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How does the social environment 'get into the mind'? Epigenetics at the intersection of social and psychiatric epidemiology

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Abstract

The social environment plays a considerable role in determining major psychiatric disorders. Emerging evidence suggests that features of the social environment modify gene expression independently of the primary DNA sequence through epigenetic processes. Accordingly, dysfunction of epigenetic mechanisms offers a plausible mechanism by which an adverse social environment gets "into the mind" and results in poor mental health. The purpose of this review is to provide an overview of the studies suggesting that epigenetic changes introduced by the social environment then manifest as psychological consequences. Our goal is to build a platform to discuss the ways in which future epidemiologic studies may benefit from including epigenetic measures. We focus on schizophrenia, major depressive disorder, post-traumatic stress disorder, anorexia nervosa, and substance dependence as examples that highlight the ways in which social environmental exposures, mediated through epigenetic processes, affect mental health.

Keywords

Epigenetics; Social environment; Psychiatric disorders; Methylation

Introduction

Nearly a century of research has shown a robust relation between features of the social environment and mental health and illness (Faris, 1939; Silver et al., 2002). The incidence of

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schizophrenia, for example, is higher in inner city areas in Western societies than elsewhere (Freeman, 1994). Increased labor stress has an adverse effect on major depressive disorder (MDD) (Kawakami et al., 1990; Wang, Schmitz et al., 2009). Large-scale natural disasters such as hurricanes (Galea, Brewin et al., 2007) and earthquakes (Wang, Zhang et al., 2009) have been associated with post-traumatic stress disorder (PTSD), whose impact is especially devastating in deprived populations (Association, 1994; Galea et al., 2008). On a more proximal level, social and interpersonal problems are known to trigger the onset of eating disorders (Treasure et al., 2010). Although these accumulated observations suggest that a variety of social environmental features act as determinants of psychiatric disorders, the pathophysiologic pathways leading to these outcomes still remain unclear.

Psychiatric disorders are attributable to the combined and interacting influences of heritable factors and environmental influences (Sweatt, 2009). Twin studies provide compelling examples of this phenomenon. For example, twin studies show the heritability of schizophrenia to be quite high (83%); yet approximately 17% of the variance in liability to schizophrenia is due to individual-specific environmental effects (Cardno & Gottesman, 2000). Since monozygotic twins carry 100% shared genetic information, the unaffected cotwins of affected monozygous probands carry susceptibility genes for schizophrenia but have not expressed the phenotype (Cardno & Gottesman, 2000), suggesting the importance of factors beyond DNA sequence variation in determining risk for this disorder. Twin studies of other psychiatric disorders generally show more modest heritabilities, ranging from 31–42% for MDD (Sullivan et al., 2000), 30–40% for PTSD (Afifi et al., 2010; Cornelis et al., 2010), 56–86% for anorexia nervosa (Scherag et al., 2010) and 50–60% for alcohol dependence (Stacey et al., 2009) (Figure 1). These twin studies suggest a critical effect of genes on psychiatric disorders; however, they also indicate that environmental factors underlie the development of psychopathological phenotypes (Kendler & Greenspan, 2006).

Here, we confront the question of how features of the social environment translate into psychopathological outcomes, or how the social environment “gets into the mind.” We focus specifically on epigenetics as a mechanism by which this process may occur. During the past decade, evidence has accumulated indicating that the social environment modifies gene expression independently of the primary DNA sequence through epigenetic processes. In the original work by Waddington, who coined the term ‘epigenetics’ from ‘epigenesis’ and ‘genetics’, epigenetics refers to the interactions of genes with their environment, which then brings the phenotype into being (Dolinoy et al., 2007; Van Speybroeck, 2002; Waddington, 1940). This definition has changed over time, and now generally refers to the heritable, but modifiable, regulation of genetic functions that are mediated through non-DNA-encoded mechanisms, in particular DNA methylation and histone modification (Kim et al., 2009). Although to date epigenetic studies have focused largely on alterations associated with cancer (e.g. Feinberg, 2007; Pike et al., 2008)), a growing literature suggests that epigenetic processes play an important role in psychiatric disorders as well (Galea et al., 2011; McGowan & Szyf, 2010; Ptak & Petronis, 2010; Tsankova et al., 2007). Nevertheless, there is a dearth of research examining how features of the social environment contribute to the epigenetic changes that may accompany psychopathological development. Despite the recognition that these features often operate on a macro level that can only be assessed through population-based epidemiologic studies (Galea, 2007), there are to date few studies that have incorporated epigenetic measures to evaluate the impact of particular environmental exposures. The purpose of this review is thus to (1) provide an overview of the studies suggesting that epigenetic changes are involved in the process by which exogenous stressors, including those experienced in the social environment, are translated into psychological/psychopathological consequences and (2) use these studies as a platform to discuss the ways in which future epidemiologic studies may benefit from including

