

Whither the epigenetics of child psychopathology? Some reflections provoked by Barker et al., (2018).

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Barker et al's. (2018) review of the role of differential DNA methylation as a mechanism connecting early experience and later psychopathology is the latest in a series of recent Annual Research Review articles addressing one of the most fundamental questions in the fields of child psychology and psychiatry – *How can adverse experiences shape development to a sufficient degree and in profound and enduring ways to create long term risk for later mental disorder and disability?* Kiser et al., (2015) reviewed the possibility of trans-diagnostic epigenetic processes in the context of genome-wide genetic variation. Teicher et al (2016) looked at this in terms of neuro-biological programming as expressed in alterations in brain structure following maltreatment. McCrory et al., (2017) provided a complementary treatment relating to brain function – in particular expounding on the concept of latent vulnerability – whereby deep-seated early brain changes can sit hidden during development only to drive emergent patterns of dysfunction later on. Like its three predecessors, the Barker et al. review, (2018) is a sober masterpiece – giving the reader both a sense of the exciting potential of the field of developmental epigenetics as applied to child psychiatry (as well as an eloquent class 101 in the basic concepts and biology), a grounding in experimental animal studies and a balanced and suitably cautious account of the current state of the art. To us this confirmed the plausibility of differential methylation as an epigenetic mechanism by which adverse environmental exposures can become neuro-biologically embedded and cause disorder (even when genetic risks are absent) while leaving us tantalisingly short of the sort of definitive evidence from human studies that such mechanisms actually do make an important causal contribution to abnormal trajectories of development to disorder.

Barker et al (2018) make so many telling points about this fledgling field of science. Like all great integrative reviews, it not only summarised the evidence but also developed our conceptual

understanding - *the key challenges, recommendations and future directions* section was particularly insightful and led us to muse further on a number of points raised – especially when set alongside the papers by Kiser et al., (2015), Tiecher et al. (2016) and McCrory et al., (2017).

- a) *How much confidence can we have that the associations between adverse exposures on the one hand, and child psychopathology on the other, with differential DNA methylation patterns that have been reported to date are in fact real and robust?* The recent history of the more established fields of psychiatric genetics and brain imaging provide a cautionary tale in this regard for the new field of psychiatric epigenetics. In particular they illustrate the risk that the field can chase after what ultimately turn out to be unreliable findings created by the scientifically toxic combination of small samples and non-protocolized hypothesis-driven candidate gene or region-of-interest analyses that in the current competitive scientific environment almost inevitably lead to un-constrained p-hacking and data dredging. In this regard, psychiatric epigenetics may be able to avoid the pitfalls of its more mature scientific peers if it (i) encourages the pre-publication of protocols for candidate epigenetic markers in small(er) targeted studies of specific exposures and in secondary data-analytical studies in large epidemiological samples and (ii) bases exploratory/discovery studies solely on large scale epigenome-wide studies with careful correction for multiple testing and, ideally, internal replication. The field should no longer rely on the post-hoc justification of the plausibility of selected genes. Although, as Barker et al point out, replication of methylation findings is still the exception rather than the norm, there are some notable examples where replication has been achieved in at least one independent sample. Assessing the value of such replications, or making sense of differing findings across studies, is complicated because the studied populations often vary markedly and exposure and outcome (if they are both measured) are often not defined or measured consistently (e.g., adversity is captured in very different ways – maternal depression, maltreatment, maternal stroking etc). The direction of travel is clearly towards much larger-scale collaborative consortia and towards standardised and

protocolised measurement and analysis. Smart methodologies to filter out or triangulate the causal variants from the non-causal ones will also be important going forward.

- b) *Where the effects reported are real and robust, in the sense of statistical reliability, how can we ensure that they implicate true, causal, epigenetic effects of environmental exposures rather than genetic effects with which they are very often confounded?* Barker et al. (2018) highlight the substantial role played by genetic factors in regulating DNA methylation patterns and the putative explanatory power of models that highlight the way differential methylation in response to environmental exposures might be moderated by fixed variations in the genome. While we might think of differential methylation as an indication of environmental action, it may not be. This is of course a manifestation of the more general challenge for epidemiological studies of gene-environment correlation (rGE). Two sorts of rGE complicate the psychiatric epigenetics story. First, there is passive rGE whereby genetic factors shared by the child and their parent determines both the adverse exposure experienced by the child (as shaped by the behaviour of the parent) and the child's long term outcomes. Such outcomes have typically been thought about in relation to psychiatric symptoms or even cognitive deficits but epigenetic effects could equally be controlled by such shared genetic factors. The methylation QTL approach (methylation sites strongly associated with genetic variation) mentioned by Barker et al. is therefore important, but even this is likely to capture only a small proportion of the total heritability of DNA methylation. Second, there is evocative rGE whereby children's genetically determined traits drive changes in the environment which in turn then have the potential to shape epigenetic profiles. So, for instance, ADHD, which in itself has a strong genetic character, may under certain circumstances evoke a hostile and potentially stressful social environment which may lead to secondary epigenetic effects in susceptible individuals. In Barker et al (2018) this is referred to as reverse causation (ADHD causing adverse exposures, leading to correlated epigenetic change). Another possibility is that causation is circular, in the sense that adverse exposures, though evoked

by a genetically influenced trait, nevertheless have causal effects on the later course or outcome of disorder, via epigenetic mechanisms. Ingenious longitudinal genetically informed designs that can segregate genetic and environmental risks are required to disentangle genetic and epigenetic effects.

