Biological Psychiatry: Celebrating 50 Years

Commentary

Epigenome-wide Associations With Attention-Deficit/Hyperactivity Disorder in Adults: The Need for a Longitudinal Life Course Approach in Epigenetic Psychiatry

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Considering that attention-deficit/hyperactivity disorder (ADHD) is generally viewed as a neurodevelopmental disorder, we have little understanding of the developmental etiology of ADHD and the dynamic nature of the underlying biology across the life course. Illustrative of this is the fact that ADHD is the most common psychiatric disorder in children, with prevalence rates ≥5% (1,2), but ADHD research in adults has been relatively unexplored.

Although twin studies suggest a heritability of 74% (3), it is likely that ADHD symptoms are the result of a complex interplay between genetic and environmental influences with a strong developmental component. It is therefore not surprising to see a slow but steady rise in studies investigating epigenetic correlates of ADHD, such as DNA methylation, that are assumed to represent developmentally dynamic interactions between genetic and environmental factors.

Most studies have focused on candidate genes in cross-sectional pediatric samples. Such designs, however, limit our ability to understand whether methylomic correlates of ADHD remain stable over time or are dynamic in nature, where different biological systems are implicated at distinct developmental periods (Figure 1A). In the latter case, only a fraction of all implicated genes or systems would be detectable at any single time. To fully understand the developmental processes linked to ADHD symptoms we need epigenetic studies in which methylation and ADHD symptoms are measured across development from birth to adulthood.

All three previous epigenome-wide studies on ADHD (4–6) have concentrated exclusively on children, and two of these studies were prospective, predicting ADHD symptoms in children through DNA methylation measured at birth. What seems to have emerged from this research is the fact that DNA methylation patterns measured at birth in cord blood are more predictive of ADHD symptoms during childhood compared with more temporally proximal methylation measured at 7 years of age. This suggests a methylomic system at birth whose detectability in blood fades away during childhood. So far, however, we can draw no conclusions as to whether these or other biological systems emerge again in adulthood.

In this issue of *Biological Psychiatry*, van Dongen *et al.* (7) studied blood-based methylomic correlates of ADHD symptoms in adults using data from three different large cohorts with a combined sample size of 4689 adults. The authors investigated the association between 394,194 methylation probes and self-reported symptoms of ADHD using data from the E-Risk Study (mean of 18 years of age at blood sampling), the Netherlands Twin Registry (mean of 37 years of age), and the Dunedin Study (mean of 38 years of age). The study's hypotheses were that peripheral DNA methylation might provide insight into 1) "epigenetic consequences of life conditions that correlate with ADHD symptoms," 2) "epigenetic mechanisms" of ADHD, or 3) epigenetic mechanisms that correlate with "causal mechanisms in the brain." Study-specific results were meta-analyzed across cohorts, followed by a range of sensitivity analyses related to ADHD subscale-specific effects, enrichment of epigenetic or genetic loci predictive of other psychiatric disorders, differentially methylated regions, and gene expression.

Considering the sample size, it might be surprising that van Dongen *et al.* (7) reported mainly null findings. Although some suggestive CpG-specific or regional effects were identified, these showed some degree of heterogeneity across cohorts and did not replicate across datasets. Several differentially methylated regions partially overlap with those linked to smoking initiation or exposure to maternal prenatal smoking, but less so with genetic or epigenetic markers for depression or autism. None of the methylation markers previously identified to be linked to ADHD symptoms in children were replicated in the current study.

The sample size and meta-analytical approach are clear strengths of the current study, which also for the first time concentrated on adults with ADHD symptoms. Two patterns emerge when considering the study's results and including previous research findings. First, if there are epigenetic consequences of ADHD-linked life conditions, these might be linked to smoking exposure (although future studies should consider widening their search space beyond the five traits that were investigated in the current study). van Dongen *et al.* (7) are cautious about a causal interpretation of this finding, which could be the result of residual confounding or shared biology. Indeed, the evidence of smoking as a causal risk factor for ADHD is limited. In fact, Mendelian randomization studies rather suggest the reverse—that childhood ADHD appears to be a risk factor for smoking initiation (8). This implies that the overlap between methylation signals for smoking and ADHD might be indicative of pleiotropic or confounding effects—or, indeed, of smoking as a downstream effect of ADHD rather than a cause for disease.

