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Review article

Role of epigenetic factors in the development of mental illness throughout life

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ABSTRACT

Psychiatric disease is believed to result from a combination of genetic vulnerability and environmental influence. At the crux are epigenetic modifications, which mediate the influence of environment on the genome. Twin and genome-wide association studies demonstrate a wide range of heritabilities across psychiatric disorders, while epidemiological and animal models implicate distinct developmental windows where environmental factors may interact with genetic vulnerability to confer risk. Certain developmental periods appear to be more prone to these influences including during gestation, in the early postnatal period, and during periods of major hormonal rearrangement. Here we review the role of environmental factors capable of epigenetic reprogramming during these periods and present evidence for the link between these modifications and disease. The cross tissue relevance of environmentally induced epigenetic change and its utility for identifying peripheral biomarkers is discussed.

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1. Introduction

Psychiatric disorders are complex diseases classified into clinical syndromes with little known etiology. Those who have psychiatric disorders live longer with the burden of their disease compared to any other (Whiteford et al., 2013). While the etiologies of these are unknown, it is thought their onset is due to an underlying genetic predisposition in combination with environmental insults. Many studies indicate that the genetic component for these disorders can vary, with heritability ranges from 0.37 in major depression (MDD) to 0.81 in schizophrenia (SCZ) (Sullivan et al., 2012). Despite the amount of information generated from genetic association studies, recent studies have focused on the role of epigenetics, specifically DNA methylation, and how it may contribute to disease risk. At the intersection of genes and environment, DNA methylation provides a mechanism for different environmental factors to alter genetic expression. In this paper, we discuss evidence for the contribution

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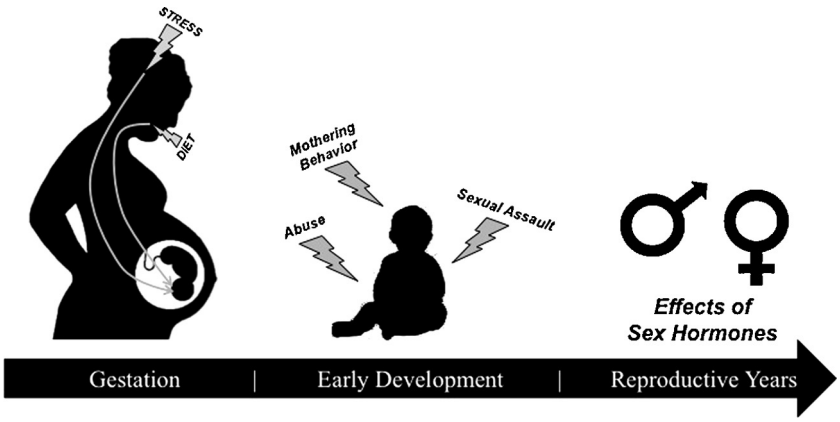

Fig. 1. Developmental periods sensitive to epigenetic change. An individual's risk to psychiatric disease may be modified by epigenetic changes induced by environmental insults. Depicted here are three particularly vulnerable timepoints: gestation, early childhood development, and reproductive years.

of both genetic and environmental factors in the etiology of psychiatric disease across key developmental windows (gestation, early childhood development, and during reproductive years) for epigenetic reprogramming (Fig. 1).

1.1. Nature and nurture in psychiatric disease

Like most complex diseases, psychiatric diseases are believed to result from the combined influences of 'nature' and 'nurture'. These two terms respectively refer to those inherited factors influencing one's development and later life outcomes as opposed to those factors external to one's self. In more modern terms, nature refers to genetic factors while nurture refers to environmental influences. Much of what is known about the degree to which these two influences play a role in disease manifestation comes from the employment of the classical twin design.

