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ADHD among adolescents with intellectual disabilities: Pre-pathway influences

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Abstract

Children and adolescents with intellectual disabilities (ID) are at heightened risk for developing ADHD. However, the validity of ADHD as a diagnosis for youth with ID remains controversial. To advance research on validity, the present study examined the hypothesized precursors to ADHD in typically developing adolescents (TD) and adolescents with ID, specifically with regard to family history of ADHD, molecular genetics, and neuropsychological functioning. Results indicated that youth ADHD symptoms were related to parental ADHD symptoms regardless of the adolescent's cognitive functioning. Additionally, findings suggested that the DRD4 genetic variant and adolescent set-shifting abilities were related to adolescent ADHD symptoms independent of cognitive functioning. This study provides an initial investigation of the biological correlates of ADHD among youth with ID.

1. Introduction

Youth with intellectual disabilities (ID) are at least three times as likely to have a mental disorder as typically developing (TD) children, with Attention-Deficit/Hyperactivity Disorder (ADHD) constituting the most frequent comorbid diagnosis (Baker, Neece, Fenning, Crnic, & Blacher, 2010; Dekker, Koot, ven der Ende, & Verhulst, 2002; deRuiter, Dekker, Douma, Verhulst, & Koot, 2008; Emerson & Hatton, 2007; Neece, Baker, Blacher, & Crnic, 2011). However, the validity of ADHD among people with ID is controversial given that previous students have documented a negative correlation between ADHD symptoms and IQ (Goodman, Simonoff, & Stevenson 1995; Rapport, Scanlan, & Denney, 1999). However, the degree to which ADHD symptoms are inherent to ID is not clear. The goal of the current study was to further examine the validity of ADHD among adolescents with moderate to borderline ID, focusing on "pre-pathway" influences, or factors thought to precede or underlie the diagnosis of ADHD (Tellegen, 1988).

1.1 The Validation Study

A groundbreaking paper by Robins and Guze (1970) described five phases necessary to establish the diagnostic validity of psychiatric illness: clinical descriptions, laboratory findings, exclusion of other disorders, follow-up study, and family study. These criteria have

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since been expanded such whereby diagnostic validity necessitates a consistent pattern of data across clinical correlates (e.g. behavioral phenotypes), family history, developmental course, and treatment response (Antshel, Phillips, Gordon, Barkley, & Faraone, 2006). Consistent with the methodology outlined in Robins and Guze (1970), a previous study with the current sample of adolescents with and without ID examined the clinical presentation of ADHD (i.e., prevalence, sex differences, and comorbidity) and evaluated its validity based on symptom presentation, developmental course, and associated functional impairment (Neece, Baker, Crnic, & Blacher, in press). Findings suggested that adolescents with ID were at elevated risk for ADHD (risk ratio: 3.4:1) compared to their typically developing peers and the symptoms endorsed, trajectory of the disorder, and levels of impairment were comparable among adolescents with and without ID, providing preliminary support for the validity of ADHD in this population of adolescents.

More recently, a “second standard” of validation has emerged where clinical description and epidemiological criteria must be further substantiated by elucidation of the etiology, pathophysiology, and underlying mechanisms (e.g. candidate genes) the disorder (Andreasen, 1995). Thus, the present study investigated “pre-pathway” influences, or potential causal factors for ADHD among youth with and without ID (Tellegen, 1988). Specifically, we examined similarities and differences among typically developing (TD) adolescents and adolescents with ID with regard to several theoretically-derived and biologically plausible factors across multiple domains including family history of ADHD, molecular genetics, and neuropsychological factors (working memory, response inhibition, and set-shifting).

1.2 Family History

There is considerable evidence that ADHD cosegregates, suggesting the potential heritability of individual differences in ADHD. Rates of ADHD among first-degree relatives are two to four times higher among ADHD probands, across ADHD subtypes, relative to non-ADHD controls (Faraone, Biederman, & Friedman, 2000). To our knowledge, no study to date has examined the family history of ADHD among relatives of children or adolescents with ID and ADHD. This is due in part of the fact that most genetic studies of ADHD exclude children with ID. However, it is clearly an important area of inquiry in terms of examining the validity of ADHD as a diagnosis for children and adolescents with ID. Family studies may reveal that it takes less familial risk for ADHD to be expressed in individuals with ID. It may also be that a different pattern of psychiatric disorders is present in families of children and adolescents with ID and ADHD. However, if adolescent ADHD functioning is associated with parental ADHD symptoms independent of the adolescent’s cognitive functioning, this further supports the notion that ADHD is the same or similar disorder among adolescents with ID.

1.3 Genetics

The underlying dimensions of ADHD are substantially heritable (h^2 = .6–.9; Faraone et al., 2005; Nigg & Nikolas, 2008; Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2004; Simonoff et al., 1998) indicating that about 70% of the variance in ADHD symptoms is accounted for by some sort of genetic influences. Thus, additive genetic influences, including variance attributable to gene x environment interaction (G x E), account for a significant majority of individual differences in ADHD. As a result, research on ADHD has rapidly moved into molecular genetic studies to identify the possible genes involved in ADHD. Molecular genetic studies of ADHD have tested a variety of candidate genes that may be involved in the development of this disorder, many of which influence the availability of dopamine in the prefrontal cortex. There is a strong empirical rationale for this approach given that dopamine neurotransmission is implicated in key dimensions of

ADHD, including working memory, inhibition, and attention across human and rodent models (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005; Sergeant, Geurts, & Oosterlaan, 2002; Nigg, 2001). Moreover, dopaminergic genes are also plausibly associated with ADHD because these genes are directly related to the site of pharmacological action of stimulant medication, which is the most common pharmacotherapy for ADHD (i.e., frontostriatal brain regions; Biederman, 1997).

