

Executive Function and Genomic Risk for Attention-Deficit/Hyperactivity Disorder: Testing Intermediate Phenotypes in the Context of Polygenic Risk

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Attention-deficit/hyperactivity disorder (ADHD) is associated with cognitive, academic, and socio-emotional deficits in childhood that foreshadow a greater likelihood of negative outcomes in adolescence and adulthood (e.g., substance use disorders).¹ The devastating and far-reaching impact of ADHD, coupled with its widespread and increasing prevalence, has inspired extensive efforts to understand its etiology in order to improve a heterogeneous nosology as well as its prevention and treatment. Twin and family-based studies suggesting that ADHD is among the most heritable psychiatric conditions (up to 80%)² highlight the need to understand genomic factors in its etiology.

Disarticulating the molecular genetic architecture of ADHD, along with other forms of psychopathology, however, has proved challenging. Initial genome-wide association studies (GWAS) of ADHD produced no significant loci,³ and promising candidate gene results have not been reliably replicated.² Such difficulties, combined with realizations that the effects of individual common variants associated with psychopathology and related intermediate phenotypes (e.g., brain volume) will necessarily be small (e.g., odds ratios < 1.1; with few exceptions, e.g., APOE rs429358, rs7412 haplotypes and Alzheimer disease) has facilitated unprecedented collaborative team science to conduct GWAS on federated independent samples.⁴ The results of such efforts have been transformative. For instance, in a meta-analytic GWAS of 36,989 individuals with schizophrenia and 113,075 controls, the Psychiatric Genomics Consortium (PGC) found 108 independent loci associated with schizophrenia with further translational research identifying potential molecular and neurodevelopmental mechanisms.^{5,6} The latest PGC effort for ADHD, which is available in preprint form, contained 20,183 individuals with ADHD and 35,191 controls, and identified the first genome-wide significant loci for ADHD ($n = 12$; odds ratios ranging from 1.08 to 1.20).⁷ Independently, the results of such well-powered discovery GWAS provide flag posts for single proteins within pathways that represent promising etiologic mechanisms and treatment targets.⁸ The influence of such discovery GWAS on subsequent research has been enhanced by a data-sharing approach spearheaded by the PGC, in which summary statistics for every locus tested in a GWAS are shared with the broader research community (<https://www.med.unc.edu/pgc/results-and-downloads>). These single-nucleotide polymorphism (SNP) statistics can be applied to independent samples in the form of polygenic risk scores that estimate individual participant genomic risk for a particular phenotype by weighting the genotype at each locus by the discovery GWAS-derived association and then averaging across all SNPs in the genome.⁹ Most importantly, this approach allows researchers to test putative mechanistic pathways through which genomic risk may manifest.

One prominent model of ADHD contends that deficits in higher-order executive function (e.g., working memory, response inhibition) represent intermediate phenotypes that lie along a mechanistic pathway through which genetic and/or environmental (e.g., lead exposure) risk for ADHD translates to its clinical expression.¹⁰ The plausibility of this model is bolstered by longitudinal work suggesting that deficits in cognition temporally precede the development of ADHD symptomatology¹¹ as well as evidence from twin studies that ADHD and executive function are undergirded by the same latent genetic architecture.¹² In a compelling and important extension of this research, a report by Nigg *et al.*¹³ in this issue of the *Journal* shows that the association between polygenic risk for ADHD and its expression is partially accounted for by deficits in executive function. Broadly, these results support theoretical arguments that cognitive phenotypes may represent a mechanism through which genomic risk translates to ADHD expression, and suggests that therapeutic efforts targeting cognition are a promising prevention approach.

In their study, children 7 to 11 of age who did ($n = 435$) or did not ($n = 221$) meet criteria for ADHD were recruited from the community into a study of executive function and ADHD genetic risk. To confront the difficulties of ADHD assessment, the study adopted a rigorous multi-informant procedure incorporating evaluations of ADHD symptomatology according to clinical interview and observation (parent and child) as well as parent and teacher report of child behavior. Eligible children completed a neuropsychological battery designed to assess 5 executive function constructs—working memory, vigilance/arousal, output speed, response inhibition, and temporal processing—each represented by latent factors (with the exception of temporal processing, which was represented by a single measure). Polygenic risk was calculated based on summary statistics provided by the largest meta-analytic GWAS of ADHD to date.⁷ The multimodal study design allowed Nigg *et al.* to implement a powerful test of a core tenet of the intermediate phenotype research conceptualization: namely, does an intermediate phenotype, in this case executive function, provide an indirect pathway linking genomic risk for ADHD to its expression (or, put another way, does executive function mediate this association)? Furthermore, their extensive evaluation of executive function permitted a domain-specific investigation using latent variables, which, because they capture shared variance across measures, frees them from measurement error introduced by individual task reliability concerns.

