Published in final edited form as:
Am J Med Genet B Neuropsychiatr Genet. 2006 July 5; 141B(5): 487–498. doi:10.1002/ajmg.b.30326.

An Examination of the Behavioral and Neuropsychological Correlates of Three ADHD Candidate Gene Polymorphisms (DRD4 7+, DBH TaqI A2, and DAT1 40bp VNTR) in Hyperactive and Normal Children Followed to Adulthood

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Abstract

Several candidate gene polymorphisms have been implicated in attention deficit hyperactivity disorder (ADHD), including DAT1 40bp VNTR, DRD4 7+, and DBH TaqI A2 alleles. We used the Milwaukee longitudinal study of hyperactive (N=122) and normal (N=67) children to compare participants with and without these respective polymorphisms on ADHD-related behavioral ratings at childhood, 8 years later in adolescence, and 13+ years later into young adulthood. Neuropsychological tests were given at the adolescent and young adulthood follow-up. No differences were found between the DRD4-7+ and 7- repeat polymorphism. The DBH TaqI A2 allele, when homozygous, was associated with being more hyperactive in childhood, having more pervasive behavior problems at adolescence, and earning less money on a Card Playing Task in adulthood. At adolescence, poorer test scores were also found only in the hyperactive group with homozygous for this allele. The DAT1 40bp VNTR heterozygous 9/10 repeat, however, differed from the 10/10 repeat pair in many respects, having greater ADHD and externalizing symptoms at all three follow-ups, more cross-situational behavioral problems at both childhood and adolescence, poorer mother-teen relations at adolescence, and lower class rankings in high school. Participants with the 9/10 pair in the control group also had lower work performance, a lower grade point average in high school, greater teacher rated externalizing symptoms at adolescence, and greater omission errors on a continuous performance test in adulthood. The DAT1 40bp VNTR 9/10 polymorphism pairing appears to be reliably associated with greater symptoms of ADHD and externalizing behavior from childhood to adulthood, and with family, educational, and occupational impairments. We also present a contrary view on the appropriate endophenotypes for use in behavioral genetic research on ADHD.

Children with Attention Deficit Hyperactivity Disorder (ADHD), or what was previously diagnosed as Hyperactive Child Syndrome, are characterized by developmentally inappropriate levels of inattentive, impulsive, and hyperactive behavior that arise early in childhood and occur across multiple settings (American Psychiatric Association, 1968, 1980, 2001). Follow-up studies of hyperactive children suggest that from 35-80 percent of

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cases diagnosed in childhood will persist into adolescence (Barkley, Fischer et al. 1990;Gittelman et al., 1985). By adulthood, 49-66% will have significant symptoms of the disorder or meet diagnostic criteria for it (Barkley et al., 2002; Mannuzza et al., 1993,1998; Rasmussen & Gillberg, 2002; Weiss and Hechtman, 1993).

Biological relatives of children with the disorder are more likely to have ADHD (Biederman et al. 1990, Biederman et al. 1992, Biederman et al. 1995, Maher et al. 1999, Samuel et al. 1999). Numerous twin studies found that genetic factors account for the majority of variance in this trait with an average heritability of .75-.80, with more recent studies using larger twin samples showing even higher heritability scores of 0.85 to 0.95 (Dick et al., 2004; Gjone et al. 1996, Levy et al. 1997, Rhee et al., 1999; Stevenson, 1992, Thapar et al. 1999, Thapar et al. 2000). Such findings initiated molecular genetic studies to identify gene polymorphisms linked to the disorder, particularly for dopamine regulators, given the pharmacological effects of stimulant medication, neuro-imaging studies implicating the prefrontal cortex and striatum, and animal studies using selective lesions of dopamine pathways.

Studies have focused mainly on the D4, D2, and D5 dopamine receptor genes (DRD2, DRD4, and DRD5), the Dopamine Transporter Gene (DAT1 40bp VNTR), and the Dopamine Beta Hydroxylase gene (DβH TaqI A2) with ADHD. The greatest research has been on DRD4 with 7 repeats and the DAT1 40bp VNTR (Comings et al. 1991, Cook et al. 1995, Comings et al. 1996, LaHoste et al. 1996, Gill et al. 1997, Swanson et al. 1997, Castellanos et al. 1998, Rowe et al. 1998, Smalley et al. 1998, Swanson et al. 1998, Waldman et al. 1998, Comings et al. 1999, Daly et al. 1999, Farone et al 1999, Rowe et al. 1999, Barr et al. 2000, Comings et al. 2000, Eisenberg et al. 2000, Kotler et al. 2000, Muglia et al. 2000, Tahir et al 2000) . Cook et al. (1995) was among the first to find preferential transmission of the 40bp allele (allele 3) of a VNTR in the 3′ UTR of the DAT1 40bp VNTR gene (12p12.3), a finding replicated by others, but not all investigators (Gill et al. 1997, Daly et al. 1999).

The DRD4 exon 3 polymorphism consists of a 48 bp VNTR which codes for a 16 amino acid repeat in the third intra-cytoplasmic loop of the receptor. Following an association study implicating the 7-repeat allele in ADHD (LaHoste et al. 1996), Swanson et al. (1998), and Smalley et al. (1998) also found preferential transmission of this allele to affected individuals by family association studies. Other studies have since replicated this association (Rowe et al. 1998, Comings 1999, Faraone 1999, Barr 2000, Muglia 2000, Tahir 2000), although several have not (Castellanos et al. 1998, Eisenberg et al. 2000, Hawi et al. 2000, Kotler et al. 2000, Sinke et al. 2000). More recently, a meta-analysis of research on the DRD4 7-repeat allele reported a small but significant association with ADHD (Faraone et al., 2001).

The protein product of the Dopamine β Hydroxylase (DβH) gene (9q34) is responsible for catalyzing the conversion of dopamine to norepinephrine. Daly et al (1999) showed preferential transmission of the DβH TaqI A polymorphism A2 allele to individuals with ADHD while Wigg et al. (2002) also found some evidence for such biased transmission in families with ADHD. In contrast, using the samples from the present study, Smith et al. (2003) reported a significant relationship of the A1 allele with the hyperactive (ADHD) group here.

Such studies are important for identifying potential polymorphisms that may have a significant association with ADHD. But they are unable to demonstrate the specific behavioral or cognitive phenotypic correlates associated with the polymorphism. To do so requires treating the polymorphism as the independent rather than dependent variable while relying on psychological measures as dependent variables in the research design. Recent

studies have begun to concentrate on behavioral phenotyping of candidate polymorphisms. Two of these studies focused on the DRD4 7 repeat allele. Swanson et al. (2000) evaluated children with ADHD comparing those with (N=13) and without (N=19) the 7 repeat allele against each other and a control group (N=21) on several neuropsychological tests of Posner's attention networks. ADHD participants with the 7 repeat allele showed no significant impairments in test performance relative to the control group while, contrary to expectations, the 7 absent group was significantly impaired. The small sample sizes of the ADHD groups, especially for the 7 repeat subset, likely restricted power to detect significant group differences.

