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The Etiology of Executive Functioning is Nature & Nurture

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Executive Function (EF) refers to the higher order cognitive control processes that influence and direct thoughts and cognitive processes. These include the ability to flexibly shift between tasks, inhibit thoughts or responses to external stimuli, and update working memory with relevant information. Notably, recent studies have found that executive functioning is a cognitive component of psychopathology and addiction(1,2). In a recent review, Miguel, Meaney, & Silveira, identified variables that can affect executive function and the development of executive dysfunction(3). Interestingly, while executive functions are highly heritable, with genetics explaining 90–100% of the variance in adolescence(4,5), EFs are also influenced by environmental factors, making the nature *vs*. nurture debate an oversimplification of the processes that lead to executive function development and dysfunction. Instead, the authors suggest that we consider dynamic gene-by-environment mechanisms that can impact executive functioning.

Heritability does not exclude environmental factors from influencing the development of Executive functioning. The authors conducted an extensive literature review on cognitive development, covering from prenatal exposure to early adulthood, to demonstrate how environmental influences during sensitive developmental periods can lead to executive dysfunction and ultimately psychopathology. For instance, exposure to prenatal deprivation and substances of abuse can reduce cognitive abilities later in life, particularly hypoxia-ischemia. Similarly, during postnatal development, violence, abuse, and environmental deprivation can all contribute to worsening executive functioning, with deprivation showing the largest effect on producing executive dysfunction. This could be due to the heavy metabolic needs of the brain to develop regions that support higher order executive functions, which are further complicated by the protracted development of these systems. Lastly, while some environments may have larger impacts on developing executive functions, cumulative exposure to environmental insults can dose-dependently worsen executive functioning. This suggests that these environments may uniquely contribute to deficits in EF, however, the authors also note that these environments overlap to such a strong degree it is difficult to account for confounding in population studies. In either sense, the evidence for environmental insults on EF development is in line with the sensitive periods of brain development. Further, these findings are well replicated across a variety of negative environments and developmental windows, meaning that despite the

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high heritability of EFs, environmental contexts will be crucial to fully grasp the etiology of EF.

To understand the mechanisms by which environments may influence EF, the authors note that the upstream genetics of EF should also be studied. Twin studies have shown that executive functions are almost entirely heritable during early adolescence and late adolescence, as measured by structural equation models of multiple EF tasks (4,5), while environmental variance becomes significant in early adulthood and late adulthood(6). Notably, executive functions remain more heritable than psychopathology in late adulthood, with significant environmental effect throughout adulthood(7). Curiously, it is the adolescence period in which EFs are almost entirely heritable and that there is increased sensitivity to environmental insult. This suggests that what underlies executive functioning development is a more complex genetic-by environment mechanism. Given the evidence of environmental influences and the high heritability and clear genetic effects on executive functioning, it is important to reconcile the high heritability of the trait with EFs developmental sensitivity to environmental insult. The authors of this review discuss several noteworthy areas of the literature that shed light on this issue.

First, with the advent of the GWAS era, the authors note that using large scale-GWAS to generate polygenic risk scores hold some promise in exploring the gene-by-environment overlap. Although few of these models have been applied to EF, they have been used in related psychiatric dimensions such as depression and ADHD. Current findings suggest that both PRS and environmental factors independently predict trait outcomes, with little evidence of complex interactions that improve prediction. However, it is important to note that PRS and environments that improve cognition are often correlated, suggesting that the heritability of EF may be partially expressed through environmental factors, i.e., gene-environment correlation. For example, a child who shows poor aptitude for inhibiting prepotent responses may lead others to be less engaged in conversations (due to a habit of interrupting). This may lead to poor conversational skills and self-control report later in development. While genetics plays a role in this scenario, the interaction with others is an environmental factor that can be modified and could make genetics appear as the primary contributing factor as genetics influenced the early aptitude for inhibition. Thus, for the case of polygenic risk scores, it is likely gene-environment correlation could explain the nature-nurture mechanism of etiology.

However, it is also possible that the PRS themselves are not sensitive predictors of gene-by-environment mechanisms. The authors argue that more complex models of gene-environment interactions may reveal the mechanisms underlying the development of executive functioning (EF). Rather than the heritable component of EF interacting with the environment, genes that are plastic to environments are more likely to contribute to the gene-environment interplay underlying EF. The authors highlight three methods that have successfully found genetic effects on depression and attention-deficit/hyperactivity disorder (ADHD) by using the degree of environmental interaction to weight single nucleotide polymorphisms (SNPs), including the Genome-wide Environment Interaction Study (GWEIS), a refined ADHD polygenic risk score (PRS), and a gene-environment module PRS. Further, the authors note that these methods can integrate with prior

knowledge on EF to generate neuro-informative scores of the inheritance of EF. For example, the authors discuss their PRS-DAT1 expression module, which interacted with perinatal hyperoxia and predicted worsening cognitive flexibility in children. These PRS can also be hypothesis-free; for instance, a PRS by environmental sensitivity score, which sums genes based on their degree of interaction with the environment, predicted ADHD and EF in children. Thus, the complex mechanisms of EF and environment interaction may require the identification of loci that have some sort of environmental plasticity and the development of the model from those loci. The authors note that it may take much larger sample sizes than a normal GWAS to estimate these environmentally sensitive effects. In their review, the authors note GWEIS researchers have discovered genome-wide environmental plastic loci for depression, but those loci fail to replicate in a separate independent sample.

Finally, While the authors discuss exploration of EF gene-by-environments using PRS developed from ADHD and educational attainment, recent work has uncovered the molecular structure of EF. In a previous GWAS of executive functioning (also published in *biological psychiatry)* using a sample of ~425,000 middle aged individuals from the United Kingdom Biobank (UKB), the authors elucidated the mechanisms underlying executive functioning. Some of these mechanisms are emerging psychopharmacological pathways, such as *DRD2*, GABA-a pathways, and NMDA pathways. Both this GWAS and the authors review concluded that candidate genes, such as *5HTTLPR*, *DRD3*, *DRD1*, and *DISC*, have been extensively studied but have rarely shown significant relationships with EF or psychopathology in well-powered samples, despite their prominence in the literature. Here, it is worth noting the that the gene-by-environment associations with EF GWAS data have never been tested. While proxies are used throughout the review to discuss the potential of gene-by-environment overlap, Future studies can now more directly focus on exploring the genetic architecture of EF and environmental plasticity thanks to large scale studies like the United Kingdom Biobank and the CHARGE consortium(8). This uniqueness means that we may find genes that can create informative expression networks in order to build neurological PRS that show environmental sensitivity to the environment using GWAS of EF specifically. Further, the large sample size of the UK biobank is more than 3X the sample of the largest GWEIS study discussed in the review, suggesting increased power to explore genes plastic to environments.

Understanding the etiology of executive functioning is essential for comprehending the etiology of psychopathology, and the authors have presented a compelling analysis of the current state of research in this area. Readers should take away a belief that gene-by-environmental processes are a worthy area of future study in the EF literature. By taking a more nuanced approach to gene-environment interactions, we can gain a deeper understanding of the complex mechanisms underlying executive function development and more effective strategies for addressing related psychopathologies.

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