



Barker, E. D., Roberts, S., & Walton, E. (2019). Hidden hypotheses in 'hypothesis-free' genome-wide epigenetic associations. *Current Opinion in Psychology*, 27, 13-17.
<https://doi.org/10.1016/j.copsyc.2018.07.009>

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Hidden hypotheses in ‘hypothesis-free’ genome-wide epigenetic associations

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The recent interest in epigenetics within mental health research, from a developmental perspective, stems from the potential of DNA methylation to index both exposure to adversity and vulnerability for mental health problems. Genome-wide technology has facilitated epigenome-wide association studies (EWAS), permitting ‘hypothesis-free’ examinations in relation to adversity and/or mental health problems. In EWAS, rather than focusing on *a priori* established candidate genes, the genome is screened for DNA methylation, thereby enabling a more comprehensive representation of variation associated with complex disease. Despite their ‘hypothesis-free’ label, however, results of EWAS are in fact conditional on several *a priori* hypotheses, dictated by the design of EWAS platforms as well as assumptions regarding the relevance of the biological tissue for mental health phenotypes. In this short report, we review three hidden hypotheses — and provide recommendations — that combined will be useful in designing and interpreting EWAS projects.

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Current Opinion in Psychology 2019, 27:13–17

This review comes from a themed issue on **Genetics**

Edited by **Brian Boutwell** and **Michael A White**

<https://doi.org/10.1016/j.copsyc.2018.07.009>

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Understanding the biological mechanisms by which early psychosocial adversity associates with long-term mental health problems may have the potential to facilitate the development of effective screening, intervention strategies and health policy decisions [1]. Recent research has focused on the degree to which adversity disrupt gene regulation through epigenetic processes, thereby providing a mechanism by which the environment can have lasting effects on measurable mental health phenotypes [2**]. High profile studies suggest that epigenetic changes associated with early adversities [3,4] and even lifestyle

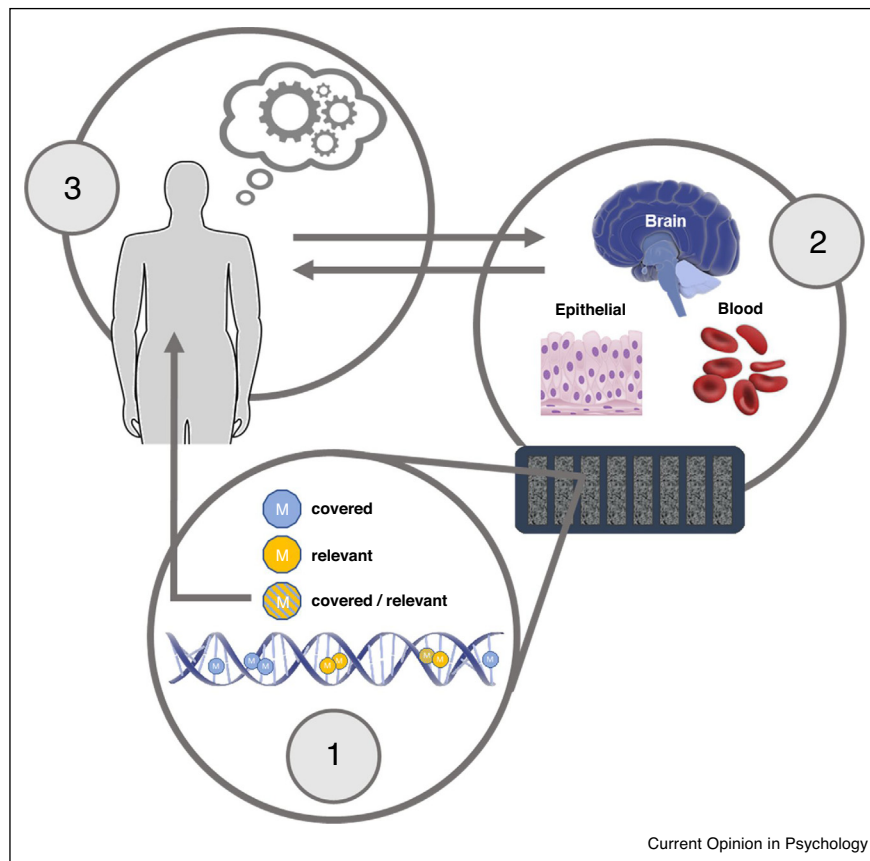
choices [5*] can be observed across the life span, and that these long-term epigenetic modifications are associated with risk for a range of health outcomes [6]. These studies have generally focused on DNA methylation (DNAm) for two reasons: it is currently the best understood epigenetic mechanism and array-based technologies are readily available, which provides coverage of hundreds of thousands of methylation sites across the genome [7]. This combination of basic science and genome-wide technology has facilitated numerous epigenome-wide association studies (EWAS), permitting ‘hypothesis-free’ examinations in relation to adversity and/or mental health problems.

