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EDITORIAL

Review: changing (shared) heritability of ASD and ADHD across the lifespan

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Introduction

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) frequently co-occur. In clinical practice, we daily struggle deciding if one, or the other, or both disorders, best describe the child's problems. A strong body of literature has convincingly shown that large overlap exists regarding genetic factors [6, 11, 26, 29]. However, this genetic overlap may significantly depend on age. It is well known that genetic influences on behavior are not at all constant during development and continuously co-act and interact with environmental factors influencing behavioral functioning [1, 30]. For example, increasing heritability can result from amplification, whereby early genetic influences become stronger across time. As a second example, genetic influences may be stable; yet novel genetic influences may emerge with time while early genetic influences may decrease [2]. Despite everyone's awareness of change in the (genetic) mechanisms underlying the development of an individual until elderly age in typical development, studies on neurodevelopmental disorders like ADHD and ASD have been strongly focused on childhood. The age of onset for ASD and ADHD is nearly always in childhood ([18]; but see [17]), which is the likely reason for this bias. However, given that it is already well known that developmental changes take place in both ADHD and ASD symptom domains separately, a focus beyond childhood is needed to further understand the potentially changing etiology of ADHD–ASD co-occurrence.

Heritability of ADHD across the lifespan

Several longitudinal twin studies on ADHD symptoms report that new, age-specific genetic effects influence ADHD symptoms in adolescence and adulthood, suggesting that ADHD symptoms are a developmentally complex phenotype characterized by both continuity and change across the life span [3, 9, 12, 13, 19]. In addition, only a modest overlap between longitudinal genetic effects underlying both symptom domains (inattention versus hyperactivity/impulsivity) appears present, suggesting it is necessary to study both separately. Moreover, several longitudinal studies report that subgroups may be formed based on various combinations of symptoms in both domains across the longitudinal course that likely has partly distinct genetic underpinnings ([7, 14, 25]). These findings strongly suggest that genetic effects implicated in childhood ADHD may not at all be directly comparable to those that influence ADHD in adulthood. This concurs with a review on molecular genetics in adult ADHD, where it was concluded that only some genes potentially related to childhood ADHD have been replicated in adults with the disorder [8]. In addition, in some cases the same genes were implicated, but different alleles increased the risk for ADHD in children versus adults (for instance, the 10-repeat in the dopamine transporter gene [DAT1] increased the risk for ADHD in children, but decreased the risk in adults) [8]. Note though that currently

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there are no unequivocal molecular genetic findings for ADHD in either childhood or adulthood, possibly contributing to these results. Moffitt et al. [17] reported about adults aged 38 years presenting with an ADHD symptom picture, who did not have childhood ADHD as assessed in early adolescence. They did not share the genetic and neuropsychological alterations of those who did have the childhood diagnosis. Even during adolescence, environmental effects (like smoking) controlled for genetic confounders may have a significant impact on future development of ADHD symptoms [33], illustrating the developmentally sensitive nature and non-static genetic influence of the ADHD phenotype beyond childhood.

Heritability of ASD across the life span

In comparison to ADHD, fewer longitudinal, genetically informative studies have examined the developmental nature of ASD symptoms into adolescence or even adulthood. Specifically, studies on the presence of new genetic effects occurring in late adolescence or adulthood compared to childhood—as reported for ADHD—have not yet been conducted. In addition, to what extent the different symptom domains of ASD are influenced by distinct genetic effects over time is unknown. A study reporting on the stability of genetic effects from childhood into early adolescence (12 years) reported that ASD traits were stable and there was a high degree of overlap in genetic influences across age, with shared environmental factors playing virtually no role [10]. In a small male sample of twin pairs and affected singletons (including adolescents), developmentally stable and strongly genetically determined social responsivity problems were found [4].

Shared heritability of ASD and ADHD across the lifespan

Twin studies suggest that the genetic mechanisms underlying the co-occurrence of ASD and ADHD traits may vary with age and depend on symptom domain. Low genetic correlations (0.27) between ASD and ADHD traits have been reported in 2-year-olds [27], whereas stronger genetic correlations (~0.40–0.60) have been reported in childhood age twin samples [5, 16, 20, 23, 28]. This contrast with the high genetic correlation (0.87) between ASD and ADHD in a sample of young adolescents (12 years old) [15], albeit findings in a similar age group suggest genetic correlations may be symptom domain specific [moderately strong between communication difficulties and traits of ADHD (~0.50), but low to moderate for other ASD domains (~0.05–0.30)] [31, 32]. A sample of late adolescent/young adults (18–33 years) showed a moderately strong genetic correlation (~0.70) between ASD and ADHD traits [24], albeit studies including a similar age range found lower genetic correlations (~0.20–0.60), strongest between repetitive behaviors and ADHD symptoms ([21]; see also [16]). A study including two elderly adult samples (mean age ~45 years, maximum ~75 years) revealed a prominent genetic correlation between attention problems (ADHD inattention scale and the ASD attentional switching scale) (0.80) [22]. The only longitudinal twin study mapping both ASD and ADHD traits has been conducted in children (8 years) followed into early adolescence (12 years) suggested that there was a somewhat stronger (but still modest) shared genetic load for ADHD and ASD overlap at age 8 years (~0.30) than at age 12 (~0.10) [31]. These studies demonstrate heterogeneity in the genetic overlap between ASD and ADHD and illustrate the dynamic nature of co-occurring ASD/ADHD traits across development.

Summary and conclusion

In summary, ADHD and ASD symptoms are developmentally complex phenotypes characterized by both continuity and change across the lifespan. Genetic factors co-act and interact continuously throughout the lifespan with environmental factors influencing behavioral functioning. Longitudinal twin studies on ADHD symptoms report that new, age-specific genetic effects influence both ADHD symptom domains in adolescence and adulthood. It is plausible that this holds for ASD as well, although there are currently no data to confirm this. However, all these findings pertain to heritability estimates based on statistical genetic studies (mostly twin studies). An elucidation of the relevance of identified gene variants over the age span rests on molecular genetic studies with patients followed over the lifespan. Molecular genetic studies on ADHD and ASD are only beginning to take lifespan developmental change into account. Findings on genetic mechanisms underlying ASD and ADHD in childhood years cannot be automatically extrapolated to adolescence and adulthood. Even after childhood onset, other crucial developmental phases may exist, wherein new genetic effects could become relevant in determining further development of these disorders. Therefore, a full understanding of the mechanisms behind ADHD–ASD co-occurrence requires a lifespan approach—in contrast to the current practice to focus on the childhood years.

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