- c) *How much do epigenetic signals drawn from peripheral tissues really reflect brain-based epigenetic effects?* Even more fundamental than the challenge of separating genetic and environmental influences is the widely recognised constraint on inference due to our reliance on peripheral tissues to measure DNAm which means we are almost always measuring DNAm proxies of the real causal agents, so further research investigating the connections between central and peripheral DNAm is vital.
- d) *What differentiates normative epigenetic processes that promote healthy development through adaptation and learning from the putative destructive epigenetic effects that derail development and cause disorder?* Barker et al. (2018) highlight the essential role of DNA methylation in keeping normal development on track. We have written recently about the double edged sword-like quality of brain plasticity – with both positive and negative impacts (Sonuga-Barke, 2017). The same applies to epigenetic processes such as DNA methylation. Where is the tipping point when positive epigenetic effects of methylation underpinning normal development turn negative and derail development? In trying to understand this, two neuro-developmental concepts may be usefully applied. The first is experience-adaptive programming whereby the organism adapts to the developmental context on the assumption (made, as it were, by evolution) that current environmental conditions are predictive of future ones – helping the organism more efficiently marshal biological resources to ensure survival later in development. Although not referred to in this way explicitly, it is this sort of model that underpins the seminal work on the NR3C1 (glucocorticoid receptor) gene studies (Weaver et al., 2004). The second is experience-expectant programming – which builds on the assumption that human infants require particular experiences to develop properly and where the lack of essential experiences during sensitive periods leads to disorder and dysfunction (see

McLaughlin, Sheridan, & Nelson, 2017 for a recent formulation). Understanding the role of epigenetic processes generally and DNA methylation in particular in the negative effects of experience-expectant processes, and differentiating them from experience-adaptive effects should be an important focus for future research.

Understanding these mechanisms requires two developments in the field. The first is better understanding of the bio-ecological contexts that these experience-driven mechanisms were adapted to. This is where animal research, and evolutionary models, are particularly important. The classic work by Weaver et al (2004) on glucocorticoid receptor gene regulation and maternal care provides an excellent example of what can be achieved in the latter mode. The second relates to how the organism senses relevant environmental changes, and transmits that information into signals that lead to orchestrated changes at the level of the epi-genome. This is critical, because a better understanding of that will also help us identify the precise environmental drivers.

- e) *Are there periods in development where epigenetic adaptations are most potent pathophysiologically and their effects on development most marked and persistent?* This question follows directly from consideration of the two epigenetic mechanisms of the effects of environmental exposures described above. This is because both explanations require the concept of a sensitive developmental period during which exposures will have especially powerful effects. Such a concept applies most obviously to the notion of experience-expectant effects on gene expression – where there is explicit reference to experiences tied to particular developmental windows. One obvious example relates to the concept of selective attachment – those naturally occurring patterns of reciprocity and selective comfort seeking that first appear in the second half of the first year of life, and are believed to play an important role in the child's healthy future development and secure sense of self (Bowlby, 1969). Little is known about the role of epigenetic processes in determining the effects of the absence of such selective attachments. However, the concept of the sensitive period also allies to the idea of experience-adaptation because it implies a 'setting' of an organism's psychobiological trajectory

such that it cannot be remodelled over time when exposed to different (e.g., enriched) environmental circumstances. In reality, given the complex and heterogeneous nature of adversity and its effects, it is likely that both experience-adaptive and experience-expectant epigenetic mechanisms are important in the long terms effects of adversity. This may help us understand why DNAm probes at birth may predict later ADHD symptoms (Walton et al., 2017), even when those same probes are not associated with ADHD symptoms contemporaneously.

- f) *Where does DNA methylation fit into the big picture of biological mechanisms regulating development?* In considering these different processes – both normative and non-normative, Barker et al make the crucial point that it is important to place the issue of DNA methylation in particular and epigenetic modifications of gene expression more generally in a broader biological context. How organismic changes in response to environmental circumstances are realised biologically is highly complex and multifaceted. For example, while it might not always be the first example we would bring to mind in this context, learning is a profoundly important biological process via which organisms adapt to meet environmental demands. Such changes take place in differentiated and localised neural circuits, involving highly orchestrated patterns of gene regulation. And learning is just one part of a whole class of mechanisms that allow organisms adapt to environmental circumstances that change too rapidly for genetic adaptation to track. Other, partially overlapping, adaptations of course include changes in noncoding RNA expression, hormone production, receptor density, vascularization, microglial function, cell-cell communication, larger patterns of structural and functional neuronal connectivity, structures of information processing and high-level cognition and so forth. Any read-out of a methylation signal must surely only give us a small clue about how the biological changes occur, as opposed to representing the whole of the mechanism itself.

In summary, this brilliant review by Barker et al. helps us to make sense of, and gain perspective on the potentially bewildering array of recent epigenetic findings by getting us to reflect on the very substantial methodological challenges inherent in developmental psychiatric epigenetics and the biological complexity of implicated processes. In this way it is able to both whet our appetite for the scientific adventures to come as we try to piece together this complicated story while giving a realistic appraisal of the exciting progress made so far.

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