More recently, Langley et al. (2004) compared larger samples of children with ADHD with (N=25) and without (N=53) the 7 repeat allele on measures of activity, impulse control, and attention. They also compared the ADHD group to a control group. Those ADHD participants with the 7 repeat allele had higher activity levels, made more errors and had shorter reaction times to the Matching Familiar Figures Test (a measure of cognitive impulsivity), and had shorter reaction times to a stop task of response inhibition than those ADHD cases without the allele. Lynn et al. (2005) also examined the relationship of this allele to variation in ADHD symptoms and novelty seeking among parents of children with ADHD. They found no association with novelty seeking ratings but did find a significant relationship with degree of ADHD symptoms. Such results conflict with those of Swanson et al. (2000) above. Surprisingly, neither the Swanson et al. or Langley et al. studies genotyped their control groups to see if differences in the 7 repeat allele may have some functional consequences for them as well.

Loo et al. (2003) examined attention and EEG correlates of the DAT1 40bp VNTR 9 and 10 repeat polymorphisms in 27 children with ADHD undergoing testing of methylphenidate response. Children homozygous for the 10 repeat polymorphism demonstrated poorer performance on a vigilance test and a different pattern of EEG response to methylphenidate relative to children with one or more copies of the 9-repeat allele. Both groups showed similar improvements on the vigilance task during methylphenidate treatment. The authors concluded that the DAT1 40bp VNTR 10 repeat, when homozygous, may be associated with greater problems with inhibition and attention and that variation at this allele mediates stimulant related changes in cortical activity. Such a finding seems to conflict with those of Winsberg and Comings (1999) who had previously found a higher incidence of the 10/10 repeat pairing in African-American children who were not responsive to methylphenidate treatment. Jacobsen et al. (2000) also found that the normal adults who were homozygous had significantly reduced dopamine transporter binding in striatum on SPECT scan relative to those having at least one 9 repeat allele. Given that methylphenidate selectively inhibits this transporter, the reduced binding in participants with the 10/10 allele pair might be consistent with the reduced methylphenidate response found by Winsberg and Comings (2000). More recently, Bellgrove et al. (2005) examined a small sample of children with ADHD (N=22) and found that those having the 10/10 genotype had significantly greater response variability on an attention task and less spatial asymmetries in their attention than did those with the 9/10 genotype or a control group. Such studies suggest that the 10/10 genotype in those with ADHD may be associated with more cognitive impairment than the 9/10 genotype.

The exploration to date of behavioral and cognitive correlates of ADHD candidate gene polymorphisms has been exceptionally limited and sometimes conflicting. This led us to examine the behavioral and neuropsychological correlates of these polymorphisms along with that of DBH TaqI A2 allele in a longitudinal study of hyperactive and control children followed for more than 13 years in the greater Milwaukee, WI region (Barkley, Fischer et

al., 1990,2002). Unlike prior studies having a similar focus, we also genotyped our control group.

This longitudinal study permitted us a unique opportunity to evaluate the psychological correlates of these three polymorphisms at three stages of development (childhood, adolescence, and adulthood). Earlier, Barkley found a high persistence of hyperactive/ADHD symptoms from childhood to adolescence (70% remain disordered) (Barkley et al., 1990) and into adulthood (45% remained fully disordered; 66% remained severely symptomatic) (Barkley et al., 2002). This stability of ADHD across childhood and into adolescence is also highly heritable and the same genes that account for its variation in childhood also appear to account for its stability over development (Hay et al., 2004; Larsson et al., 2004; Reitveld et al., 2004). Thus, if a particular polymorphism was associated with ADHD symptoms and related cognitive impairments in childhood, it might be expected to be so at subsequent follow-up evaluations. Our study was able to examine this developmental association of the polymorphism with behavioral and cognitive measures at three developmental stages.

Just as genetic effects of particular genotypes may extend over time in the life of individuals, so may they extend outward from the individual to affect consequences at a considerable spatial distance from the particular polymorphism. This is the concept of the extended phenotype or the “actions of genes at a distance” (Dawkins, 1982) that has proven so useful to evolutionary biology and specifically ethology. This view holds that genetic alleles may have effects that extend well beyond the proteins, cells, and bodies that carry them to affect behavior and beyond to their influences on others, the larger social ecology, and even its larger physical context. We have therefore chosen for analysis not simply psychological tests that have had some success in distinguishing ADHD from control groups in prior studies and that are regarded as prime candidates for endophenotypes in genetic research on ADHD (Castellanos & Tannock, 2002). We also chose ratings of ADHD and related behavior (inhibition, attention, externalizing) and a few selected measures of potential genetic consequences “at a distance” which have been previously linked to ADHD symptoms (Gordon et al., 2005). These were grade point average in high school, class ranking, and employer ratings of ADHD and of work performance that may be considered part of its extended phenotype.

Method

Participants

This study utilized a group rigorously diagnosed as hyperactive in childhood (N=158) and a matched community control group (N=81) followed concurrently. These two groups were originally evaluated in 1979-80 when they were ages 4 to 12 years. The majority of these participants (Hyperactive N = 123; Normal N = 66) were evaluated again in 1987-88 when they were ages 12 to 20 years (see Barkley et al., 1990). This project re-assessed them in 1992-96 at which time all were between 19-25 years of age (mean = 20.8 yrs.). The average time between childhood entry and adult follow-up was 13.8 years (SD=1.5). All of the participants in both groups were located. The participation rate at adult follow-up was 93% (147 of 158) for the hyperactive group and 90% (73 of 81) for controls. Information on the recruitment and selection of our groups can be found many other published reports (see Barkley, Fischer et al., 1990; 2002). The gender composition was 91% male and 9% female and the racial composition was 94% white, 5% black, and 1% Hispanic, neither of which differed between the groups.

Procedures

All participants were evaluated at both the adolescent and the adult follow-up points on a single day using a battery of measures that assessed psychiatric disorders, history of mental health treatments, and outcomes in major life activities. The neuropsychological tests, behavioral observations, and rating scales were collected at this session. The neuropsychological tests were given at both follow-up evaluations in the same order to all participants. This session lasted 4-5 hours. All participants signed written informed consent statements approved by the medical college's institutional review board and all were paid for their participation at study entry and at each follow-up.