The results of this study show that polygenic risk for ADHD is associated not only with ADHD but also with working memory and vigilance/arousal, even after accounting for multiple testing. Furthermore, using a mediational framework, the authors find support for an

intermediate phenotypic conceptualization by showing that working memory and vigilance/arousal indirectly link polygenic risk for ADHD to its expression, accounting for 43% and 49% of this association, respectively. These results support early evidence from twin studies that the genetic architecture underpinning ADHD and executive function is shared. More speculatively, alongside evidence of temporal precedence,¹¹ as well as abundant caution that nonexperimental tests of mediation can in no way establish causation, these results raise the intriguing possibility that genomically conferred risk for ADHD may mechanistically arise, at least partially, due to its impact on working memory and vigilance/arousal. Notably, the other domains of executive function assessed (i.e., inhibition, output speed, temporal processing) showed similar directions of association with polygenic risk, but did not survive multiple test correction.

There are, of course, several limitations of this study, as well as a host of future directions that this study inspires. First, it remains unclear whether polygenic risk for ADHD is associated with executive function deficits in a domain-specific manner. In this study, the authors tested only whether specific components of executive function (e.g., working memory) are associated with ADHD polygenic risk and disorder expression. A compelling way to more fully test whether deficits may be domain specific is to evaluate whether unique aspects of specific executive functions are predicted by ADHD polygenic risk after accounting for domain-shared contributions represented by a general executive function latent variable. Similar approaches have been used to test whether polygenic risk scores for psychopathology are uniquely associated with specific substance involvement (e.g., alcohol), after accounting for general substance involvement liability.¹⁴ In the present study, significant correlations across tasks within different domains, as well as similar associations across domains with ADHD polygenic risk scores, raise the possibility that the executive function deficits seen here may not be domain specific. Given that this study was composed of a relatively small sample size for investigating cross-trait polygenic risk score associations, where one could expect to explain 0.01% to 3% of the variance currently,⁹ the nonsignificant associations with specific domains of executive function might represent false negative results. Second, polygenic risk score approaches are arguably most useful in unselected (i.e., not case-control) samples, because they allow for the testing of potential mechanistic pathways free from disorder expression and its confounds (e.g., medication use) in larger samples. In the present study, it remains possible that the associations between ADHD polygenic risk scores and executive function may be attributable to the expression of ADHD symptomatology (i.e., instead of executive function mediating the association between ADHD polygenic risk scores and ADHD expression, the expression of ADHD may mediate links between ADHD polygenic risk scores and executive function). Although longitudinal data permit speculation that executive function deficits precede the expression of ADHD, the design of the current study, in isolation, leaves open the possibility that the presence of ADHD symptomatology or its correlates leads to deficits in executive function, which are, in turn, indirect links to ADHD polygenic risk. Extending these data to samples not enriched for ADHD would be informative in this context.

It is also important to consider limitations common to all studies using a polygenic risk approach. Practically, cross-trait polygenic risk score prediction remains relatively poor, with most current estimates explaining at most 3% of variance.⁹ Better-powered discovery GWAS will undoubtedly improve such prediction by providing more precise estimates of association, as has been exemplified by progress in schizophrenia research.⁵ However, in the meantime, emerging analytic techniques, such

as MTAG, or Multi-Trait Analysis of GWAS,¹⁵ which harnesses the genomic correlation of related traits to improve the precision and power of GWAS associations, may also be used to improve polygenic risk score-based estimates.⁹ Second, because polygenic approaches represent risk aggregated across the genome, they provide no insight into the molecular architecture of risk and, as such, cannot pinpoint targetable or actionable molecular pathways.¹⁶ Although this study shows that genomic risk for ADHD is partially accounted for through genomic effects on executive function, the pathways underlying this genetic association remain unknown. In addition, although biologically informed approaches to represent polygenic risk are available, they are often constrained by relatively poor priors.¹⁶ Perhaps most intriguing from a mechanistic framework are developments that have allowed the heritability of single traits to be functionally partitioned.¹⁷ Partitioning cross-trait genomic correlations in a similar fashion might facilitate a more mechanistic understanding of pathways or genomic regions underlying shared risk.

A natural extension of this research would be to further complete mechanistic pathways. For instance, an intriguing extension might examine whether executive function-related neuroimaging metrics mediate links between genomic risk for ADHD and cognition. Similar analyses have suggested that reward-related brain function indirectly links polygenic risk for ADHD to elevated alcohol use in adulthood.¹⁸ Relatedly, given multiple non-mutually exclusive intermediate phenotype models of ADHD (e.g., executive, motivational) and a heterogeneous nosology,¹ it will be important to supplement case-control studies with extensive phenotyping of putative intermediate phenotypes for joint comparison and integration. Furthermore, twin research showing that different clinical presentations (e.g., predominantly hyperactive versus inattentive) have substantial shared but also unique genetic architecture¹⁹ suggests that approaches combining heterogeneous presentations of ADHD (as in anxiety disorders),²⁰ as well as stratified analyses or more homogenous recruitment strategies (e.g., as has been done in depression),²¹ may both be informative.

Overall, the findings reported by Nigg *et al.* represent an important advancement in our understanding of how the polygenic architecture of ADHD may cognitively influence its clinical expression. More broadly, their report exemplifies how an intermediate phenotype perspective can be harnessed within a polygenic framework that is cognizant of statistical power as well as inherent limitations of nosological boundaries and poor mechanistic knowledge. It is integrative studies such as this that incrementally contribute to our understanding of the etiology of ADHD, which may ultimately limit the individual and societal impact of ADHD by facilitating improved identification, prevention, and treatment.

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