We focused on two genetic variants that are involved in dopamine neurotransmission and may be implicated ADHD. The DRD4 gene, which produces a blunted response to dopamine (Van Tol, Wu, Guan, & Ohara, 1992), has demonstrated the most consistent association with ADHD across numerous meta-analytic studies (Faraone et al., 2001; Loo et al., 2010; Wu, Xiao, Sun, Zou, & Zhu, 2012), and, thus, was examined in our sample of adolescents with and without ID. The dopamine transporter gene (DAT1) may be the candidate that is the most biologically plausible given that stimulant medications inhibit the dopamine transporter thereby increasing extracellular dopamine (Li & Lee, 2012; Spencer et al., 2007). Some previous studies have found an association between the DAT1 gene and ADHD (Brookes et al., 2006; Chen et al., 2003; Cook, Stein, Ellison, & Unis, 1995; Faraone et al., 2005, Loo et al., 2010; Loo et al., 2008; Todd et al., 2005), while others have not (Li, Sham, Own, & He, 2006). However, given the strong theoretical basis for the association between DAT1 and ADHD this variant was also examined in the current study. To the authors' knowledge this study is the first to examine molecular genetics in children or adolescents with ADHD and ID, specifically investigating whether two of the susceptibility genes that have been most implicated in ADHD (DRD4 and DAT1) are also associated with this disorder in a sample of adolescents with ID.

1.4 Neuropsychological Functioning

Executive function (EF) deficits represent putative mechanisms through which the underlying pathophysiology ADHD eventuates in disorder (i.e., endophenotypes). EF refers to the strategic allocation of attention and responses and consists of a set of cognitive processes such as planning, working memory, attention, problem solving, verbal reasoning, inhibition, mental flexibility, and monitoring of actions (Nigg & Nikolas, 2008). These abilities are necessary to effectively suppress a prepotent response (e.g., cognition, behavior) in the service of achieving a higher-order goal (Barkley, 1997, Willcutt et al., 2005). In addition to ADHD symptoms, deficits in EF have also been associated with impairments in functional outcomes (Barkley, Fischer, Smallish, & Fletcher, 2006; Biederman et al., 2006). The present study examined four domains of EF; verbal working memory, spatial working memory, response inhibition, and set shifting, all of which have been found to be impaired in children and adolescents with ADHD (Barkley, 1997; Nigg, 2006).

1.4.1 Working Memory—Working memory requires the ability to encode, tore, manipulate, and retrieve information, typically in the face of interference. Working memory is influenced by dopaminergic functioning (Goldman-Rakic, 1993) and may be one mediator of the relationship between the genetic factors discussed earlier and ADHD. Biologically, verbal and spatial working memory are regulated by the left hemisphere and right hemisphere, respectively, (Baddeley, 1998; Jonides, Smith, Koeppe, & Awh, 1993; Paulesu, Frith, & Frackowiak, 1993) suggesting that these two facets are empirically separable. Meta-analyses of at least 20 studies found modest effect sizes for verbal working memory deficits in ADHD (d=.43 in Martinussen et al., 2005 and d=.54 in Willcutt et al., 2005). Although fewer studies have examined spatial working memory in children and adolescents with ADHD, the meta-analyses available have found fairly large effect sizes for spatial working memory (d=1.06 in Martinussen et al., 2005 and d=.72 in Willcutt et al., 2005). Despite

research indicating that they are distinct constructs, no study to our knowledge has examined verbal and spatial working memory separately in a sample of persons with ID.

Limited findings investigating working memory in youth with ID have focused on children generally finding that children with ID exhibit more working memory deficits than age-matched TD youth. However, these children typically perform similarly or even better than children matched for mental age (Henry & MacLean, 2002; Jarrold & Braddeley, 1997; Jarrold, Braddeley & Hewes, 2000; Rosenquist, Conners, & Roskos-Ewoldsen, 2003; Van der Molen, Van Luit, Jongmans, & Van der Molen, 2007) suggesting that cognitive functioning alone can not fully account for the variance in performance on assessments of working memory. Similar findings with our sample of adolescents would support the notion that ADHD may be a construct that is separate and distinct from IQ.

1.4.2 Response Inhibition—Response inhibition refers to individual differences in the ability to suspend a response during an active moment-to-moment behavior (Nigg & Nikolas, 2008). In studies of response inhibition, neuroimaging and brain injury studies converge around the primacy of circuitry in the inferior frontal gyrus and the caudate in the basal ganglia (Nigg & Nikolas, 2008). Using the Logan stop task (Logan & Cowan, 1984), meta-analytic evidence suggests children with ADHD exhibit impaired response inhibition (d=.61; Willcutt et al., 2005). One study found that adults with ADHD and ID made significantly more commission errors on a continuous performance test compared to adults with ADHD alone, even with statistical control of IQ. Thus, adults with comorbid ADHD and ID may show cognitive profiles reflecting a “double deficit” (Rose, Bramham, Young, Paliokostas, & Xenitidis, 2008). No study to our knowledge has examined a similar construct of response inhibition among children or adolescents with ID.