Genetic Analyses

Genotyping was performed on 122 of the 158 ADHD subjects and 67 of 81 control subjects; all were Caucasian. Genomic DNA was extracted from Peripheral Blood Lymphocytes using the Puregene DNA isolation kit (Gentra Systems). Our methods are described in detail in the paper by Smith et al. (2003). For DAT1 40bp VNTR, genotyping was available on 111 hyperactive participants: 47 for the 9/10 allele pairing (heterozygous for the 10-repeat) and 64 for the homozygous (10/10) pairing. For the 61 control participants, samples were: 9/10 = 26, 10/10 = 35. For DRD4, there were 116 participants (Ns: Hyperactive = 76, Control = 40) who were classified as DRD4-7 absent (7- or having 6 or fewer repeats) and 72 (Ns: Hyperactive = 46, Control = 26) who were 7+ present (having at least one allele with 7 or more repetitions). And for the DBH TaqI, there were 58 participants homozygous for the TaqI A2 allele (Ns: Hyperactive = 35, Control = 23) and 129 heterozygous (1/2) or homozygous for Allele A1 (1/1) (Ns: Hyperactive = 85, Control = 44). The hyperactive and control groups did not differ in the proportions of any of these genotypes ($X^2 = 0.53$, $p = .46$).

Measures From Childhood (Study Entry)

No neuropsychological tests were collected at the childhood entry point into this study as that research focused on mother-child interactions. Four scales assessing ADHD related symptoms were collected at the childhood study entry point and examined in this paper. *Conners Parent Rating Scale — Revised* (CPRS-R; Goyette et al., 1978). This 48-item scale is widely used in research on hyperactive/ADHD children (See Barkley, 1990, p. 288-289). Items assess five behavioral factors: conduct problems, learning problems, psychosomatic, impulsive-hyperactive, and anxiety. A 10-item Hyperactivity Index is also computed. It is believed to represent the most frequently occurring items in children with hyperactivity (restless, always on the go, impulsive, cries easily, fails to finish things, destructive, distractible, mood changes quickly, easily frustrated, disturbs others). Scores were determined by summing the responses across all items for that factor and then dividing by the number of items to get the mean response. The Hyperactivity Index of this scale was used at the childhood study entry point to select the hyperactive group, as noted above. We used the scores from the Hyperactivity Index and the more specific Impulsive factor score.

***Werry-Weiss-Peters Activity Rating Scale* (WWPARS; see Barkley, 1981, pp. 111-113; Barkley, 1990, pp.660-662)—**The original scale was developed to evaluate children's levels of hyperactive behavior in home and school situations (Werry & Sprague, 1970). It was subsequently modified to a 22-item scale by Routh, Schroeder, and O'Tuama (1974) who deleted the school items. The modified scale was employed here at study entry to select the hyperactive children based on a threshold of +2 SDs above the mean for a small sample of normal children (N=140) studied by Routh et al. (1974). While the scale may appear to be redundant with the Conners Hyperactivity Index discussed above, each provides some unique information about childhood symptoms of ADHD. The WWPARS

items deal strictly with activity level across various settings while the CPRS Hyperactivity Index contains a items related to restlessness along with other items pertaining to inattention, impulsiveness, and emotional behavior. The correlations between the two scales are: r = .43 for the hyperactive group and r = .59 for the control group, showing just 18-35 percent shared variance.

Home Situations Questionnaire **(HSQ; Barkley & Murphy, 1998)—**The HSQ evaluates the pervasiveness and severity of children's behavior problems across multiple home situations. Parents rate their child's behavior problems across 16 different home and public situations. The score used here was the *Number of Problem Settings* calculated simply by counting the number of settings answers YES.

Child Behavior Checklist **(CBCL; Achenbach & Edelbrock, 1983)—**The original version of this widely used rating scale became available shortly after this study began. This version contains 138 items rated on a scale of 0-2 and is designed for use with parents in rating children between 4-16 years of age. For this version, 11 subscales can be scored but we used only the Externalizing factor score in this paper.

Measures From the Adolescent Follow-up

The HSQ was repeated at this follow-up along with the CBCL parent form. Also, at this follow-up we used the Youth Self-Report Form (CBCL-YSR; Achenbach & Edelbrock & Edelbrock, 1987) and the Teacher Report Form (CBCL-TRF; Achenbach & Edelbrock, 1986) of the CBCL. The TRF is comparable to the parent CBCL and contains 126 items that assess behavioral and emotional problems in children 6-16 years of age. The CBCL-YSR is a self-report version of the CBCL completed by adolescents, ages 11-18 years of age. Again, to limit the number of analyses, we used just the Externalizing factor scores from theses rating scales.

Our parent interview contained the diagnostic criteria for ADHD as contained in the DSMIII-R (American Psychiatric Association, 1987). For this paper, we report the number of ADHD symptoms endorsed for the teen during this parent interview and the age of onset for these symptoms as retrospectively reported. Age of onset was recorded for both hyperactive and control groups concerning any symptoms of ADHD endorsed as problematic (see Barkley et al., 1990).

A number of measures of parent-teen conflict were collected (Barkley et al., 1991). For this report we chose to analyze just one of these measures which reflected the quality of parent-teen relations and communication, this being the *Conflict Behavior Questionnaire* (CBQ; see Barkley, 1990 for the scale and its development). The CBQ is a 20 item true/false self-report inventory assessing perceived communication and conflict between parents and adolescents. The mothers completed a form on their teen and the teens completed two, one for each parent.

Several psychological tests of inhibition, attention, and executive functioning were collected at this follow-up. They included the following:

Gordon Diagnostic System **(GDS; Gordon, 1987)—**This continuous performance test uses a small console containing a screen, a large blue button beneath the screen, and a computer chip inside that presents single digits on the screen at the rate of 1 per second (200 ms display time with 800 ms pause). The subject is seated alone in an exam room and is required to observe the display screen as digits are shown. When the target digit sequence ("1" followed by a "9") appears, they are to press the blue button. At the adolescent follow-up (Fischer et al., 1990), a 12-minute version of this test was employed (60 targets). The

device also has a distraction task. Administered in its 9 minute format, this task is similar to the vigilance task except that numbers are flashed to the left and right side of the target display screen to provide a distraction. A total of 45 target pairs were presented. For both tasks we used omission and commission errors.

Matching Familiar Figures Test -20 **(MFFT-20; Kagan, 1966)—**We employed a longer 20 item version of Kagan's original MFFT to evaluate cognitive impulsiveness. Teens were shown a page containing a sample picture below which was a set of six similar pictures only one of which exactly matched the sample picture. The teen pointed to the picture that exactly matched the sample. Scores were the mean time to the first response and the total number of incorrect responses.

Wisconsin Card Sort Task **(WCST; Grant & Berg, 1948)—**We chose this task to evaluate abstract reasoning and problem solving thought to represent higher executive functions. The task requires the participant to sort cards into categories based on an unspecified rule that the participant must deduce from the feedback they receive from the examiner as they sort the cards initially by trial and error. Sorting rules can be by color, number, shape, etc. The scores used here were the total number of errors, perseverative errors, and categories successfully achieved.