The logic underlying EWAS is comparable to genome-wide association studies (GWAS [8*]). Rather than focusing on DNAm in proximity to candidate genes, the genome is screened for DNAm, thus enabling a more comprehensive representation of variation associated with complex disease. As with GWAS (e.g. [9,10]), despite their ‘hypothesis-free’ label, results of EWAS are in fact conditional on several *a priori* hypotheses, dictated by the design of EWAS platforms as well as assumptions regarding the relevance of the biological tissue for the mental health phenotypes under investigation. In this short report, we review three hidden hypotheses (see [Figure 1](#)) — and provide recommendations — that combined will be useful in designing and interpreting EWAS projects.

Hidden hypothesis 1: EWAS coverage is sufficient for complex psychiatric problems

Array-based platforms have become widespread in psychology research, largely due to their ease of use, relatively high through-put, and well standardised and validated pipelines for processing, quality control, and analysis techniques. In particular, the Illumina 450k and EPIC arrays feature 480 000–850 000 probes targeting nearly 99% of RefSeq genes, as well as a range of other genomic categories, such as CpG islands, shores and shelves, miRNA promoters and enhancers, where DNAm can be influenced by and/or impact transcription in distal genomic regions [11**]. Compared with the Illumina 450k, the newer Illumina EPIC 850k array provides much greater coverage of ENCODE and FANTOM5 enhancers [12**], and shows higher genetic influence underlying DNAm probes [13]. Nevertheless, these microarrays are limited in the number of sites they can assess, and thus lack true genome-wide measurements [14].

Figure 1



Hidden hypotheses in epigenome-wide approaches. Note: (1)=Hypothesis 1: EWAS coverage is sufficient for complex psychiatric problems; (2)=Hypothesis 2: peripheral tissue is meaningful for mental health problem(s); and (3)=Hypothesis 3: biology can be meaningful to phenotype of interest.

Furthermore, during the design process of the 450k and EPIC arrays, CpG sites were chosen as potentially biologically informative based on consultation with a consortium of DNA methylation experts [15]. Whilst the coverage of genes and CpG islands on these microarrays are comprehensive, it does not represent a complete picture of methylated cytosines across the genome. Selection was, in part, based on data from a number of phenotypes (some medical in nature such as cancer), and thus is not specifically targeted to brain-based, stress-related complex mental health phenotypes. This is an important point: if a sizeable proportion of the CpG sites tested are not relevant to the phenotype of interest, the likelihood of detecting relevant results is reduced.

Hidden hypothesis 2: peripheral tissue is meaningful for mental health problem(s)

The second hidden hypothesis relates to the tissue that is used to quantify DNAm. The majority of mental health research is based on DNAm profiles obtained from peripheral tissues from living persons, such as blood and saliva. When investigating outcomes such as conduct

disorder or depression, however, the brain is often the main tissue of interest when it comes to mechanistic interpretations of results [16**]. To this end, research suggests that the correspondence of methylation profiles from blood and saliva to the brain is in fact quite limited, but can be higher with cross-tissue genetic influence [13,17]. This presents a critical disadvantage if the investigator would like to use the peripheral tissue as a surrogate of the central nervous system (CNS; the brain).

One promising avenue is to establish DNAm as a biomarker for mental illness. A biomarker does not have to be mechanistic (i.e. CNS surrogate). Indeed, blood-based biomarkers have been used for diagnostics, predictive risk, disease monitoring and/or treatment response in cancer, cardiovascular and infectious disease [18,19]. However, even within a biomarker framework, the assumption is often that distinct peripheral tissues are interchangeable and equally suited for biomarker detection, when in fact it is highly probable that peripheral tissues themselves correspond differently to environmental adversity and/or disease state [14]. For instance,

biomarkers for mental health traits (e.g. depression) may be more detected in blood than saliva, as blood is more central to inflammatory processes related to stress and disease [16**].

Hidden hypothesis 3: biological relevance for the phenotype of interest

The last hypothesis relates to the assumption that biology can be informative to the phenotype itself. Focal phenotypes (e.g. oppositional defiant disorder, anxiety) in mental health research are often complex and multiply determined [20]. The lack of established robust biomarkers for mental health problems (e.g. [19]) may suggest that some of these traits might not strongly associate with detectable biological processes. Furthermore, effect size associations in EWASes are often very small suggesting that—while significant—distinguishing the importance of DNAm in the aetiology of the mental health phenotype may prove difficult [21**]. Perhaps unsurprisingly then, most EWAS in mental health include some form of gene ontology analysis, which queries the role of larger biological systems based on existing databases [22]. These analyses result in general statements such as ‘neurodevelopment’ or the ‘immune system’ being involved in the aetiology of a given phenotype. Whether these broad categories play indeed a substantial role in the aetiology of the mental health problem is often hard to determine given the post hoc nature of the interpretation. Relatedly, many EWASes have tried to infer downstream effects of observed variation in DNAm such as differences in gene expression. Many of these studies find very little in terms of functional relationships, but a small number do report downstream biological associations (e.g. [21**]). In general, it has proven difficult to pinpoint EWAS-related biological relevance of observed DNAm changes, even if they are in genes which seem ‘plausible’ based on reported functionality and previous literature.