1.4.3 Set Shifting—Set shifting, also referred to as task shifting or cognitive shifting, is the mental process of re-directing one’s focus of attention away from one fixation point and toward another fixation point. These abilities likely involve attentional networks in the prefrontal cortex; however, different areas of the prefrontal cortex have been implicated (e.g. lateral prefrontal cortex; Dove, Pollmann, Schubert, Wiggins, Cramon, 2000; inferior prefrontal cortex; Konishi et al., 1998). ADHD is reliably associated with impaired cognitive flexibility, including poor set shifting compared to control children (effect size for set-shifting d=.65; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; d=.46, Willcutt et al., 2005).

Despite the large number of studies examining neuropsychological functioning among youth with ADHD, very little research has examined the cognitive parameters of children and adolescents with ADHD and ID. This may be because participants with ID may be less likely to understand the tasks or less able to sustain attention long enough to complete neuropsychological evaluation. Some have argued against examining neuropsychological deficits in the context of general cognitive delays (Pennington & Bennetto, 1998; Pulsifer, 1996). However, research suggests that among youth with ID, there is significant variability in neuropsychological profiles and strengths/weaknesses can be identified, especially among youth with mild or borderline ID (Swillen et al., 1999; Udwin & Yule, 1991). If EF deficits are a distinct characteristic of ADHD, one would expect ADHD functioning to be associated with set shifting abilities, and other aspects of executive functioning, above and beyond the child’s intellectual functioning.

1.5 The Present Study

When a disorder is valid in different populations, there is an assumption that the same causal factors underlie its presentation across groups. Thus, in an effort to further understand the

validity of an ADHD diagnosis for adolescents with ID, we examined pre-pathway factors thought to precede ADHD among adolescents with and without ID. Toward this aim, the following hypotheses were investigated: 1) After controlling for youth IQ, maternal ADHD symptoms will be associated with the adolescent's ADHD symptoms, b) The homozygous 10-repeat genotype (10/10) of the DAT1 gene and the 7-repeat allele of the DRD4 gene, rigorously implicated in the etiology of ADHD, will be significantly associated with ADHD among adolescents who are typically developing with ADHD and among adolescents with comorbid ADHD and ID, and c) Adolescent ADHD will be associated with neuropsychological deficits (i.e. working memory, response inhibition, and set shifting) even after controlling for adolescent intellectual functioning.

2. Material and Method

2.1 Participants

Participants were 164 families of youth aged 13 years. They were participating in a longitudinal study of young children, with samples drawn from Southern California (87.9%) and Central Pennsylvania (12.1%). Most families (73.2%, n=120) had been recruited 10 years earlier, with the intake assessment conducted near the child's 3rd birthday. Another 8 families of children with ID entered the study at child age 5. Additionally, 19 families of TD adolescents and 17 families of adolescents with ID entered the study at child age 13. There were no significant differences in demographic characteristics based on geographic region or cohort.

Youth in the ID group were recruited through agencies that provide services for people with developmental disabilities and, more recently, through schools. In California, practically all families with children with intellectual and developmental disabilities register for services with one of a network of Regional Centers. Youth in the TD group were initially recruited though pre-schools and day-care programs and later through middle schools. For all recruitment, school and agency personnel mailed brochures describing the study to families who met selection criteria. Interested parents phoned the research center to obtain information about the study and, if interested, to set up an initial home visit.

Inclusion criteria for the current sample were as follows: for the ID sample: (a) IQ 50–84 on a prorated WISC (3 subscales); (b) Vineland standard score of 84 or less; and (c) not meeting any exclusionary criterion. Inclusion criteria for the TD sample were: (a) IQ 85 or above, (b) no premature birth or developmental disability diagnosis, and (c) not meeting any of the exclusionary criteria. Exclusion criteria for both sub-samples included adolescents who were non-ambulatory, had severe neuro-impairment, had a diagnosis of Fragile X or autism at intake assessment (age 3), or had another disability that would affect their ability to fully participate in the procedures described below. Subjects were included in the sample if they had a complete laboratory assessment at age 13. About a third of participants (36.6%) were classified as ID (N=60) and the remaining as TD (N=104).

Table 1 shows demographic characteristics at child age 13, by intellectual group status (ID, TD). In the combined sample there were slightly more boys than girls (60.2% boys) and 54.7% of the youth were white non-Hispanic, with others divided among Hispanic (17.2%), African American (8.9%), Asian American (1.6%) and other or mixed (17.2%). Seventy percent of participants were married. Sixty-seven percent of families had an annual income above $50,000 in 2009–2010, and the average years of schooling was three years of college for mothers and fathers. The status groups did not differ on child gender, child race/ethnicity, mother marital status, and mother race/ethnicity. However, in the TD sample mothers and fathers completed significantly more years of education and families reported a

higher income on average. These variables were included as covariates when indicated (see Data Analysis section).