epigenetic measures. English language papers were identified in PubMed using keywords relevant to psychiatry (e.g. mental, depression, schizophrenia, PTSD), epigenetics (e.g. methylation, imprinting), and study design (e.g. epidemiology, twin study, postmortem studies). References from papers identified through keyword searches were also assessed for their relevance. Papers that were available by June 2010, were included in this review.

Epigenetic mechanisms and regulation of gene expression

As noted above, two major mechanisms of epigenetic regulation have been identified: 1) DNA methylation, and 2) Histone modification. Additional mechanisms have also recently been identified, including non protein coding RNAs such as micro-RNAs, which can interact with other epigenetic mechanisms to regulate epigenetic processes such as chromatin modification (Mattick et al., 2009) and DNA methylation (Havecker et al., 2010). Because the bulk of evidence to date implicating epigenetic processes in psychiatric illness involves DNA methylation and, to a lesser extent, histone modification, below we provide a brief overview of each of these two major mechanisms.

DNA methylation

The human genome is chemically modified by methylation. DNA methylation occurs when a methyl group is added to the 5-carbon position of cytosine residues in DNA. This process typically occurs at cytosine-phosphate-guanine (CpG) sites, where a cytosine residue is followed by a guanine residue in the linear sequence of DNA (Issa, 2004). Such sites are typically methylated in human DNA; however, CpG islands--locations in the human genome at which the frequency of CpG sites is greater than 50% for 200 bases or more --often show reduced methylation due to their proximity to DNA coding region sequences, for which they act as a promoter to induce downstream expression of the gene (Issa, 2004). Most regulation of gene expression by DNA methylation demonstrates an inverse correlation between the degree of promoter DNA methylation and the level of expression (Jaenisch & Bird, 2003). Notably, this regulation occurs in the absence of gene sequence alteration.

Histone modification

Histone, a main protein component of chromatin, acts as a spool around which DNA winds. Without histones, the unwound DNA in chromosomes would be exceedingly long. Histone regulates the structure of chromatin and gene expression. Histone modification occurs on the amino-terminal tail of histone, which induces the structural change of chromatin from repressed to permissive state, or the opposite direction, causing alterations in gene transcription (Tsankova et al., 2007). This epigenetic mechanism is becoming increasingly well understood as result of several studies into the role of histone acetyltransferases and histone deacetylases. Histone acetyltransferases add acetyl groups to relax chromatin structure for the space of transcription; in contrast, histone deacetylases remove acetyl groups from histone and condense DNA, which in turn reduces transcription. Generally, the acetylation of histones marks transcriptionally active chromatin, while deacetylation is generally associated with transcriptional silencing (Kouzarides, 2007). The process of histone modification often involves other additional mechanisms, for example, methylation, phosphorylation, ubiquitination, and sumoylation (Tsankova et al., 2007).

Empirical evidence for the role of epigenetic mechanisms in the relation between the social environment and psychiatric disorders

Evidence for the involvement of epigenetic mechanisms in the onset of major psychiatric disorders extends to schizophrenia, post-traumatic stress disorder, depression, anorexia nervosa, and substance use disorders. In addition, investigations involving animal,

postmortem, and human population studies have indicated that certain social environmental features are associated with persistent changes in epigenetic marks that have life-long phenotypic consequences. Although the long-term consequences of such epigenetic effects on human health remain to be determined, here we review recent studies that suggest social environmental features can modify gene expression independently of the primary DNA sequence through epigenetic processes.

