eta^2 = .003$, $p = .791$	No; $\Delta\eta^2 = .007$, $p = .581$	No; $\Delta\eta^2 = .004$, $p = .766$	No; $\Delta\eta^2 = .010$, $p = .467$	No; $\Delta\eta^2 = .014$, $p = .379$	No; $\Delta\eta^2 = .000$, $p = .976$	No; $\Delta\eta^2 = .001$, $p = .875$	No; $\Delta\eta^2 = .022$, $p = .223$

Note—S, suppression effect. *S, significant suppression effect. See note to Table 1 for the meaning of other abbreviations.

teracted significantly with RT on Trails A in predicting ADHD diagnostic status ($p = .036$, $\eta^2 = .045$). The *HhaI* SNP interacted significantly with go task RT in predicting ADHD diagnostic status ($p = .013$, $\eta^2 = .054$), and there were trends toward significance for the interactions with stop signal RT ($p = .074$, $\eta^2 = .030$) and the Stroop color–word condition ($p = .056$, $\eta^2 = .043$). The *DraI* SNP interacted significantly with performance on the Tower of London task in predicting ADHD diagnostic status ($p = .028$, $\eta^2 = .046$). Consistent with predictions, in all instances in which the test for moderation was significant or represented a statistical trend, the association between ADHD and the *ADRA2A* SNPs was stronger for children who showed a relative weakness on the putative endophenotype measure. These significant moderation results also imply that some of the associations between ADHD and EF performance depend on genotype. All of the results for the tests of mediation and moderation were very similar when ethnic background was controlled, suggesting that population stratification was not responsible for the associations between ADHD and the *ADRA2A* SNPs or for their moderation by the EF measures.

Finally, we also examined whether there was consistency in the EF measures' associations with the *ADRA2A* SNPs and in their moderation of the associations of those SNPs with ADHD. To examine this issue, we correlated p values for the association and moderation effects of each EF measure separately for each *ADRA2A* SNP. We found moderate correlations between these two utility criteria for each of the *ADRA2A* SNPs, with the extent of association and the extent of moderation correlated at .37 for the *MspI* SNP, $-.33$ for the *HhaI* SNP, and .42 for the *DraI* SNP.

DISCUSSION

These analyses were intended both to demonstrate the type of analyses we believe are needed to appropriately evaluate endophenotypes for ADHD and to provide new data on the validity and utility of EF measures as putative endophenotypes. There are both positive and negative conclusions from this study regarding the promise of including these particular EF measures as endophenotypes in molecular genetic studies of ADHD. The positive conclusions are that several of the EF measures met most of the validity criteria as endophenotypes (except for distributional normality), showed association with the *ADRA2A* SNPs, and moderated their association with ADHD in the expected direction (i.e., such associations were stronger in children showing EF deficits). To our knowledge, such results have not previously been reported in the literature. The negative conclusions are the failure of any of the EF measures to mediate the associations between ADHD and the *ADRA2A* SNPs and the lack of predictability of the EF measures' utility in the candidate gene analyses from the degree to which they met the criteria for validity as endophenotypes. Also requiring comment is the lack of correspondence between the EF measures' associations with the *ADRA2A* SNPs and the degree to which they moder-

ated the associations between those SNPs and ADHD. We will discuss each of these points further.

Criteria for the Validity of Putative Endophenotype Measures

As we have reported elsewhere (Nigg et al., 2004), there was considerable variability in the degree to which the individual component EF measures met the criteria for their validity as endophenotypes. The only EF measure that clearly met all of the validity criteria for endophenotypes—aside from distributional normality, which was met by none of the measures—was RT on the stop signal task (i.e., SSRT). This index was correlated with ADHD in the population, showed greater deficits in ADHD probands than in their unaffected siblings and in those siblings than in nondisordered controls, and was moderately correlated in siblings. Similar results were reported by Schachar et al. (2005). The majority of the other EF measures met most of the criteria for validity but fell slightly short on others. Examples of such indices were the total points achieved on the Tower of London task and RT variability on the stop signal task (i.e., SSSD), both of which were correlated with ADHD in the population, showed greater deficits in ADHD probands than in their unaffected siblings and in those siblings than in nondisordered controls, but were modestly correlated in siblings (i.e., $r = .14$ and $.16$, respectively). Other indices showed more pronounced violations of certain validity criteria. For example, RTs on Trails A and B and performance in the Stroop word and color naming conditions met all of the criteria, except that the unaffected siblings of probands did not reliably show deficits relative to the nondisordered controls. With regard to Trails B, though, we previously found deficits in the unaffected relatives of ADHD probands, relative to controls (Nigg et al., 2004), so the difference with the present findings may have been due to the inclusion of parents, as well as a larger sample of siblings, in the previous publication. Both the Trails B – A index and the Stroop color–word interference conditions met many of the validity criteria, except that both showed nonsignificant correlations with ADHD symptoms in the population, and the Trails B – A index showed a fairly low sibling correlation ($r = .09$). Finally, RT in the go condition (i.e., GoRT) and the Stroop interference index showed either slight negative ($r = -.07$) or zero sibling correlations, as well as only modest deficits in ADHD probands, relative to their unaffected siblings and the nondisordered controls (i.e., $\eta^2 \leq .01$).

Does Validity of the Endophenotype Measures Predict Their Utility in Finding Associations With Candidate Genes?