2.2 Procedures

The present study used data collected when the adolescents were 13 years old. The Institutional Review Boards of the participating universities approved all study methods. Parents typically completed a battery of questionnaires independently prior to the center visit; however, if parents had not completed their packet of questionnaires particular key measures were completed at the center visit. During this assessment session, measures were taken of family demographics (interview with mother), adolescent intelligence (WISC-IV), adolescent adaptive behavior (Vineland), and adolescent neuropsychological functioning. Prior to the assessment, mothers were asked to take their children off psychostimulant medication if they were comfortable with doing so. Two youth remained on stimulant medication during the center assessment session.

Saliva samples were collected from adolescents and genotyped. Adolescents deposited their saliva into a vial, which was then transported to the UCLA Genotyping and Sequencing Core Facility for genotyping. Technicians were blind to diagnostic status and confidentiality was protected by labeling each sample with a unique case identifier known only to the author. Genomic DNA was isolated from buccal cells using standard methods.

D_4 receptor (DRD4) gene is located on 11p15.5 and contains a 48 base pair variable number tandem repeat polymorphism in exon 3. This locus consists of 2 to 11 repeats, although 4 and 7 repeats are the most common. Youth were classified based on the number of 7-repeat alleles they had. Two groups were used: (1) adolescents who had zero 7-repeat alleles (66.9%), most of whom had two 4-repeat alleles (4/4) and (2) adolescents who had one or more 7-repeat alleles, most of whom had one 4-repeat allele and one 7-repeat allele, or two 7-repeat allele (33.1%). DRD4 frequencies did not deviate from the Hardy-Weinberg equilibrium (χ^2=0.71, p>.05), suggesting that the observed allele frequencies in the current sample did not deviate from the expected frequencies in the population.

Dopamine transporter (DAT1) contains a 40-bp VNTR polymorphism in the 3¢UTR. The 9-repeat (440 bp) and 10-repeat (480 bp) polymorphisms are the two most common alleles in the population. The DAT1 analyses compared individuals homozygous for the 10-repeat allele (i.e., 10/10 repeat) versus individuals with at least a one copy of the 9-repeat allele (i.e., 9/9 + 9/10 repeat groups). The frequency of DAT1 genotypes was as follows: 2.6 percent of the sample had two 9-repeat alleles (9/9); 43.9% had one 9-repeat allele and one 10-repeat allele (9/10), and 53.5% had two 10-repeat alleles (10/10). Similar to the DRD4 genotype frequencies, these frequencies did not deviate from the Hardy-Weinberg equilibrium (χ^2=3.46, p>.05). Given that very few adolescents had the 9/9 genotype, these participants were removed from the analyses. Four additional participants with rare genotypes were removed from these analyses (7/10, 8/10, 9/11). Therefore, the DAT1 genotype variable compared adolescents with the 10/10 genotype to adolescents with the 9/10 genotype.

2.3 Measures

2.3.1 Youth Diagnostic Measures

2.3.1.1 Wechsler Intelligence Scale for Children – Fourth Edition (WISC–IV; Wechsler, 2003): Full Scale IQ (FSIQ) was estimated using three subtests of the WISC-IV (Vocabulary, Matrix Reasoning, and Arithmetic). Sattler and Dumont (2004) reported that this prorated IQ correlated highly (r=.91) with the FSIQ from the full WISC-IV administration. While they did not specify whether this correlation was consistent across all

levels of cognitive functioning, their normative sample included a substantial number of children with mild and moderate ID, learning disabilities, ADHD, and other childhood disorders.

2.3.1.2 Vineland Scales of Adaptive Behavior-II (VABS; Sparrow, Cicchetti, & Balla, 2005): The Vineland is a commonly-used semi-structured interview that asks caregivers to report on adaptive behaviors that their children usually do. The standardized Adaptive Behavior Composite score was used which has a mean of 100 and standard deviation of 15. This score was comprised of three subscales: *communication*, *daily living skills*, and *socialization*. The VABS has good reliability (alphas in the low 80s for most subscales) and validity (Sparrow et al., 2005).

2.3.1.3 Conners' Parent Rating Scale-Revised S (CPRS; Conners, 2000): The CPRS was used to assess youth ADHD symptoms. It has 27-items on a 4-point Likert scale and yields three subscales -- oppositional, cognitive problems/inattention, and hyperactivity -- as well as an overall ADHD Index score. The CPRS has good predictive power for ADHD (Pillow, Pelham, Hoza, Molina, & Stultz, 1998) and discriminant validity (Deb, Dhaliwal, & Roy, 2008).

2.3.2 Family History Measures

2.3.2.1 Conners Adult ADHD Rating Scale-Short Form (CAARS; Conners, Erhardt, & Sparrow, 1999): Mothers' and fathers' current ADHD symptoms were assessed using the CAARS. This is a 26-item self-report measure of ADHD symptoms for adults that yields five subscales: DSM-IV Inattentive Symptoms, DSM-IV Hyperactive-Impulsive Symptoms, DSM-IV ADHD Symptoms Total, ADHD Index, and an Inconsistency Index. The ADHD Index, which is the index that consists of the best set of items on CAARS for identifying adults "at risk" for ADHD (Conners, et al., 1999) was used in the current study. Additionally, participants who had an Inconsistency Index greater than that the standardized cut-off (Inconsistency Index > 8) were removed from analyses for mother reports (n=9) and father reports (n=1)). This measure has been shown to have good reliability as well as convergent and discriminate validity (Kooij et al., 2008)..