Second, while we still do not fully understand the epigenetic mechanisms of ADHD, findings from the current study suggest

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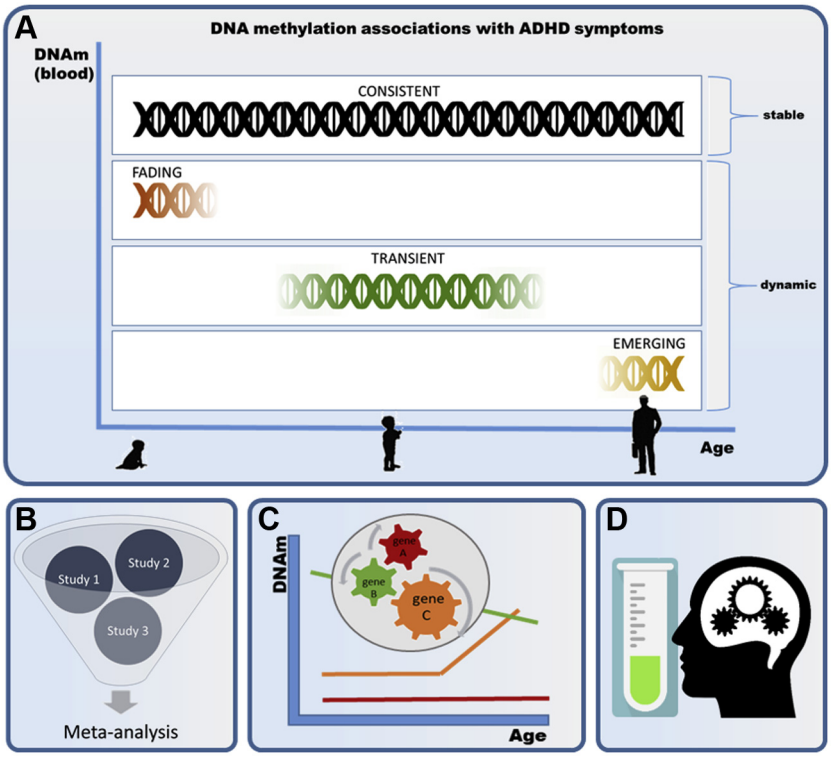

Figure 1. **(A)** Possible models describing the relationship between DNA methylation (DNAm) and psychiatric traits, such as attention-deficit/hyperactivity disorder (ADHD), over the course of development. Methylomic correlates of ADHD could remain stable over time (top panel) or be dynamic in nature (lower three panels), where different genes or biological systems (in red, green, and yellow) are implicated at distinct developmental periods. van Dongen *et al.* (7) provide little evidence for strong methylation signals in blood that are visible during adulthood. **(B, C)** To fully understand the relationship between DNAm and ADHD across the life course, we need to **(B)** continue meta-analytical efforts as demonstrated by van Dongen *et al.* (7), combining datasets across developmental stages, and **(C)** study the changing methylome across the life course to elucidate potential interacting or cascading biological systems. **(D)** In combination, these efforts will help identify biomarkers of risk or causal mechanisms.

that blood-based methylomic signals, measured at birth and predictive of ADHD in childhood, fade away within the first 7 years of life, and neither these nor other strong methylomic signals seem to re-emerge again in adulthood.

Where should we go from here? First, we need to keep the momentum going regarding meta-analytical approaches and replication efforts (Figure 1B). van Dongen *et al.* (7) meta-analyzed results across three cohorts. Other initiatives, such as the Pregnancy and Childhood Epigenetics consortium, also pave the way toward large-scale collaborations. In the Pregnancy and Childhood Epigenetics consortium, similar efforts are currently underway to elucidate methylomic associations with mental health traits, such as ADHD across development, using the data from several thousand participants. However, such research endeavors are not easy. Large-scale meta-analyses rely on extensive collaborations, often taking several years to complete, and individual contributions are difficult to acknowledge within the current model of authorship listings. To maximize such efforts also calls for changes in research practice—e.g., establishing repositories and routines to publish complete (summary) data and re-evaluating the current standards of researcher contributions (9).

Second, we need to study the longitudinal trajectories of DNA methylation over longer periods of development (Figure 1C). A cross-sectional snapshot of methylation markers at a given time point might be less useful to shed light into the dynamic character of the methylome across the life course and its relation to ADHD. For example, it is possible that ADHD-linked methylation markers at birth set into motion a cascade of secondary processes that impact long-term methylation trajectories, which are not easily detected at any single time point during development.

Third, we must remind ourselves of what we are trying to achieve (Figure 1D). Are we searching for predictors of ADHD risk or related health conditions; for causal, mechanistic methylation markers of ADHD; or for methylomic consequences of ADHD-linked life conditions? Each aim calls for slightly different study designs, populations, and tissues. For example, while the observation of a methylation signal that fades away after birth might be true with respect to blood-based methylation signals, we do not know whether these also hold true for brain tissue. It is possible that (potentially mechanistic) methylation patterns remain stable in brain tissue across development or that new patterns emerge later in development as a result of earlier cascading processes. All we currently seem to know is that the predictive power or biomarker potential of these early peripheral signals, detectable only at birth, cease to be predictive of later ADHD symptoms after birth.

In conclusion, van Dongen *et al.* (7) provide an important contribution to the field of epigenetic psychiatry by highlighting the dynamic and transient nature of the human methylome. Future studies need to build on these findings to elucidate how longitudinal changes in the methylomic system link to psychiatric symptoms across the whole lifespan.

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Article Information

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