The classical twin design relies on a comparison of the concordance rates for a given trait between monozygotic (MZ) to dizygotic (DZ) twins. This design has long been regarded as one of the most elegant systems through which to infer the influence of inherited factors on a trait, as the degree of both genetic and environmental variation occurring in both groups is known. MZ twins arise from a single fertilized egg, while DZ twins result from two eggs being fertilized by two separate sperm (Gringras and Chen, 2001). These alternate origins result in MZ twins sharing approximately 100% DNA sequence identity while DZ twins share about 50% of all segregating DNA polymorphisms, on average (Boomsma et al., 2002; Martin et al., 1997; Wong et al., 2005). Importantly, the degree of shared environment in both MZ and DZ twins is high, so in the traditional model, if the DZ twin group is more variable for a trait, it is said to be under the influence of heritable factors. Heritability (Boomsma et al., 2002; Gottesman, 2004) is the degree to which a trait is due to genetic differences, but does not indicate what specific genetic factors are involved in influencing trait development. Conversely, the remainder of the variation for a trait not accounted for by heritability estimates is generally attributed to the effects of non-shared environmental influence.

1.2. Heritability in psychiatric disease

Using the classical twin design, relatively large ranges of heritabilities and environmental influences have been identified for numerous psychiatric diseases (Wong et al., 2005). For example SCZ and bipolar disorder (BP) exhibit relatively high levels of inherited risk, between 60 and 80% (Bertelsen et al., 1977; Cardno and Gottesman, 2000; Kieseppa et al., 2004; Lee et al., 2013a,b). An evaluation of 36 MZ and 53 DZ twins found panic disorder to be twice as frequent in MZ twins than DZ twins (Torgersen, 1983) suggesting that the disease is caused purely by genetic factors. Alzheimer's disease exhibits a high heritability (Kringlen, 1999), while neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) exhibit high heritabilities when assessed in childhood (Posthuma and Polderman, 2013). On the other end of the scale, MDD usually exhibits a generally low heritability around 30% (Bierut et al., 1999; Kendler et al., 1993; McGuffin et al., 1991; Middeldorp et al., 2005; Sullivan et al., 2000; Torgersen, 1986), while most reviewed heritability values for suicidality range from 26 to 70% (Pedersen and Fiske, 2010). Other psychiatric disorders such as anxiety, somatoform disorders, and alcohol abuse exhibit lower heritabilities according to twin studies (Kringlen, 1999). The results and interpretation of such modern twin studies have fueled the search for the implicated genetic and environmental factors.

In recent years, this search has culminated in genetic screening technologies that have enabled comprehensive investigations of common genetic variation on the genome-wide level. The degree to which the pool of genome-wide significant results from genome-wide association studies (GWAS) has grown across psychiatric diseases and has generally reflected initial heritability estimates (Ripke et al., 2013); although it should be kept in mind that those diseases with the highest heritabilities are currently also the best powered to date (Ripke et al., 2013). The comparative deluge of genome-wide significant results in MDD, however, stand as a marked contrast to the results of SCZ and support the notion that psychiatric diseases with low heritability estimates may therefore be more under the control of environmental influences. What is not attributed to genetics in heritability studies falls into the category of non-shared environmental influence and, in the case of MDD, this portion represents a relatively large (~70%) piece of the pie. In a recent review of the current state of genetic evidence in MDD, Cohen-Woods et al. (2013) suggest that the conflicting genetic results in MDD may be a consequence of a failure to account for environmental influence.

A recent large scale analysis of available GWAS data across a range of psychiatric diseases including SCZ, BP, MDD, ASD, ADHD, among others demonstrates a striking overlap in the amount of common genetic risk contributing across various combinations of these disorders (Lee et al., 2013a,b). For example, SCZ was most genetically similar to BP, but also shared genetic etiology with MDD and to a much lesser extent, ASD. Cumulatively, the data suggest that a common genetic etiology is shared across a range of phenotypically distinct psychiatric disorders. GWAS techniques have also enabled the quantification of heritability based on genetic variation at single nucleotide polymorphisms