2.3.3 Neuropsychological Measures—Three broad domains of executive function were examined: working memory, response inhibition, and set-shifting.

2.3.3.1 Digit Span subtest of WISC-IV Integrated (Wechsler et al., 2004): Verbal working memory was assessed using the Digit Span subtest of the WISC-IV Integrated. The adolescent was verbally presented with a string of individual numbers and was asked to repeat back the same sequence of numbers (Digit Span Forward). The task was repeated again, with different numbers, but the adolescent was asked to repeat the numbers backwards (Digit Span Backward). Digit Span Forward is thought to measure the adolescent's "mentalization" abilities, or his/her ability to temporarily store information in memory, whereas Digit Span Backward is thought to measure mental "manipulation" abilities, or how well the youth can transform information in active memory. Previous versions of this subtest have high internal consistency (Cronbach's alpha between .80 and . 90; McGrew & Flanagan, 1998) and test-retest reliability (Sattler, 2001).

2.3.3.2 Spatial Span subtest of WISC-IV Integrated (Wechsler et al., 2004): Visio-spatial working memory was assessed using the Spatial Span subtest of the WISC-IV Integrated. The adolescent was presented with a flat, rectangular white surface with 10 randomly located blue blocks attached to the surface. The examiner touched a series of blocks one at a time and the youth was then required to touch the blocks in the same order

(Spatial Span Forward) or in the reverse order (Spatial Span Backwards). Similar to the Digit Span subtest described above, Spatial Span Forward is thought to capture the youth's spatial mentalization abilities while Spatial Span Backwards is an indicator of the adolescent's spatial manipulation abilities. For all four working memory subtests (Digit Span Forward, Digit Span Backward, Spatial Span Forward, and Spatial Span Backwards), scaled scores were used, which have a mean of 10 and a standard deviation of 3.

2.3.3.3 Stop-Signal Task (SST; Logan & Cowan, 1984): Response inhibition was measured using the Stop-Signal Task, which is a computerized task where adolescents are asked to perform responses to a standard two-choice reaction task in which a random stop-signal (i.e. beep) is presented on 25% of the trials, requiring the inhibition of the response to the target signal. The SST (Logan & Cowan, 1984; Quay, 1997) requires the participant to quickly and accurately inhibit a motor response, yielding a measure of inhibition called the stop-signal reaction time (SSRT). The SSRT, used as an indicator of response inhibition, is calculated by subtracting the mean stop-signal delay, or the average time between the presentation of the stimulus and the stop signal, from the mean reaction time on no-signal trials (i.e. trials where there is no stop signal).

Quality control statistics indicated that the average probability of inhibiting one's response was about 50% in the combined sample (49.56%) and there were no differences in the probability of response between the ID and TD subsamples. Twenty-one subjects (16%) were found to have inhibited significantly more or less than 50% of the time and, therefore, were removed from the analyses because the subtraction method used to calculate the SSRT was not appropriate for these subjects (Verbruggen, Logan, & Stevens, 2008).

2.3.3.4 Trail Making Test (Reitan, 1979): Set-shifting, or the ability to display cognitive flexibility in the face of changing demands, was measured using the Trail Making Test from the Halstead–Reitan Neuropsychological Battery (Reitan, 1979). Two versions of trails were used: (1) Trails A, in which the targets are all numbers (1,2,3, etc.), and (2) Trails B, in which the subject alternates between numbers and letters (1, A, 2, B, etc.). The goal of the task is to finish the test as quickly as possible. The primary executive measure is time to complete Form B (in seconds) where the participant had to shift from one fixation point (e.g. numbers) to another fixation point (e.g. letters). Form A time is viewed as a warm-up task and was not further analyzed. The dependant variable was log transformed due to the non-normal distribution of the scores. This is procedure is consistent with other studies measuring set-shifting in children with ADHD (Nigg et al., 2004).

2.4 Data Analytic Plan

As suggested by Cohen, Cohen, West and Aiken (2002), all outliers were set equal to plus or minus 3 standard deviations from the mean in order to reduce the influence of extreme data points on the results. For all analyses, demographic variables that had a significant relationship ($p<.05$) with the independent variable(s) *and* the dependent variable(s) were tested as covariates in the analyses. Covariates were retained in the final model if they predicted the dependent variable at $p<0.10$.

Analyses examining the relationship between parental ADHD symptoms and youth ADHD symptoms used Pearson's correlation coefficients and the association between these variables controlling for intellectual functioning used partial correlations. To investigate whether DRD4 or DAT1 genotype predicted ADHD symptoms above and beyond intellectual functioning, two univariate analyses of variances were used which included intellectual functioning and genotype as predictors. Finally, similar to the family history analyses, Pearson's correlation coefficients were employed to examine the relationship

between neuropsychological variables and ADHD symptoms and partial correlation coefficients were examined to determine the relationship between these variables independent of intellectual functioning.