Measures From the Young Adult Follow-up

Parent Interview of ADHD Symptoms—The adult follow-up had been underway several years when it became apparent that self-reports concerning ADHD might be substantially different from the reports of parents. This occurred in the New York follow-up study that found such disparities at their late adolescent follow-up point (Mannuzza & Gittelman, 1986). Also, at this time, the criteria for ADHD in DSM-IV were published (American Psychiatric Association, 1994, 2001). A structured interview was therefore created from the DSM-IV item list to be used with parents. The parents, mostly mothers, of nearly all participants were interviewed by phone about the presence or absence of the 18 items for ADHD judged as occurring "often" or more. The internal reliability (coefficient alpha) was .92 for the DSM-IV inattention item list (nine items) in this interview and .91 for the hyperactive-impulsive list (nine items). Parent reports were used instead of self-reports given that parents reported far more ADHD symptoms than participants and parent reports correlated more highly with various domains of major life outcomes than self-reported symptoms (Barkley et al., 2002).

Young Adult Behavior Checklist and Young Adult Self-Report Form **(YABCL and YASR; Achenbach, 2001)—**These scales are upward extensions of the CBCL and CBCL-YSR, respectively, for adults. The young adult version contains 137 items pertaining to behavior problems scored as 0, 1, or 2. The YABCL was completed by a parent of the participants while the YASR was completed by the hyperactive and control young adults.

High School Performance—Official school transcripts were obtained from the last high school attended. To get grade point average for the last year attended, letter grades were converted to the following metric: A = 4, B = 3, C = 2, D = 1, and F (or failure) = 0 and then averaged across all graded classes for that year. Where grades were expressed on a numerical scale, the following metric was used to obtain comparable scoring to that used for letter grading systems: 90-100 = 4, 80-89 = 3, 70-79 = 2, 60-69 = 1, and 0-59 = 0. Class ranking represented the individual's percentile out of all students in that grade as indicated on the transcript.

Job Performance—The current supervisors rated the behavior and job performance of the participant blinded to group status. Employers rated the 14 DSM-III-R items for ADHD on a 5-point Likert scale (0-5) (Rarely to Almost Always). A general rating of current job performance was also obtained using a 5-point Likert scale (Poor to Excellent). These supervisors were told simply that the participant had volunteered to be in a psychology study focusing on job satisfaction and performance. No details about the psychiatric history of the participant were disclosed.

Gordon Diagnostic System **(GDS; Gordon, 1987)—**This is the same task used at the adolescent follow-up. For this follow-up, the length of the task was increased from 12 to 15 minutes and from 60 to 75 target presentations. Once more raw scores for the number of omission and commission errors served as measures. The distraction task used at the adolescent follow-up however was not used here.

Cancellation Task **(Ruff, Evans, & Light, 1986; Ruff, Niemann, Allen, Farrow, & Wylie, 1992)—**The Ruff 2 and 7 Selective Attention Test is a paper-and-pencil cancellation task which requires the participant to cross out numerical targets as quickly as possible. These targets are embedded either in strings of digits or in strings of alphabetical capital letters. Test-retest reliability coefficients after 6 months range from .84-.97. This task is sensitive to the early detection of AIDS dementia (Schmitt, Bigley, McKinnis, Logue, Evans, & Drucker, 1988) and to impairment from head injury (Ruff, Marshall, Crouch, Klauber, Levin, Barth, Kreutzer, Blunt, Foulkes, & Eisenberg, 1993) but to be unrelated to the presence of major depression (Ruff, 1994). We used the number of omissions and commissions.

Card Playing Test **(Newman, Widom, & Nathan, 1985)—**This task has been used to study inhibitory responses to punishment in psychopaths. A computer presents a series of cards on the screen one at a time. At first, only the back of the card is visible with a question mark on it. At this point, the participant is to decide to bet as to whether this card is a face card. If it is, they wins 5 cents. If it is a number card, they lose 5 cents. The participant begins the task with 50 cents and is told that this is not a standard deck of cards so it is not possible to predict how many cards will appear or to count cards. The participant must make a choice each time a card appears to bet or quit and cannot pass. At any trial, they can quit playing and keep all of their winnings. The ratio of face cards to number cards changes progressively throughout the testing period such that the rate of reinforcement (percent of face cards) is relatively high (90%) initially but gradually changes to a relatively low rate later in the task approaching zero rates of reinforcement by the end of the task. The typical scores taken from this task are the number of cards played and the earnings (in cents). The scores are typically interpreted as reflective of response perseveration or a diminished sensitivity to punishment. Validity of this task has been previously demonstrated through group differences children with and without conduct disorder (CD) and ADHD children with and without CD (see Fischer et al., 2005), and between prison psychopaths and non-psychopaths (Newman, Patterson, & Kosson, 1987).

Results

For each genotype of interest, we conducted two-way (group x genotype) analyses of variance on the 36 dependent measures. Any significant main effects for group were ignored as these have been reported in previous publications (Barkley et al., 1990,2002; Fischer et al., 1990,2005). We focused on main effects for the genotype (polymorphism) and its possible interaction with the grouping variable. Given so few previous investigations of the phenotypic effects of these polymorphisms, our study should be considered exploratory in nature. Behavioral phenotypic effects of these polymorphisms are also believed to be of a

low magnitude and our sample sizes, particularly for the interaction term, were of modest power to detect such effects. As a result, we chose to employ the more generous alpha level of .05 for defining statistical significance despite the relatively large number of statistical tests that were conducted.

DAT1 40bp VNTR Heterozygous (9/10) vs. Homozygous (10/10) Genotypes

The results for the 9/10 and 10/10 genotypes of the DAT1 40bp VNTR gene within each group are shown in Table 1 along with the omnibus two-way statistical tests, where significant. There were 15 main effects that reached significance for the genotype. Differences were found at childhood, adolescence, and adulthood. In all instances, the heterozygous phenotype (9/10) had the more adverse effect than the homozygous (10/10) one. Noteworthy is that effect sizes were of a small magnitude in childhood but more than doubled to moderate magnitude by adolescence.

At childhood, individuals with the 9/10 genotype had higher levels of hyperactivity, impulsiveness, and greater CPRS Hyperactive Index scores, had more pervasive behavioral problems (HSQ), and higher externalizing scores on the CBCL than did the 10/10 genotype. The main effect on the CPRS Impulsivity score must be qualified by a significant group x genotype interaction. Pair-wise comparisons showed that the two genotypes were significantly different in the control group but not in the hyperactive group. Also, hyperactives with the 9/10 genotype were significantly different from controls with the 9/10 genotype. So were hyperactives with the 10/10 vs. controls with the 10/10 genotype.