Recommendation for hidden hypothesis 1: EWAS coverage

An alternative to using arrays with limited coverage is to use next-generation sequencing-based approaches to interrogate the whole methylome [21**]. However, these methodologies are high in cost and time intensive. Despite the limitations described above, pragmatic and strategic study design can maximise utility and interpretation of results of the Illumina 450k and EPIC arrays. For example, for researchers interested in targeting CpGs likely to associate with ‘brain-based’ mental illnesses, an *a priori* set of CpGs (e.g. a ‘systems approach’) could be isolated from the array data, which could still span thousands of loci. The suggestion is to prioritize CpGs within biological systems that are known to associate with variation in post-mortem brain samples [23**] or even structural or functioning brain imaging [24] if this is of primary interest to the investigator.

The second recommendation for optimising the use of EWAS CpGs is to target those probes with underlying genetic influence—methylation quantitative trait loci (mQTLs). This approach may have the advantage that cross-tissue concordance (e.g. blood, saliva, post-mortem brain) appears higher for CpGs that show cross-tissue genetic influence [13]. Another advantage of mQTLs is that CpGs under considerable genetic influence are less affected by confounds [11**,13,25]. However, while mQTLs are a worthwhile approach, it is a relatively new area and at present, there is a small proportion of methylation sites with consistently reported mQTLs [11**,13]. Furthermore, large-scale and detailed information on tissue-specific mQTLs is still sparse.

Recommendation for hidden hypothesis 2: peripheral tissue and phenotype

One strategy to maximise the interpretability of EWAS projects is to examine DNAm as a biomarker for mental health problems that have mechanistic underpinning in tissues other than the brain, such as blood. A wide-range of psychiatric disorders have been associated with immune function as measured by peripheral inflammation [26]. Furthermore, there is good evidence from animal studies, and increasing evidence in humans, that peripheral inflammatory markers can affect brain areas implicated in certain psychiatric disorders [27]. Consequently, adversity-related immune processes and DNAm may be well measured in blood samples (see [28**]). For biomarkers to be useful, they must be cost effective, drawn from accessible tissue and predictive of future risk [29]. Biomarkers for brain-based disorders (e.g. depression) have proven more difficult to establish [19]. Liu *et al.* [30] performed an EWAS on blood tissues across 13 population-based cohorts and reported that a composite biomarker (consisting of 144 CpGs) discriminated drinkers from non-drinkers. It was thus suggested that a blood-based DNAm diagnostic test could be developed. It is important to note, however, that in addition to methodological considerations [31], the Liu *et al.* study was cross-sectional, thus it may prove difficult to use this specific biomarker as a predictor of future alcohol use, as the variation in DNAm may be the result of chronic drinking (i.e. reverse causality [32]). Importantly, large-scale meta-analyses based on new and growing consortia (e.g. PACE [33**]) are beginning to report consistent epigenetic effects on traits such as schizophrenia or smoking behaviour (e.g. [34,35]) which suggests that we may begin to be able to utilise this information to further optimize DNAm biomarker approaches.

Recommendation for hidden hypothesis 3: phenotype and biology

Several suggestions have been put forward to address the complex nature of the biology that may underlie mental health problems. Most notably, the Research Domain Criteria (RDoC) initiative has proposed alternative

approaches to study mental illness by integrating many different levels of information including genetics, neurocircuits and behaviour [36]. Methylation-based research can be integrated into an RDoC perspective. Here, researchers could employ a two-stage analysis, first investigating epigenetic effects on intermediate dimensions of mental health and then, using the results as biomarkers to query the more complex phenotypes. For, example, if externalising difficulties (e.g. ADHD, aggression) are the focal phenotype, rather than performing an EWAS directly on the disorder(s), the researchers could instead, as the first step, perform an EWAS on brain imaging endophenotypes of the externalising phenotype (e.g. [24]). In the second step, the results of the EWAS could be used to create poly-epigenetic genetic biomarker score (e.g. [28**]) to be (potentially) associated with the disorder. This type of two stage of EWAS may examine the epigenetic changes associated with antecedents of diagnosable mental health conditions, which would be could be more useful as a risk biomarker than a biomarker of the actual diagnosis.

Conclusion

The recent interest in epigenetics, from a developmental perspective, stems from the potential of DNA methylation to index both exposure to adversity and vulnerability for mental health problems [2**]. To this end, there has been substantial activity in examining EWASes of adversity-related disorders, such as conduct disorder [37] and psychosis [38]. Of interest, from these EWAS, DNAm in genes that underlie stress response, neurotransmitter activity and immune regulation have been identified. These preliminary findings may provide a useful framework for more in-depth investigations—potentially as CNS surrogates or biomarkers—of the biological pathogenesis of a mental health problem. However, we argue that understanding hidden hypotheses within the EWAS is an important first step in interpreting the results in relation to mental health phenotypes.

Conflict of interest statement

Nothing declared.

Acknowledgement

This manuscript was supported by a grant from the Economic and Social Research Council (ES/R005516/2) to EDB.

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