

Early life trauma, DNA methylation and mental illness

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The aetiological factors that result in severe mental illness - schizophrenia, bipolar disorder and depression - are complex and remain poorly defined. Genetics certainly play an important role; there is strong evidence for heritability in each of these disorders with estimated contributions ranging between 30-50% for depression [1] and 60-80% for schizophrenia [2]. This genetic aetiology mainly derives not from single genetic mutations but from the additive or interactive combination of many genetic risk factors that contribute to the development of these diseases. However, so far we can only account for a very small proportion (currently estimated <8% for the 100+ risk genes in schizophrenia) of the total genetic risk [2]. In addition to these mainly unidentified genetic risk factors, environmental influences are also thought to contribute to the eventual emergence of symptoms that result in a psychiatric diagnosis.

The environmental risk factors for psychiatric disease are numerous and varied. For example, the risk of schizophrenia is increased in early life adversity – including exposure *in utero* to starvation or influenza and complications during childbirth – as well as in those who use cannabis intensively in early adolescence [3]. A variety of other influences can increase disease risk; a factor common to many of these environmental risks for the development of psychiatric disorders is stress. Stress, both recent and in early life, is a well-established risk for depression, and early life stress such as childhood trauma is recognised as important in several other disorders including schizophrenia [4] and, outside psychiatry, diabetes and cardiovascular disease [5].

The mechanism that these disparate influences have in common may relate to their effects, direct or indirect, on the developing brain. Strongly implicated in stress responses is the hypothalamic-pituitary-adrenal (HPA) axis, both controlling and regulated by cortisol secretion. A dysregulation of this system occurs following chronic stress, which may then affect the developing brain to result in dysfunction later in life, manifesting as mental illness.

One can envisage that such environmental factors might have a greater or lesser influence on brain development depending on the genotype of a particular functional polymorphism - a gene-environment (GxE) interaction. Thus genetic polymorphisms may modulate the influence of environment on the developing brain (and vice versa) and thereby on the consequent emergence of psychiatric disease. Such interaction is not the only way in which environment and the genome may interact to affect function of the brain. Epigenetic factors such as DNA methylation - essentially enzymatic transfer of a methyl group to a cytosine residue in a CpG sequence of DNA - can have a direct effect on the genome by affecting gene transcription. CpG islands, sequences with a relatively high density of CpG sites, may be found in 5'-regulatory regions. Here an effect of DNA methylation is to modify or suppress the binding of transcription factors to regulatory sequences resulting in changes to the expression of gene products. The same effect on transcription factor binding may be true, of course, of genetic polymorphisms in those DNA sequences. While we can consider such polymorphic sequence variability as immutable and a heritable risk, DNA methylation may influence expression in similar ways but can be dynamic and reversible, driven by the activities of methylating and demethylating enzymes, and potentially providing an opportunity for therapeutic intervention.

As well as a growing body of research demonstrating differences in DNA methylation in a breadth of somatic and psychiatric diseases, there is accumulating evidence to show how multiple environmental influences including drug treatment and drug abuse, exercise, psychotherapy and psychological stress can influence methylation of specific genes.

DNA methylation is one mechanism that could mediate the effect of early life stress on neuronal function, resulting eventually in psychiatric disorder. There is much evidence for this, with many implicated candidate genes. One established finding in people with depressive illness is abnormal methylation of the glucocorticoid receptor gene (*NR3C1*) involved in the HPA axis, which is contributing to a dysfunctional stress response and is associated with stressful events in childhood [6]. A further well-studied gene is that coding for brain derived neurotrophic factor (BDNF), in which regulatory sequences are hypermethylated in depression [7]. BDNF is a critical factor in maintaining normal neuronal function; BDNF deficits may result in neuronal atrophy and much evidence supports a dysfunction of BDNF in depression. These two systems, BDNF and the HPA axis, are closely related: stress can suppress the expression of BDNF [8].

Several models of depression rely on stressful challenge in adult animals, such as learned helplessness and chronic unpredictable mild stress, and they can also result in changes in DNA methylation [9]. In addition, aspects of psychiatric disease can be modelled by early life stress in rodents, including the effects of brief periods of maternal separation of new-born animals or more chronic post-weaning rearing in isolation rather than in social groups. These are considered to mimic symptoms of depression and schizophrenia respectively. They have also demonstrated changes in DNA methylation specific to many implicated candidate genes, of which *NR3C1* and *BDNF* [10, 11] are just two examples. This can be valuable in providing an understanding of the findings in humans. While in such human studies the direction of causality between DNA methylation and disease symptoms may be unclear, animal studies have shown that stressful events early in life can produce equivalent changes in DNA methylation, indicating a sequence of events in which early life stress induces changes in DNA methylation which may then contribute to psychiatric disorder.

The relationships between stress, methylation and disease are not necessarily straightforward. This is exemplified in a recent study of both patients with first-episode schizophrenia and rats undergoing isolation rearing as a model of the disease [11]. Increased methylation seen in a much-studied regulatory sequence in *BDNF* exon IV in DNA from the animal brains indicates a clear causal relationship between isolation-induced early life trauma and *BDNF* methylation. Methylation in the equivalent sequence in schizophrenia patients was also found to be correlated with the reporting of childhood trauma, which is more frequent in the disease group, although a significant association between methylation and schizophrenia was not seen. Here then we have a biological correlate of the environmental risk factor which, if not an epiphenomenon, presumably interacts with other factors, particularly genetic, to result in the development of disease symptoms.

The study of DNA methylation following childhood trauma and adversity is providing a biological link between two historically different, if not antagonistic, fields of psychiatry. Biological psychiatry has long struggled to accommodate psychotherapy - and *vice versa*. Yet

such talking therapies have, for depression at least, an equivalent efficacy to pharmacotherapy, although they appear to be effective in different subjects. People with depression following early life trauma have a poor response to antidepressant drugs [12] but respond relatively better to psychotherapy [13]. Interestingly, effects on DNA methylation have been observed following psychotherapy [14] and thus might mediate such treatment-induced improvement in symptoms, reversing disease-associated deterioration following early life trauma.

A major concern in human studies relating to brain function is the limited access to the target organ. Apart from a few post-mortem studies, human DNA methylation research inevitably uses DNA isolated from peripheral sources such as blood or buccal cells; that DNA methylation is to some extent organ-specific questions the extrapolation to effects on brain function [15]. How big a problem this is remains unclear; it is sometimes addressed by citing evidence indicating concordance in levels of, and changes in, methylation of specific sites between brain and peripheral tissues, although differential influences have also been seen. Nevertheless, abnormal findings of peripheral DNA methylation associated with developmental adversity and potentially relating to psychiatric disease risk are empirically meaningful [16], whether or not we fully understand how they influence or reflect mental function. A further problem comes from difficulty in the retrospective determination of early life adversity or trauma resulting in stress, which may suffer from reporting bias of the proband or relative. Only long-term prospective studies can fully and effectively address this limitation to research.

Thus there is still much to learn. As I have implied, there is substantial evidence demonstrating the effect of various early life adversities on DNA methylation, and of the association between methylation and psychiatric disorders yet, as others have pointed out [17], little research has attempted an integration of both these steps. Nor has there been much focus on identifying the molecular mechanism – such as effects on transcription factor binding – underlying the consequences of changes in DNA methylation, an essential step towards therapeutic intervention. Nevertheless this rapidly expanding field of research is providing us with new and exciting findings that are leading to a better understanding of the complex relationships between environmental stress, genes and the development of severe mental illness.

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