At adolescence, the 9/10 genotype was associated with a greater number of ADHD symptoms, a later age of onset of those symptoms, and again more pervasive behavioral problems and higher parent-rated CBCL externalizing scores than was the 10/10 phenotype. It was also associated with greater perceived mother-teen conflict (mother reports), but not for teen-mother reports on this same scale. Reports of teens on their fathers, however, was marginally significant (p=.077). No significant effects were evident on the self-reported (YSR) CBCL externalizing score but a significant group by genotype interaction occurred on the teacher-rated (TRF) CBCL externalizing score. Again, pair-wise comparisons found the heterozygous genotype to have significantly higher externalizing scores only within the control group but not in the hyperactive group. Hyperactives with the 9/10 genotype showed a marginally significant difference from controls with the 9/10 genotype (p = .06) but hyperactives with the 10/10 differed significantly from controls with this genotype. On the psychological tests, there was a significant group x genotype interaction for GDS Omission Errors from the distraction task. Again pair-wise comparisons found that the controls with the heterozygous genotype made more errors than the homozygous genotype while these genotypes did not differ within the hyperactive group. Hyperactives with the 9/10 genotype did not differ from controls with this genotype but hyperactives with the 10/10 did differ significantly from controls with that genotype.

At adulthood, the 9/10 genotype was once again associated with a significantly greater number of parent rated ADHD symptoms and higher YABCL (parent-rated) externalizing scores than the 10/10 genotype. The heterozygous genotype also had a lower grade point average in high school and a lower class ranking than did the homozygous genotype. The main effect for grade point average must be qualified by a significant interaction of group x genotype in which, again, pair-wise comparisons showed that only in the control group was the heterozygous genotype significantly lower in than the homozygous genotype. Comparison of the hyperactive 9/10 with the control 9/10 did not differ but comparison of the 10/10 hyperactives differed from the controls with the 10/10 genotype. There was also a significant group x genotype interaction on employer ratings of work performance. Once more, the 9/10 genotype in the control group was rated as significantly worse than the 10/10

genotype controls while these two genotypes did not differ in the hyperactive group. But hyperactives with the 9/10 were significantly more impaired than controls with the 9/10 genotype. And so were hyperactives with the 10/10 versus controls with that genotype. The self-ratings on the YASR externalizing factor and the employer ratings of ADHD symptoms showed no significant effects. On the psychological tests collected at this follow-up, a significant main effect for genotype was found on the score of amount of money earned on the Card Playing Task with the heterozygous genotype having earned more money (taken more risks) than the homozygous genotype. No significant effects were found on any other psychological tests.

Within the hyperactive group, we also compared those who continued to meet DSM-IV diagnostic criteria for ADHD (using parent report) to those who no longer did so (Ns = 59 and 43, respectively) on the proportion having the 9/10 vs. 10/10 genotypes. Of those receiving a diagnosis of ADHD at adult follow-up, 51% had the 9/10 genotype vs. 35% of those who did not receive the diagnosis. The comparison was not significant, however (X^2 = 2.57, p = .11).

DBH TaqI A2 Allele: Homozygous (2/2) or Not

We found just 3 significant main effects for genotype (Table 2). The DBH TaqI A2 homozygous group had significantly more hyperactivity in childhood, more pervasive behavioral problems at adolescence, and earned less money on the Card Playing Task at adulthood. Effect sizes were small.

Significant group x genotype interactions were found on two tests at adolescence: total errors on the MFFT and three scores from the WCST (see Table 3). Pair-wise comparisons showed that the two genotypes did not differ in the control group on any measures. In the hyperactive group, the A2 homozygous group made more errors on the WCST than the non-homozygous group but not on the other three measures. Comparison of the hyperactive and control groups who were A2 homozygous revealed no significant differences. But the A2 homozygous hyperactive group was significantly worse on all four scores than the non-homozygous control group. In short, the A2 homozygous group largely accounts for the significant differences between hyperactive and control groups on these four measures at adolescence.

We compared just those hyperactive participants who received a diagnosis of ADHD at adult outcome with those who did not in the proportion having the A2 homozygous condition and found no significant difference (X^2 = 0.58, p = .45).

DRD4 7+ vs. 7- Genotypes

There were no significant main effects in comparing the participants with a 7+ allele versus those with 7- on any measures. Nor were their any significant interactions of genotype with group on any measures. We compared just those hyperactive participants who received a diagnosis of ADHD at adult outcome with those who did not in the proportion having the 7+ genotype and found no significant difference (X^2 = 0.19, p = .66). To more closely compare our results to earlier studies of this polymorphism, we also compared those participants with at least one copy of the specific 7 repeat allele to those with no such copy of the 7 repeat. Again, no significant differences were found.

Discussion

The present paper examined the potential behavioral correlates of three gene polymorphisms having some established linkage to ADHD in a sample of hyperactive and community control children followed from childhood across 13 or more years into young adulthood.

Following the concept of the extended phenotype (Dawkins, 1982) we also examined not only psychological tests, but behavioral ratings of ADHD symptoms and additional measures having some relationship to ADHD symptom severity, these being the quality of mother-teen relationships at adolescence, school performance as reflected in grade point average and class ranking in high school, and occupational functioning as reflected in employer ratings of ADHD symptoms and work performance evaluations.

No significant behavioral or other correlates were found for the DRD4 7+ polymorphism relative to the 7- allele. Our findings concur partially with the findings of Swanson et al. (2000) who found no significant impairments in laboratory measures of various aspects of attention associated with the 7 repeat. However, they did find some deficits in the group of children with ADHD who had the 7- polymorphism. We found no such relationship, which would have been evident in our study in a group x genotype interaction. And our results certainly contradict the findings of Langley et al. (2004) who found some deficits in cognitive impulsiveness on the MFFT and in response inhibition for the 7 repeat participants with ADHD. Differences between our study and these others in the tests used could be a factor in this disparity. Like Langley et al. (2004), however, we did use the MFFT and found no relationship of those scores to the 7+ polymorphism. Nor did our measures of response inhibition show such a relationship to this allele. Our results suggest that the behavioral correlates of this particular polymorphism may not be found in the types of measures we collected or, if present, are below the magnitude capable of detection in this study given our sample sizes.

Our findings for the DBH TaqI A2 polymorphism showed a few main effects for those who were homozygous for this polymorphism (A2/A2) on increased childhood hyperactivity, greater pervasiveness of behavioral problems at adolescence, and a single test score at adulthood — earning less money in the Card Playing Task, a measure considered to reflect sensitivity to punishment (or risk-taking). It is difficult to know what to make of these few main effects which could merely reflect chance findings given the number of statistical tests and lack of consistency in findings across development. We did find a few interactions of group with polymorphism status on two of the tests collected in adulthood, these being the GDS omission scores (inattention) and the three scores from the WCST (problem-solving). Further analysis of the interaction essentially revealed that the hyperactive group homozygous for the A2 allele was impaired on these tasks relative to the non-homozygous group in the control participants, which is to say that homozygosity for this allele accounted for the hyperactive versus control differences found on these tasks. While this is of some interest in suggesting some role of the TaqI A2 homozygous genotype in deficits in these cognitive activities, we are the first to find such effects and prefer to withhold confidence in such a finding pending replication by others.