3. Results

3.1 Preliminary Analyses

Adolescent ADHD symptoms were significantly higher in the ID group (Mean CPRS ADHD Score=16.7; SD=9.3) compared to the TD group (Mean CPRS ADHD Score=7.0; SD=7.8); t = 5.61, p <. 001. Additionally, when the relationship between cognitive functioning and ADHD symptomatology was examined using two continuous variables, there was a significant negative correlation between adolescent IQ as measured by the WISC-IV and number of ADHD symptoms (r= −.45, p<.001). These findings are consistent with previous studies indicating that adolescents with ID are at significantly higher risk for ADHD than typically developing youth. (Reilly & Holland, 2010)

Family History—Table 2 depicts the correlations between mother and father reports of youth ADHD symptoms (CPRS scores) and parental ADHD symptoms (CAARS scores). Adolescent ADHD symptoms (CPRS ADHD Index) were significantly correlated with mother and father reports of their own ADHD symptoms (mother r=.25, p<.01; father r=.31, p<.01). These correlations remained significant even after controlling for youth intellectual functioning (mother r=.23, p<.01; father r=.29, p<.01). Furthermore, with the exception of the cognitive problems subscale, adolescent ADHD symptoms related to all subscales of the CAARS according to both mother and father reports.

Additionally, parent and youth symptoms of inattention and hyperactivity were correlated and robust to informant including father reports (inattention r=.21, p<.05; hyperactivity r=.36, p<.001) and marginally significant using mother reports (inattention r=.15, p<.10; hyperactivity r=.16, p<.10). After controlling for intellectual functioning, adolescent and paternal symptoms of hyperactivity were still significantly correlated (r=.33, p<.01) and symptoms of inattention were marginally related (r=.20, p<.10). These family history relationships indicate that intellectual functioning alone did not explain the relationship between youth and parental ADHD symptoms.

3.2 Molecular Genetics

Point-biserial correlations indicated that there was a significant correlation between ADHD symptoms and DRD4 genotype in the ID group (r=.35, p<.05) but not in the TD group or combined group. For the DAT1 genotype, there were so significant correlations between genotype and ADHD symptoms in the combined, TD, or ID groups. Table 3 shows univariate analyses of variance that were conducted to determine whether DRD4 and DAT1 genotype predicted ADHD symptoms above and beyond intellectual functioning. Results indicated that DRD4 marginally predicted ADHD symptoms above and beyond youth intellectual status (F=3.87, p=.058). DAT1 genotype was unrelated to ADHD symptoms after controlling for cognitive functioning.

3.3 Neuropsychological Functioning

Table 4 reports the correlations between adolescent ADHD symptoms and measures of neuropsychological functioning with and without controlling for IQ in the combined sample.

ADHD symptoms were associated with lower working memory scores on all four subscales (Digit Span Forward, Digit Span Backward, Spatial Span Forward, and Spatial Span Backward) in the combined sample. Additionally, after controlling for IQ, there was a

marginal association between ADHD symptoms and two working memory scores (Digit Span Backward and Spatial Span Forward).

Poor response inhibition, indicated by higher stop-signal reaction times, had a significant relationship with youth ADHD symptoms. However, this relationship was no longer significant after controlling for intellectual functioning.

Youth ADHD symptoms had a significant relationship with set-shifting abilities in that participants with more ADHD symptoms took longer to complete Trails B, which is suggestive of poorer set-shifting abilities. Additionally, after covarying IQ, the relationship between set-shifting abilities (Trails B) and adolescent ADHD symptoms remained statistically significant.

In sum, correlation analyses indicated that all neuropsychological variables were significantly related to ADHD symptoms. Additionally, the association between ADHD symptoms and set-shifting abilities remained significant above and beyond adolescent intellectual functioning.

4. Discussion

We examined similarities in the hypothesized precursors to ADHD in typically developing adolescents (TD) and adolescents with intellectual disability (ID). Although youth with ID are at very high risk for developing ADHD, no study had systematically investigated the "pre-pathway" factors that may contribute to the development of ADHD in this vulnerable population. Despite innovations in understanding the genetic and neurobiological substrates of ADHD, it is clear that ADHD has multiple causal risk factors, reflecting the principle of equifinality (Cicchetti & Rogosch, 1996). Thus, the variables examined in the current study are only a small subset of the potential factors that should be considered as potential contributors of the development of ADHD. Nevertheless, given the absence of literature examining any of these factors in populations with ID, the present study is the first to rigorously examine the biological correlates of ADHD in a sample of adolescents with and without ID.

Our first research question examined parental ADHD symptoms. ADHD has been found to "run in families" and rates of ADHD among first-degree relatives of TD children with ADHD are significantly higher than rates among parents of children without ADHD (Faraone et al., 2000). Analyses examining ADHD symptoms among parents of adolescents in the present sample provided the same evidence of family aggregation. Teen ADHD symptoms were correlated with both mother and father ADHD symptoms and this relationship remained significant even after controlling the youth's intellectual functioning, indicating that there was an association between parent and adolescent ADHD functioning that is independent of cognitive functioning. This suggests that offspring ADHD, regardless of ID status, is positively associated with ADHD symptoms in biological relatives.

