Relative Immaturity in Childhood and Attention-Deficit/Hyperactivity Disorder Symptoms From Childhood to Early Adulthood: Exploring Genetic and Environmental Overlap Across Development

Isabell Brikell, MSc, Ralf Kuja-Halkola, PhD, Jan-Olov Larsson, PhD, Benjamin B. Lahey, PhD, Jonna Kuntsi, PhD, Paul Lichtenstein, PhD, Per-Anders Rydelius, PhD, Henrik Larsson, PhD

Objective: Attention-deficit/hyperactivity disorder (ADHD) has been linked to immaturity relative to peers in childhood, yet it is unclear how such immaturity is associated with ADHD across development. This longitudinal twin study examined the genetic and environmental contributions to the association between parents' perception of their child's immaturity relative to peers (RI) in childhood and ADHD symptoms across development.

Method: 1,302 twin pairs from the Swedish Twin Study of Child and Adolescent Development were followed prospectively from childhood to early adulthood. Parent ratings of RI were collected at 8 to 9 years and parent and self-ratings of ADHD symptoms were collected at 8 to 9, 13 to 14, 16 to 17, and 19 to 20 years using the Child Behavior Checklist Attention Problems scale. In addition, ADHD symptoms corresponding to *DSM* criteria were used for sensitivity analysis. Analyses were conducted using longitudinal structural equation modeling with multiple raters.

Results: RI-related etiologic factors, predominantly influenced by genes, explained 10-14% of the variance in ADHD symptoms from 8 to 9 up to 16 to 17 years. The influence of these RI-related factors on ADHD symptoms attenuated to 4% by 19 to 20 years of age. The remaining variance in ADHD symptoms was primarily explained by genetic factors independent of RI, which remained relatively stable across development, explaining 19% to 30% of the variance in ADHD symptoms from 13 to 14 up to 19 to 20 years.

Conclusion: The results show that RI is significantly associated with ADHD symptoms, particularly during childhood and adolescence, and that the association is primarily explained by a shared genetic liability. Nevertheless, the magnitude of associations across development was modest, highlighting that RI is merely one aspect contributing to the complex etiology of ADHD symptoms.

Key words: ADHD, immaturity, development, longitudinal twin analysis

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by age-inappropriate symptoms of inattentiveness, hyperactivity, and impulsivity.[1] ADHD has been suggested to be related to a delay in neurodevelopmental maturation.[2-5] Already prior to being described in the *DSM-III,* ADHD was linked to late maturation in observational studies showing that children with ADHD exhibited behaviors that would be normative in younger children, who are naturally more hyperactive, impulsive, and have less developed attentional capacities.[3,6] Further evidence for the role of maturation in ADHD comes from longitudinal research. Meta-analysis of follow-up studies show that while 65% of children with ADHD continue to experience symptoms at an impairing level, only about 15% meet full diagnostic criteria by early adulthood, suggesting that maturation with age is related to symptom reduction. [7] More recently, longitudinal neuroimaging studies have found that ADHD appears related to delayed, but otherwise normal, neurodevelopment and that remission of symptoms is related to a catch up in neurodevelopmental maturation.[4,8] Therefore, although ADHD is a highly heritable disorder showing genetic stability across development,[9,10] some of these genetic effects may be explained by immaturity-related etiologic factors.[11] However, there is a paucity of genetically sensitive, longitudinal studies addressing the association between immaturity and ADHD symptoms.

In addition, several recent studies have shown that children who are born just before the school year cutoff and, hence, are the youngest and potentially more immature children in their grade, are significantly more likely to be diagnosed with ADHD.[12-15] These findings could for some children be related

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Supplemental material cited in this article is available online.

to a delay in neurodevelopmental maturation.[2,12] However, they also have been proposed to reflect an increased risk of misdiagnosis of ADHD among the youngest children in the school year owing to parents' and teachers' subjective comparisons of immaturity across children in the same grade.[13] However, not all studies have found an increased risk of ADHD in children who are relatively young for their grade.[16,17] Due to a lack of longitudinal studies, it also remains unclear how being young for one's grade would relate to ADHD in adolescence and adulthood. Assuming that the reported higher rates of diagnosed ADHD in the youngest children in the school year are explained at least in part by comparisons of perceived immaturity across children, it is important to gain a better understanding of how parent-rated immaturity relative to peers contributes to ADHD symptoms across development.[6,13] Considering the age-dependent decline of ADHD symptoms,[7] it is possible that such immaturity is more important for ADHD in childhood compared with adulthood, when maturational differences begin to even out.[2,12]

The aim of the present study was therefore to clarify how relative immaturity (RI), measured by parent ratings in childhood, contributes to ADHD symptoms across development from childhood into early adulthood. Using longitudinal data from the Swedish Twin Study of Child and Adolescent Development (TCHAD),[18] we specifically aimed to answer the following questions: Firstly, how is RI in childhood related to ADHD symptoms across development and what are the contributions of genetic and environmental factors? Secondly, are there unique etiologic factors that contribute to ADHD symptoms over and above factors related to RI? A decreasing association between RI and ADHD symptoms with age might support the hypothesis that ADHD is, for some children, related to a delay in neurodevelopmental maturation. In parallel, a substantial influence of unique etiologic factors on ADHD symptoms, after controlling for RI, would indicate that ADHD is an etiologically complex disorder in which RI is merely one aspect associated with increased ADHD symptoms.