In contrast, significant main effects for the DAT1 40bp VNTR 9/10 group compared to the homozygous 10/10 group were numerous and relatively coherent within and consistent across developmental assessments. The heterozygous group was more hyperactive, impulsive, externalizing and showed more pervasive (cross situational) behavioral problems at both the child and adolescent evaluation points. This may exemplify a developmental continuity for the phenotypic effect of the 9/10 genotype. Greater ADHD symptoms and externalizing problems were also evident at the adult outcome which may further support the interpretation of a continuity of phenotypic effects. Just as surprising was the increasing magnitude of the effect size attributable to this heterozygous genotype (from small to moderate) suggesting that, as with intelligence, the genetic influence on individual differences on these phenotypic traits may increase from childhood to adolescence. Such phenotypic effects not only extended across time (e.g. development), but also outward from the individual into the social ecology where further consequences of the genotype could be

detected — in this case in mother-teen relations, grade point average, and class ranking in adolescence, and, to a lesser extent, workplace performance ratings by employers in adulthood. Care must be taken, however, to note that any interpretation of continuity of phenotypic effects across development here is confounded by the use of somewhat different measures for each construct or trait at each of the developmental time points in this study. This precluded our direct examination of development as a factor in our analyses.

Our results contradict the findings of Loo et al. (2003) and Bellgrove et al. (2005) who found that poorer performance on attention tasks was associated with the homozygous 10/10 group of children with ADHD. We found only one difference between the 10/10 vs. 9/10 comparisons on any psychological tests, that being a group x genotype interaction on omission scores. And even here only the 9/10 controls were significantly more impaired than 10/10 controls. It is possible that the use of different continuous performance tests between these two studies may have contributed to this disparity. Also, neither of these studies examined the relationship of these genotypes to parent or teacher ratings of ADHD or other impairments associated with the disorder as we had done. But our results for those various behavioral ratings and school and work performance also contradict the implications of these earlier studies in showing more adverse effects associated with the 10/10 than 9/10 genotype. We found the opposite. Why this should be the case is unclear. The 9/10 genotype is associated with greater dopamine transporter binding and better methylphenidate response in children with ADHD (Winsberg & Comings, 1999). Since most children with ADHD are positive responders to this drug, it is the 9/10 genotype that may have a greater association with clinical cases of ADHD and its severity, as we found, than does the 10/10 genotype. Clearly these conflicting findings warrant further research to clarify the matter.

Some interesting group x genotype interactions were also evident for the DAT1 40bp VNTR genotype comparisons on childhood ratings of impulsiveness, teacher ratings of externalizing problems and inattention (omission) scores at adolescence, and on work performance ratings and high school grade point average by adulthood. In all cases, no differences were found between the two genotypes in the hyperactive group but were evident between the genotypes in the control group. Again, in the control group, the heterozygous group was more impaired on these measures than the homozygous group. It is possible that such findings could be due to the fact that the hyperactive group is already relatively more extreme in their scores on these measures than the control group. This could result in there being little further effect that the heterozygous polymorphism can exert that would be statistically significant within that group. And yet, at least at adolescence and adulthood, a ceiling effect was not evident on those measures that proved to be significant arguing against this line of reasoning. More likely, we believe, is the hypothesis that the 9/10 genotype may have an effect that is either weaker or simply more difficult to detect when it occurs in the context of other ADHD candidate genes (as would be the case in the ADHD group here) than in their absence (as would more likely be the case in the control group). In any event, given these findings of some genetic effects that were specific to the control group, future research should genotype control as well as ADHD samples for analysis of phenotypic effects.

An important issue raised by our results is that of what psychological measures are most useful in behavioral genetic studies of genotype-phenotype linkages in ADHD. Castellanos and Tannock (2002) have proposed the concept of an endophenotype to guide this issue. Endophenotypes are quantitative indices of disease liability or risk. In this case, they are indices that predict the risk of having ADHD (Castellanos & Tannock, 2002). They should be continuously quantifiable, predict risk probabilistically, be closer to the site of the primary causative agent (in this case, genetics), than to the diagnostic category, and should derive from the field of neuroscience so as to help bring to bear the power of experimental

control across model organisms in the study of ADHD and its risk factors. In so doing, these authors suggest that psychological tests, especially those that measure delay aversion, inter-trial variability in timing tasks, and working memory, may hold the most promise for advancing behavioral genetic studies of ADHD.

We disagree. It is not clear to us why only neuroscience generally and neuropsychological tests specifically should be selected as the endophenotypes worth studying. Behavioral ratings of the ADHD symptom dimensions (hyperactive-impulsive behavior and inattention) should also qualify given that they fulfill the first three qualifications of an endophenotype. Indeed they are likely to predict liability or risk for disorder better than neuropsychological tests (which are poor at doing so; Grodzinsky & Barkley, 1999), have better ecological validity (relationships to behavior in natural settings; Barkley, 1991), sample behavior over longer time periods (months rather than minutes), are stable over development (Barkley et al., 2002), are predictive of domains of major life impairments (Barkley et al., 2002; Gordon et al., 2005), and are more sensitive to drug interventions for ADHD than are those psychological tests proposed for use as endophenotypes. And given that psychological tests are just other ways of measuring behavior and are not necessarily more proximal to the etiological factor of interest or more sensitive to the underlying mechanisms giving rise to disorder than are behavior ratings, we see no reason to prefer the former over the latter absent any empirical evidence for doing so. The fact that the latter are more subjective does not automatically disqualify them from consideration on principle alone as such ratings reflect the ecological impact of the proband's behavior on others and their social judgments of them. An exclusive reliance on tests could result in missing the detection of potential phenotypic effects of gene polymorphisms that behavior ratings or other measures may better detect. Our study found just such a result for the DAT1 40bp VNTR polymorphism comparisons. Had we examined only neuropsychological test scores, only two significant findings would have emerged and those possibly due to experiment-wise error.

We believe the alternative concept of the extended phenotype (Dawkins, 1982) to be a more useful view. Dawkins has cogently argued that there is no reason to limit the discussion of phenotypic effects of genes to either the boundaries formed by the skin (the organism) or even cognition or behavior. The physical distance from the gene to the phenotype chosen for study is relatively arbitrary and is largely based on the aim of the study. Phenotypic effects can and do radiate further into the natural and social ecology of the organism than merely ending at the skin or at the behavior of the organism. These extended phenotypic effects, or genetic effects at a distance, can be detected in the responses of other organisms to the individual and in the phenotypic footprint (changes) they make to the social and natural environment. All should be considered just as much a part of the individual's phenotype as neuropsychological test scores. Examining the phenotypic effects of genes, especially those for behavioral traits, and their "actions at a distance" (Dawkins, 1982, pp. 228-249) in fact may offer a far better perspective on the adaptive problems that the phenotype/genotype complex arose to solve in the course of its evolution than do more proximal, and likely myopic, measures from neuropsychology or neurosocience.