In interpreting the family history findings, it is important to consider the role of the environment as well. More specifically, it may be that shared factors in the family environment rather than, or in addition to, genetic factors accounted for increased ADHD symptoms in both children and their parents. Evidence from twin studies of ADHD may inform this counterargument. The majority of these models implicate genetic and non-shared environmental effects, rather than shared environmental effects, in accounting for variance in ADHD (Hudziak et al., 2000). However, the role of shared environment effects explaining similarities in ADHD symptomotology among adolescents with ID and their parents remains a question for future research. Additionally, future studies should examine family history of ADHD more closely, focusing on the subtypes of ADHD among parents

(Faraone, et al., 2000). Some studies find specificity in the family history of ADHD for the subtypes (e.g. parents with the inattentive subtype of ADHD are more likely to have children that have the inattentive subtype of ADHD versus the other subtypes) (Stawicki, Nigg, & von Eye, 2006); however, other studies do not find this association (Rasmussen et al., 2004).

To investigate the genetic underpinnings of ADHD further, we examined two biologically plausible and functional polymorphisms implicated in ADHD and related phenotypes. The first candidate gene we considered was the 7-repeat allele of the 48 base pair sequence within the coding region of DRD4, which is the gene that had the most robust association with ADHD across previous studies (Faraone, 2000; Loo et al., 2010). Our findings were consistent with earlier studies and indicated that the homozygous 7-repeat genotype (7/7) of DRD4 was associated with ADHD symptoms, and this association remained marginally significant even after controlling for intellectual functioning. Conversely, in examining the DAT1 gene, results did not support the association between this genotype and ADHD; however, studies examining the association between DAT1 and ADHD have been less consistent than studies examining the DRD4 allele. A meta-analysis by Gizer and colleagues (2008) found that individuals with at least one copy of the 10-repeat DAT1 allele had higher levels of ADHD compared to those with no 10-repeat copies; however, the effect was quite small (OR = 1.27) and the findings did not distinguish between homozygotes with two copies of the 10-repeat allele (10/10) and heterozygotes with one copy. Conversely, other meta-analyses do not support the association between the DAT1 gene and risk for ADHD. One limitation of this research is the absence of a consistent definition for DAT1 genotypes across studies. For example, some investigators have compared children with one copy of the 10-repeat allele (e.g. 8/10. 9/10, 10/10) to children without one copy (e.g. 8/9, 9/9, 9/11), yielding heterogeneous groups without regard to the biological consequences of each genotype whereas other studies compare specific genotypes (e.g. 9/10 vs. 10/10). This limits our ability to compare findings across investigations.

Our study includes a very preliminary investigation of molecular genetics and ADHD among adolescents with ID and findings must be considered within the context of their limitations. Most notably, the sample size was small and thus the analyses were underpowered to detect the small effects of these single candidate genes. Additionally, we only considered two potential candidate genes, of which there are several. However, even with an adequate sample size and a broad array of genetic variants, molecular genetic studies of psychological disorders are criticized given the multigenetic nature and heterogeneity of mental disorders. Nevertheless, despite the difficulty of these investigations, researchers have identified a series of specific candidate genes for ADHD that are fairly consistent across studies and demonstrate a reasonable effect size. Future studies should examined candidate genes in conjunction with quantitative methods (e.g. twin studies) that demonstrate the importance of genes in the etiology of ADHD, thereby enabling the identification of genes involved in complex disorders as well as the study of molecular mechanisms and gene-environment interactions (Asherson & Curran, 2001). Additionally, new studies should distinguish between the subtypes of ADHD given that specific genetic variants may be linked to specific subtypes. Finally, later investigations may look at the association between candidate genes and endophenotypes of ADHD among children and adolescents with ID. Endophenotypes are meditational or intervening constructs that are thought to be closer to the immediate product of the genes and genetically simpler than the explicit phenotype of the disorder, thereby enhancing the power to detect genetic effects (Waldman, 2005).

Neuropsychological factors, specifically aspects of executive functioning, are some of the primary endophenotypes that have been associated with ADHD. These cognitive functions

are thought to mediate the relationship between the genetic origins and complex phenotype of the disorder. We investigated whether these cognitive functions were associated with ADHD in adolescents with or without ID. Executive functioning is strongly correlated with general intellectual functioning and, therefore, one would expect significant differences between typically developing youth and youth with ID. However, if these cognitive endophenotypes are part of the mechanisms underlying ADHD symptoms, then ADHD functioning should be associated with these processes above and beyond intellectual functioning. Our results provided mixed evidence for the association between neuropsychological functioning and ADHD in adolescents with and without ID. All working memory variables were correlated with the number ADHD symptoms; however, some of these relationships appeared to be accounted for by intellectual functioning. Set-shifting abilities had the strongest association with ADHD symptoms independent of IQ, suggesting that cognitive flexibility may be less associated with the underlying pathophysiology of ADHD than other aspects of neuropsychological functioning, which is consistent with previous research.

In sum, findings examining pre-pathway influences of ADHD provided mixed results. Observed associations were generally in the expected direction and the absence of consistent significant findings may be due to a lack of statistical power. As discussed earlier, research examining biological correlates of ADHD is an emerging body of literature, and, therefore, our constructs may be less well defined, less reliably measured, and have smaller effects than constructs that have been investigated and refined for many years. More research is needed to identify additional biological correlates and to refine the classification and measurement of current correlates. Additionally, future studies should continue to examine biological correlates of ADHD among children and adolescents with ID using a larger sample in order to further assess the validity of this diagnosis for this population. Nevertheless, this is a critical area to address in investigating the validity of ADHD among youth with ID. At the core of understanding whether ADHD is the same disorder in adolescents with and without ID is the question of whether the disorder has the same origin(s) in the two groups. The disorder may look very similar as previous studies have found (Baker et al., 2010; Neece et al., 2011, Neece et al., in 2012) but the etiological correlates may be different, suggesting that although the presentation is similar, the disorder is not the same in the two groups.