METHOD

Sample

TCHAD is a prospective, longitudinal twin study targeting all 1,480 twin pairs born in Sweden from May 1985 through December 1986 who were alive and living in Sweden in 1994.[18] Twins and their parents were contacted by mailed questionnaires at 8 to 9, 13 to 14, 16 to 17, and 19 to 20 years. Parent ratings were collected at all 4 time points (response rate 75%, 73%, 74%, 78%) and twin self-ratings at 13 to 14, 16 to 17, and 19 to 20 years (response rate 78%, 82%, 59%).[9] In total, 1,302 twin pairs (51% girls) contributed to the present study, including 520 monozygotic (MZ) pairs, 380 same-sex dizygotic (DZ) pairs, and 402 opposite-sex DZ pairs. Zygosity was determined by DNA, when available, or by algorithms derived from discriminant analyses of twins' and parents' responses to validated zygosity questionnaires. Each data collection wave was approved by the ethics committee of Karolinska Institutet (Stockholm, Sweden).

Relative Immaturity

There is considerable variation in normal child development, even among children born in the same year. Although there is no gold standard for how to measure a child's maturational level, biological and cognitive measurements such as dental status, functional magnetic resonance imaging, and formal IQ tests can be useful tools. However, such assessments often are not feasible in larger cohort studies. Therefore, RI in TCHAD was assessed by parent ratings on 2 items assessed in twins 8 to 9 years old. Item 1 asked parents to estimate their child's level of maturity in relation to an average child of the same age on a 5-point scale (1 = very mature, 2 = somewhat mature, 3 = average, 4 = somewhat immature, 5 = very immature). Item 2 asked parents to estimate their child's perceived age independent of chronologic age. The correlation between the 2 items was 0.75. The variables were standardized and summed to create a continuous measurement, with higher scores indicating greater immaturity. The RI measurement has been evaluated in 2 prior studies from our group.[19,20] Within the TCHAD sample, RI was found to be weakly correlated to early physical maturation (birth weight, $r_s = 0.19$; age at walking, $r_s = 0.10$; age at teething, $r_s = 0.06$) and more strongly correlated to indicators of early mental maturation (ability to handle scissors, $r_s = 0.38$; ability to tell the time from a watch, $r_s = 0.24$).[19] In a separate case-control study, children whose parents perceived them as immature relative to same-age peers were compared to age-matched controls. Results showed that higher RI was related to a more childish body appearance, fine motor function problems, peer problems, and lower general knowledge.[20] The more immature children also had somewhat lower mean IQ based on the Wechsler Intelligence Scale for Children (mean 96.0, SD 16.9 vs mean 103.6, SD 14.5, $p = .045$) and more commission errors in a continuous performance test, suggesting that the RI measurement captures aspects of mental and physical maturation.[20] The RI measurement also was significantly correlated with birth month within each year (1985, $r = 0.39$; 1986, $r = 0.50$). In Sweden, all children start school in August the year the child turns 7, meaning that age within the same grade can vary up to 12 months. Children born in December 1986, who were the youngest in their school year, had significantly higher mean RI compared with children born in January. The same was true when comparing children born in December 1985 with those born in May 1985 (data collection in 1985 included only twins born from May onward) (Table S1, available online).

ADHD Symptoms

Parent ratings of ADHD symptoms were collected using the Attention Problem (AP) scale from the Child Behavior Checklist (CBCL)[21] at 8 to 17 years and the Adult Behavior Checklist (ABCL) at 19 to 20 years.[22] Self-ratings were collected using the AP scale from the Youth Self-Report form (YSR)[23] at 13 to 17 years and the Adult Self-Report form (ASR) at 19 to 20 years.[22] The CBCL, YSR, ABCL, and ASR are empirically derived, standardized questionnaires consisting of similar, developmentally appropriate items for parent and self-ratings of problems experienced during the past 6 months. All items were rated on a 3-point Likert scale (1 = not true, 2 = sometimes true, 3 = often true) and summed, with higher scores reflecting greater attention problems. The AP scales assess inattention and hyperactivity problems and have been found to predict ADHD status.[24,25] Therefore, we consider the AP scales as measurements of ADHD symptoms. The psychometric properties of the AP scales have been evaluated in population-based and clinical samples, with results showing good reliability and convergent and discriminant validity.[21,23] The AP scales were slightly skewed and therefore log-transformed before model fitting, resulting in decreased skewness (mean skew before transformation 1.66, mean skew after transformation 0.22). Because the AP scales are derived by factor analysis, items included vary across ages and raters, with the largest differences between the CBCL and YSR and the ABCL