From this perspective, the problems with social conflict and reciprocity (peer and family relations) and even the reactions they elicit from others, measures of academic success and even the loss of lifetime income it engenders, and employment functioning, to name just a few actions at a distance of ADHD-linked polymorphisms, may be as legitimate "endophenotypes" of people with ADHD as are cognitive tests. The effects of a child with ADHD on the perceptions of others about them, to the extent that those perceptions vary as a function of children's behavioral phenotypes, are valid indices of the child's extended phenotype. We believe that the length of the chain of phenotypic effects related to candidate genes for ADHD should not be arbitrarily terminated at the brain, its imaging, or the

neuropsychological test performance that may relate to it. The phenotype of interest in our view may be fruitfully extended into the social ecology of the individual as far as empirical evidence of such an effect can be found and especially to the point where it intersects with the socially competitive and sexually reproductive interests (inclusive fitness) of the organism and particularly its genes (Dawkins, 1982). We recognize, however, that such measures of extended effects can be influenced by a number of other non-genetic factors the further from the genotype one explores. Yet that makes such findings of genetic effects all the more impressive when they are found at such phenotypic distances.

Note should be made of the limitations of our study. One is the relatively small sample sizes we had available for examining phenotypic effects. These polymorphisms are believed to have relatively small effects on behavior and thus may require larger samples for adequate power to detect those effects. Nevertheless, we were able to detect significant and surprisingly substantial effects of at least one polymorphism, that being the DAT1 40bp VNTR gene (9/10 vs. 10/10). A second limitation may be the number of measures chosen for analysis that may have increased experiment-wise Type I error. We limited ourselves to those measures that were directly related to ADHD, to neuropsychological tests we collected presumed to index it, but also to some extended phenotypic measures (education, work, family relations) that had previously been shown to be specifically affected by ADHD symptoms. The pilot exploratory nature of our study led us to err on the side of Type I rather than Type II errors as the latter we believe would be more detrimental than the former to this early stage of research into phenotypic effects related to ADHD candidate polymorphisms. Though it is possible that some of our findings are therefore due to Type I error, this is unlikely to account for the numerous and developmentally continuous phenotypic effects documented for the DAT1 40bp VNTR heterozygous polymorphism (9/10). It is also possible that our hyperactive group is not directly equivalent to the clinical diagnosis of ADHD as currently prescribed in DSM-IV. In our defense, DSM criteria were not available at the start of this project but we employed the best available at the time for selecting the hyperactive group. At adolescent follow-up, more than 70% met DSM-IIIR criteria for ADHD, and more than 66% were still two standard deviations above the control group on DSM-IV ADHD symptoms at young adulthood, all of which suggests that the majority of our hyperactive group would have qualified for ADHD Combined Type (DSM-IV).

In conclusion, our study sheds new light on the behavioral and social phenotypic effects of three polymorphisms of interest in genetic research on ADHD. We detected no phenotypic effects for the DRD4 7+ vs. 7- genotypes (or the 7 repeat allele specifically) on our battery of ratings, tests, and measures of educational success or workplace performance. Only a few such effects were evident for comparisons of the DBH TaqI A2 homozygous versus heterozygous or A1/A1 allele pairs and these were not replicated by other measures at that development period nor consistent across development. At most, the homozygous A2 genotype may have some effect of psychological tests of impulsiveness and executive functioning (problem-solving) in contrast to controls without the homozygous condition. But our results show relatively numerous, coherent, and potentially developmentally continuous effects of the heterozygous 9/10 pair of DAT1 40bp VNTR alleles relative to the homozygous 10/10 condition on ADHD symptoms and related externalizing behavior and the situational pervasiveness of those behavior problems. And they show that such phenotypic effects extend into the social ecology of the heterozygous individuals, adversely affecting high school performance, mother-teen relations, and workplace functioning.

Acknowledgments

This project was supported by a grant (MH42181) from the National Institute of Mental Health and from a small grant from the Howard Highs Foundation to the first author, and a NEMC New Investigator award to Dr. Navia.

The contents of this paper, however, are solely the responsibility of the authors and do not necessarily represent the official views of these awarding institutions. The authors would like to thank Lori Smallish for her assistance with the data collection at the Milwaukee site.

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Table 1

Comparison of DAT1 9/10 with 10/10 Genotypes in Hyperactive and Control Groups

Group (G):	Hyperactive						Control							
DAT1 Genotype (D):	9/10			10/10			9/10			10/10			Significant	Cohen's
Measure	N	M	SD	N	M	SD	N	M	SD	N	M	SD	*F (p)*	*d*
Childhood Ratings:														
Hyperactivity Rating WWP	47	30.2	6.5	64	28.5	6.2	26	9.8	5.5	35	6.2	5.0	D=7.5 (.007)	.18
Hyperactive Index CPRS	47	20.5	5.0	64	20.4	4.3	26	6.1	3.5	35	3.6	3.3	D=3.9 (.048)	.11
Impulsive Factor CPRS	47	2.5	0.4	63	2.4	0.5	26	1	0.6	35	0.5	0.5	D=13.4 (.001) GxD=5.3 (.023)	.20
HSQ # of Problem Settings	31	11.9	2.1	40	11.1	1.9	26	4.4	2.8	35	3.2	2.4	D=6.1 (.015)	.22
CBCL External	28	73.7	8.0	41	73.3	7.2	24	50.9	11.7	29	44.6	9.7	D=3.9 (.05)	.11
Adolescent Ratings:														
ADHD Symptoms #	35	9.6	3.0	45	8.6	3.9	22	2.6	2.9	29	0.7	1.3	D=7.1 (.009)	.29
ADHD Onset (years)	35	4.6	3.3	45	3.2	2.4	22	4.8	4.9	29	2.0	3.6	D=11.0 (.001)	.54
HSQ # Problem Settings	35	8.1	4.4	44	6.2	4.2	22	3.1	2.9	29	1.5	1.9	D=6.85 (.01)	.43
CBCL Externalizing	35	70.1	7.4	42	67.1	9.9	22	56.9	10.6	29	49.1	8.6	D=10.8 (.001)	.43
CBCL YSR External	34	57.4	12.1	42	53.5	8.0	22	47.8	12.1	29	45.6	7.0	NS	
CBCL TRF External	21	57.5	8.1	34	60.2	8.3	19	52	9.4	24	46.7	7.2	GxD=5.6 (.02)	
CBQ Mom on Teen	35	12.5	5.6	45	10.5	5.9	22	6.1	5.5	29	3.1	4.2	D=6.3 (.014)	.37
CBQ Teen on Mom	35	4.7	4.7	45	4.4	4.0	22	2.8	4.2	29	3.0	4.2	NS	
CBQ Teen on Dad	35	6.0	5.7	45	4.8	5.2	22	4.6	5.7	29	2.5	3.6	D=3.2 (.077)	
Adolescent Tests:														
MFFT Mean Reaction Time	34	14.7	18.7	40	21.9	24.5	22	13.8	15.5	28	14.4	13.5	NS	
MFFT Errors	34	17.0	8.0	40	16.9	8.2	22	13.5	5.9	28	12.4	5.6	NS	
GDS Omission Errors	34	4.8	6.0	40	6.1	11.0	22	2.4	3.7	28	1.5	1.9	NS	
GDS Commission Errors	34	7.3	11.7	40	3.5	3.6	22	1.8	2.4	28	1.2	1.1	NS	
GDS Distract Omissions	34	7.5	5.7	40	10.7	11.3	22	8.4	8.2	28	4.5	4.7	GxD=5.5 (.02)	
GDS Distract Commissions	34	9.4	16.5	40	7.6	14.7	22	3.3	4.3	28	2.5	3.6	NS	

