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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 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

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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, 2012). 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 × environment interaction (G × 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 (Nigg, 2001; Sergeant, Geurts, & Oosterlaan, 2002; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). 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, Doyle, Mick, & Biederman, 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., 2008, 2010; Todd et al., 2005), while others have not (Li, Sham, Owen, & 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