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Highlights

Children and adolescents with intellectual disability (ID) are at heightened risk for developing ADHD

We expanded the literature base examining the validity of ADHD by investigating "pre-pathway" variables, or factors thought to precede or underlie the diagnosis of ADHD, in a sample of typically developing (TD) adolescents and adolescents with ID.

Youth ADHD symptoms were associated with mother and father ADHD symptoms independent of youth cognitive functioning

The DRD4 genetic variant was associated with youth ADHD symptoms, and this relationship remained marginally significant after controlling for youth IQ.

Set-shifting abilities were related to adolescent ADHD symptoms above and beyond the youth's intellectual abilities.

Table 1

Demographics Characteristics

	ID n = 60	TD n = 104	χ^2 or *t*	Effect Size (Cohen's *d* or odds ratio)
Children				
Gender (% boys)	60.1	51.9	χ^2=0.92	OR=1.45
Race (% Caucasian)	52.5	57.7	χ^2=0.22	OR=0.82
WISC IQ (SD)	63.9 (13.7)	107.3 (13.7)	t= 19.29***	*d*=3.17
VABS Adaptive Behavior (SD)	72.1 (10.7)	95.7 (10.2)	t= 14.00***	*d*=2.27
Parent and family				
Marital Status (% married)	69.5	72.1	χ^2=0.03	OR=0.88
Mother's Race (% Caucasian)	54.2	64.4	χ^2=1.24	OR=0.66
Mother's Education (M. grade)	14.8 (2.8)	15.9 (2.4)	t= 2.72**	*d*=0.44
Family Income (% > $50K)	57.6	72.8	χ^2=3.27	OR=0.51
Father's Education (M. grade)	13.7 (2.9)	15.8 (2.8)	t= 4.11***	*d*=0.75

† p<.10.

* p<.05.

** p < .01.

*** p < .001.

Table 2

Mother and Father Reports of Youth ADHD Symptoms (CRPS) and of Their Own ADHD Symptoms (CAARS)

	Bivariate Correlations (no covariates)					Partial Correlations (controlling for IQ)				
	CAARS ADHD Index	**CAARS Inattention/Memory**	**CAARS Hyperactivity**	**CAARS Impulsivity**	**CAARS Problems with Self-Concept**	**CAARS ADHD Index**	**CAARS Inattention/Memory**	**CAARS Hyperactivity**	**CAARS Impulsivity**	**CAARS Problems with Self-Concept**
Mother Report										
CPRS ADHD Index	.25**	.22**	.14†	.26**	.15†	.23**	.16†	.16†	.19*	.18*
CPRS Cognitive Problems/Inattention	.16*	.15†	.09	.17*	.09	.13	.09	.09	.09	.12
CPRS Hyperactivity	.25**	.16†	.12	.34***	.13	.26**	.14	.14	.34***	.14
CPRS Oppositional	.31***	.27**	.27**	.23**	.22**	.30**	.31***	.25**	.16†	.20*
Father Report										
CPRS ADHD Index	.31**	.34***	.30**	.26**	.24*	.29**	.36***	.29**	.24*	.22*
CPRS Cognitive Problems/Inattention	.20*	.21*	.19*	.21*	.15	.16	.20†	.15	.16	.13
CPRS Hyperactivity	.39***	.33***	.36***	.39***	.24*	.37***	.35**	.33**	.41***	.19†
CPRS Oppositional	.41***	.31**	.48***	.33***	.30**	.37***	.33**	.44***	.29**	.26*

† p<.10.

* p<.05.

** p < .01.

*** p < .001.

Table 3

Univariate Analyses of Variance Predicting Youth ADHD Symptoms from Genoptype

	Sum of Squares	df	Mean Square	F
DRD4 Genotype				
Intellectual Status	1399.611	1	1399.611	24.574***
DRD4 Genotype	220.314	1	220.314	3.868 †
Intellectual Status * DRD4 Genotype	186.084	1	186.084	3.267 †
DAT1 Genotype				
Intellectual Status	2062.057	1	2062.057	35.049***
DAT1 Genotype	25.339	1	25.339	.431
Intellectual Status * DAT1 Genotype	8.641	1	8.641	.147

† p<.10.

* p<.05.

** p < .01.

*** p < .001.

Table 4

Correlations between ADHD Symptoms and Neuropsychological Variables

	CPRS ADHD Index (no covariates)	CPRS ADHD Index (controlling for IQ)
Digit Span Forward Scaled Score	−.31***	−.03
Digit Span Backward Scaled Score	−.23**	−.22†
Spatial Span Forward Scaled Score	−.35***	−.20†
Spatial Span Backward Scaled Score	−.25**	.10
STOP-IT Stop-Signal Reaction Time	.18*	.09
Trails B	.19*	.29*

† p<.10.

* p<.05.

** p < .01.

*** p < .001.