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Epigenetics: comments on Sokolowski and Boyce

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Introduction

The four linked papers by Sokolowski and Boyce review the relationship between genes, environment and behavioural, psychological and neurodevelopmental outcomes, summarised as two opposing states: ‘vulnerability’ and ‘resilience’. The focus of their chapter is epigenetics, defined as “the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence.”[1] At its core are a set of small molecules that sit on top of (epi) our genes (genetics) and by doing so influence the molecular machinery that regulates gene activity. Changes in the distribution of the sum total of epigenetic molecular marks throughout the genome (the epigenome) drive early development of humans as well as all other multicellular organisms. Such developmental changes, from the single-celled zygote, through to the differentiation of hundreds of different cell types in humans was historically termed ‘epigenesis.’[2,3]

Epigenetic marks are themselves influenced by genetics and environments, both externally to, and within individuals. One of the main goals of epigenetics research has been to understand how environment influences the activity of our genes and how this can predispose states of health or disease.[4] As the first one thousand days of human life are especially sensitive to

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environment, much of the research in the area has focused during this time period and equivalent periods in animal models.[5,6] These four papers discuss and expands upon the above-mentioned concepts and cites milestone studies that have begun to assign the epigenetic state of specific genes to specific earlier environments and late states of resilience and vulnerability (fragility). The authors explain how the field of epigenetics is still in its infancy and point the way forward to future studies. Most importantly, they discuss the implications for medical tests and interventions, and for policy.

Research and Conclusions

In ‘Biology of the Epigenome’, Sokolowski and Boyce introduce epigenetics, initially in lay terms, then building in more technical terms, including specific mechanisms, namely DNA methylation, histone modification and non-coding RNAs. They discuss the history of the use of the word ‘epigenesis’ that was used to describe the process of human development and its current usage as ‘epigenetics’. One minor omission is the citation of Aristotle as the originator of the term ‘epigenesis’.[2] The authors review studies that have shown that the one thousand days following conception is the time when we are most vulnerable to environment-induced epigenetic change. They rightly indicate that knowledge of disease-specific epigenetic states will lead to a better understanding of disease mechanisms and, more important for policy, to disease-specific biomarkers. They cite autism spectrum disorders as one example of a brain-related disorder that has been investigated using epigenetic methods, although they don’t mention that such research has not yet led to diagnostic biomarkers, most likely due to the methodological differences between studies. Finally and importantly, they briefly detail the challenges of epigenetic research, which include choosing the most appropriate and convenient tissue with which to analyse in relation to resilience and sensitivity; how to separate cause and effect; and the importance of analysing multiple epigenetic mechanisms to provide a more complete picture of epigenetic state.

In ‘Gene-Environment Interplay and Epigenetic Processes’ Sokolowski and Boyce discuss, in a clear and concise way, how genes and environment interact and focus on epigenetics as one proven example. However, there was probably no need to discuss DNA sequence-environment interactions, although such studies have shed light on studies of mood disorders.[7] In addition, more examples of specific studies of environment-induced epigenetic change could have been provided, although such studies are featured in the following paper by the same authors. The authors are correct to point out that epigenetic marks can be affected by genetics as well as

environment, and by an interaction of both.[8] Conclusions and implications for this paper focus on understanding the effects of early life social interaction but are not as strongly phrased as the previous paper.

In ‘Epigenetic Embedding of Early Adversity and Developmental Risk’, Sokolowski and Boyce discuss how epigenetic changes can mediate the effect of early life adversities such as poverty, neglect and trauma, on risk for disorders of mental health, educational achievements and chronic disorders in general. They focus on the question of whether, using epigenetics, we will be able to predict which children are more likely to be resilient or vulnerable. By detecting both kinds of children, resources and interventions can be focused on the latter. The authors review a few animal studies that have linked early life adversities such as neglect, maltreatment and social dominance on neurodevelopment and on endocrine and immune systems, all of which appear to be mediated at least in part through epigenetic change. They also review human studies linking early life adversities such as famine, abuse, institutionalisation, and socioeconomic disadvantage with epigenetic change in neurodevelopmental pathways. They reiterate the challenges mentioned in their first paper. What was missing, however, was a discussion on the social implications of epigenetic tests themselves, as studied by others.[9,10] For example, would a positive test result for vulnerability stigmatise both parents and offspring and raise these children’s future insurance premiums?

In their final paper, ‘Epigenetics and the Role of Developmental Time’, Sokolowski and Boyce discuss the issue of how developmental timing can influence epigenetic state and brain plasticity. In particular, they focus on the emerging topic of how the pre-conceptional environments of parents could be passed down to their children through epigenetic processes. They again provide key examples from animal and human studies. One pertinent example is that children of holocaust survivors who developed PTST have epigenetic alterations with a gene involved in response to stress. The authors rightly mention that most epigenetic marks are completely reset twice per generation, during early somatic and germ cell development, and that we don’t currently know which genes escape this resetting.

In summary, Sokolowski and Boyce bring their readers up to speed with the history and mechanisms of epigenetics, focusing on how epigenetic state in early life environment can be influenced by social, biological and physical environments, to predispose individuals to vulnerability or resilience. They argue that epigenetics research has tremendous implications for policy at many levels.

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Implications for the Development and Policy

Clearly, there is a wealth of evidence to indicate that adverse environments during pregnancy, childhood and adolescence, can confer risk for adverse mental and physical health and that many of these environments are mediated by epigenetic change. This has several policy implications. The first is that children and adolescents should be provided with optimum environments by parents and, more importantly, by society, to maximise resilience and minimise vulnerability. In doing this, instead of pointing the finger of blame at parents and children, we should target as many resources as possible to provide both with resources to nurture resilience. Such resources will be specific, e.g. guidelines on raising resilient children, and general, such as government investments targeting families of low socioeconomic status. As studies linking epigenetic state to future states of resilience and vulnerability are replicated across multiple cohorts and countries, it will become feasible to test children of all ages to predict those who are likely to benefit from targeted interventions. However, before such tests are undertaken, all stakeholders, especially current and future parents, should be surveyed about their attitudes and concerns of such tests. In addition, discussions need to be had about a positive test result for vulnerability, which could result in stigmatisation and discrimination from other children, from schools, and from their future employers and insurers.

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