Group (G):	Hyperactive						Control							
DAT1 Genotype (D):	9/10			10/10			9/10			10/10			Significant	Cohen's
Measure	N	M	SD	N	M	SD	N	M	SD	N	M	SD	*F (p)*	*d*
WCST Total Errors	34	30.6	24.0	40	31.6	22.2	22	25.6	15.6	28	25.2	18.2	NS	
WCST Perseverative Errors	34	19.9	26.5	40	19.1	16.4	22	13.3	8.5	28	13.7	10.9	NS	
WCST Categories Achieved	34	5.1	1.5	40	5.0	1.6	22	5.5	0.9	28	5.4	1.3	NS	
Adult Functioning:														
ADHD Symptoms # (parent)	45	10.5	5.8	57	8.4	6.2	26	2.9	3.5	35	0.8	1.4	D=6.6 (.011)	.33
YABCL External (parent)	41	26.2	17.1	58	18.8	16.0	25	9.2	9.6	35	4.6	5.5	D=6.8 (.01)	.40
YASR External (self)	45	17.0	10.6	58	14.5	9.9	25	12.9	8.6	31	12.0	8	NS	
ADHD Rating (employer)	38	50.8	18.3	43	51.9	17.6	21	40.0	10.4	29	37.3	7.5	NS	
Work Performance (empl.)	38	3.4	1.0	43	3.2	0.9	21	3.8	0.9	29	4.4	0.8	GxD=5.5 (.02)	
Grade Point Average (records)	47	1.7	0.7	62	1.7	0.8	26	2.2	1.0	35	2.8	0.7	D=5.8 (.017) GxD=4.3 (.039)	.21
Class Ranking (records)	25	72.7	24.4	38	65.9	25.6	22	56.0	34.5	33	41.1	26.0	D=4.1 (.038)	.36
Adult Tests:														
GDS Omission Errors	47	3.6	8.8	62	2.4	3.7	26	1.1	1.7	35	0.7	1.2	NS	
GDS Commission Errors	47	1.8	4.1	62	1.8	5.2	26	0.8	1.2	35	0.2	0.5	NS	
Cancellation Omissions	47	19.4	20.4	62	24.5	17.6	26	17.3	11.1	35	17.5	14.2	NS	
Cancellation Commissions	47	1.2	5.4	62	0.4	1.3	26	0.2	0.5	35	0.1	0.4	NS	
Card Playing: # Cards Played	46	36.8	28.8	60	35.9	32.4	25	37.4	22.5	35	41.1	30.1	NS	
Card Playing: Amount $	47	103.5	42.9	61	92.2	41.9	25	122.0	23	35	104.7	37.5	D=5.0 (.026)	.33

M = Mean; SD=standard deviation; D = main effect for DAT1 genotype; GxD = interaction of group x DAT1 genotype; ADHD = attention deficit hyperactivity disorder; YABCL = Young Adult Behavior Checklist; YASR = Young Adult Self-Report Form; WWP = Werry-Weiss-Peters Activity Rating Scale; CPRS = Conners Parent Rating Scale; HSQ = Home Situations Questionnaire; CBCL = Child Behavior Checklist; CBQ = Conflict Behavior Questionnaire; GDS = Gordon Diagnostic System; MFFT = Matching Familiar Figures Test; WCST = Wisconsin Card Sort Test. Cohen's d = measure of effect size for the main effect of genotype, provided it was significant.

Table 2

Significant Main Effects for the Comparison of DBH Taq1 A2 allele absent vs. present Genotypes

DBH Genotype:	**A2/A2**			**A2/A1; A1/A1**				**Cohen's**
Measure	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	***F(p)***	***d***
Childhood Ratings:								
Hyperactivity WWPARS	58	22.1	12.5	129	21.2	11.9	4.01(.047)	.07
Adolescent Ratings:								
HSQ # Problem Settings	47	5.7	5.0	93	4.5	4.0	4.47(.036)	.28
Adult Tests:								
Card Playing: Amount $	57	93.8	45.9	126	108.2	35.4	5.40(.021)	.35

SD=standard deviation; ADHD = attention deficit hyperactivity disorder; YABCL = Young Adult Behavior Checklist; WWPARS = Werry-Weiss-Peters Activity Rating Scale; CPRS = Conners Parent Rating Scale; HSQ = Home Situations Questionnaire; CBCL = Child Behavior Checklist; GDS = Gordon Diagnostic System. Cohen's *d* = measure of effect size.

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Table 3

Significant Comparison of DBH TaqI A2A/2 vs. A2/A1 or A/1/A1 Genotypes in Hyperactive and Control Groups

Group (G):													
			Hyperactive						**Control**				
DBH Genotype (D):		**A2-**			**A2+**			**A2-**			**A2+**		**Significant**
Measure	**N**	**M**	**SD**	**N**	**M**	**SD**	**N**	**M**	**SD**	**N**	**M**	**SD**	***F (p)***
Adolescent Tests:													
MFFT Errors	24	18.6	6.9	56	16.3	8.0	20	11.1	4.1	34	13.8	6.2	GxD=3.78(.05)
WCST Total Errors	24	38.5	25.9	56	27.0	19.6	20	20.1	12.6	34	28.2	17.8	GxD=7.13(.009)
WCST Perseverative Errors	24	26.3	27.0	56	16.1	16.7	20	11.2	8.1	34	14.7	10.2	GxD=4.73(.031)
WCST Categories Achieved	24	4.6	1.9	56	5.3	1.3	20	5.7	0.9	34	5.3	1.2	GxD=4.57(.034)

M = Mean; SD=standard deviation; D = main effect for DBH genotype; GxD = interaction of group x DBH genotype; MFFT = Matching Familiar Figures Test; WCST = Wisconsin Card Sort Test