In light of the considerable and not unexpected variability in the degree to which the individual EF component measures met our criteria for validity as endophenotypes, a logical next question concerns the extent to which their validity predicts their utility as endophenotypes in candidate gene association studies. We evaluated this in the present study by examining the EF measures' asso-

ciations with the *ADRA2A* SNPs, as well as their mediation and moderation of such associations with ADHD. Interestingly, although several of the EF measures were associated with the SNPs examined, mediation was not observed for any of the EF measures, contrary to most theories of how genetic effects and EF measures contribute as endophenotypes for ADHD. One possibility is that the effects of *ADRA2A* are mediated via alternative EF measures—such as more focused measures of working memory that were not utilized here—or via alternative endophenotypic constructs or that the lack of mediation may have been due to methodological obstacles. Another possibility is that some of the selected endophenotypes are related to ADHD via environmental, rather than genetic, pathways. We examined the extent to which the EF measures' validity predicted their utility as endophenotypes, using a series of regression analyses in which *p* values for the analyses addressing the validity criteria for each of the EF measures were the predictors and *p* values for the association and moderation effects for each *ADRA2A* SNP were the criterion variables (results not shown to save space). Evaluating the prediction of utility via validity in these particular analyses was hampered by the unfavorable ratio of the number of EF measures to the number of validity criteria used as predictors in these regression analyses (i.e., 11 EF measures vs. five validity criteria), which is analogous to using five predictors with a sample size of only 11 participants in conventional applications of regression. Another challenge to these analyses was the considerable overlap or collinearity among the validity criteria for each of the EF measures; in other words, correlations among the validity criteria could prevent any of them from showing clear unique and incremental predictive validity in explaining variation in the EF measures' associations with the *ADRA2A* SNPs, as well as their mediation and moderation of such associations with ADHD.

Relations Between the Endophenotype Measures' Utility in Finding Associations and in Moderating Such Associations Between ADHD and Candidate Genes

We also examined the degree to which there was congruence in the EF measures' associations with the *ADRA2A* SNPs and in their moderation of the associations of those SNPs with ADHD. We found moderate correlations among these two utility criteria for each of the *ADRA2A* SNPs, with the extent of association and the extent of moderation correlated at .37 for the *MspI* SNP, -.33 for the *HhaI* SNP, and .42 for the *DraI* SNP. This suggests that with only some exceptions, the EF measures that show association with the *MspI* and *DraI* SNPs are not those that moderate the association of those SNPs with ADHD. Indeed, for the *HhaI* SNP, the EF measures that show association are less likely to be those that moderate the association with ADHD. These results may not come as a surprise, given that the presence of an interaction is, at times, accompanied by the absence of main effects. The exceptions to this overall lack of congruence are (1) Trails A and B and the Stroop interference index, which were associated (or marginally so) with the *MspI* SNP and showed at least a trend toward moderation of the association of that SNP with ADHD, (2) Trails B and the Stroop color-word score and interference index, which were associated (or marginally so) with the *HhaI* SNP and showed at least a trend toward moderation of the association of that SNP with ADHD, and (3) the Tower of London task, which was marginally associated with the *DraI* SNP and moderated the association with ADHD.

gally so) with the *MspI* SNP and showed at least a trend toward moderation of the association of that SNP with ADHD, (2) Trails B and the Stroop color-word score and interference index, which were associated (or marginally so) with the *HhaI* SNP and showed at least a trend toward moderation of the association of that SNP with ADHD, and (3) the Tower of London task, which was marginally associated with the *DraI* SNP and moderated the association with ADHD.

Understanding the Function of *ADRA2A* and its Role as a Risk Factor for ADHD

In this study, we extended our understanding of the function of *ADRA2A* by establishing its association with commonly used EF measures. The EF measures that showed association and linkage most consistently across the three SNPs were those that involve working memory (Tower of London), motor set shifting (Trails B RT), and to a lesser extent, performance on output speed measures (Trails A RT and the Stroop naming speed indices). Nonetheless, the Tower of London and Stroop indices did not show reliable familiarity in our prior extended analysis of first degree relatives (Nigg et al., 2004), whereas Trails B did. Therefore, Trails B emerges as the most promising of this subset of potential endophenotypes.

In addition, the association between ADHD and the *ADRA2A* SNPs was considerably stronger in children who also showed deficits on several EF measures, as indicated by the significant results of the moderation analyses. These analyses also suggest that the relation between ADHD and deficits on several EF measures vary as a function of genotype on the *ADRA2A* SNPs. Our results suggest that the association of *ADRA2A* with ADHD is not limited to parent or teacher ratings of symptoms but extends to a subset of putative endophenotype variables (i.e., EF measures) previously found to be associated with ADHD. The results also build important connections between this gene's association with ADHD and the research reviewed in the introduction on the expression of *ADRA2A* in the PFC and its role in underlying working memory and other EFs in several species.

Although the results were somewhat mixed for these particular EF measures, the overarching theme is that a comprehensive examination of the validity and utility of putative endophenotypes, such as that presented herein, has rarely been conducted, resulting in considerable uncertainty regarding the merits of many of these candidate endophenotype measures. Future investigations should extend the focus on associations between candidate genes and a variety of EFs in these and other domains, as well as testing for the mediation and moderation of such candidate gene associations with ADHD and its constituent diagnostic subtypes and symptom dimensions.

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