Schizophrenia

Schizophrenia is the most chronic and disabling of the severe mental disorders, associated with abnormalities of brain structure and function. Schizophrenia is characterized by profound disruption in cognition and emotion, affecting the most fundamental human attributes: language, thought, perception, affect, and sense of self (Association, 1994). A number of studies have indicated that risk of schizophrenia is increased in inner city and urbanized areas in Western societies compared to areas that are less urbanized (Freeman, 1994; Mortensen et al., 1999; Pedersen & Mortensen, 2006). Similarly, the incidence of schizophrenia is higher among migrants and their children than in native born residents (McGrath et al., 2004). A number of environmental explanations have been suggested for the risk-increasing effect of cities and migrants, such as social isolation, infectious disease, drug abuse, and nutritional intake (Brown & Derkits, 2010; Murray et al., 2003).

Among psychiatric disorders studied to date, schizophrenia provides some of the strongest and most direct evidence that epigenetic changes accompany mental illness. Work based on the reelin gene (*RELN*) as well as the dopamine receptor subunit 2 (*DRD2*) (Petronis et al., 2003) and catechol-o-methyltransferase (*COMT*) gene (Abdolmaleky et al., 2006) have all shown epigenetic associations with schizophrenia, although some studies have failed to replicate these findings (Tochigi et al., 2008; Zhang et al., 2007). Furthermore, work based on the insulin-like growth factor (*IGF2*) gene provides additional, albeit indirect, evidence that epigenetic processes influence human phenotypes (e.g. brain weight; Pidsley et al., 2010) known to be associated with schizophrenia (Harrison et al., 2003) and are themselves influenced by environmental exposures (Heijmans et al., 2008) known to increase risk of psychiatric disorder (Hoek et al., 1998) (described in more detail below). These data illustrate the extent to which environmentally sensitive molecular changes, via epigenetic processes, may contribute to psychiatric phenotypes.

One of the most well studied DNA methylation changes contributing to schizophrenia is that in the promoter region of *reelin* gene (*RELN*). Reelin is a glycoprotein that is expressed during development and in adult GABA (γ-aminobutyric acid)-containing neurons, and is important for proper neural positioning during brain development (Tissir & Goffinet, 2003). Dysregulation of brain neural connectivity in the developing brain has been suggested as a possible cause of schizophrenia (Karlsgodt et al., 2008). The down-regulation of *RELN* may well result from hypermethylation of the *RELN* promoter (Costa et al., 2002), and post-mortem studies of patients with schizophrenia have revealed significant down-regulation of *RELN* expression in several brain regions (Abdolmaleky et al., 2005; Grayson et al., 2006; Grayson et al., 2005). Of note, postmortem brain tissues obtained from schizophrenic patients have also shown significant hypermethylation in relation to healthy controls, (Abdolmaleky et al., 2005; Grayson et al., 2005) (although this finding has failed to replicate in at least one other study (Tochigi et al., 2008)). Reelin expression is increased by the treatment with valproate (an anticonvulsant and mood stabilizer), and this effect is accompanied by decreased methylation of the *reelin* promoter. Thus, the methylation of the *reelin* promoter region may play a key role in the onset of schizophrenia (Chen et al., 2002; Tremolizzo et al., 2002).

DNA methylation including that in the *reelin* region is related to the intake of methionine and folate. Methionine, whose derivative S-adenosyl methionine serves as a methyl donor, induces methyl group transfer in mammalian DNA methylation reactions (Waterland, 2006). Repeated methionine administration causes hypermethylation of the promoter and results in downregulation of *reelin* transcription in the mouse model of schizophrenia (Tremolizzo et al., 2002). In contrast, there are several pathways by which prenatal folate deficiency could plausibly influence the risk of schizophrenia. One possible pathway is that folate deficiency can disturb the methylation of DNA, affecting neurodevelopmental processes (Brown & Susser, 2008; Waterland & Jirtle, 2004). These data confirm that nutritional intake—a process with clear social environmental contributions—can affect epigenetic processes, which have been associated with schizophrenia. Indeed, emerging evidence suggests that the social environment contributes to schizophrenia *via* nutritional deficiency. A cohort study of individuals who were prenatally exposed to famine during the Dutch Hunger Winter showed a significant 2-fold increase in the cumulative risk of schizophrenia in the birth cohort exposed to the famine (Hoek et al., 1998; Susser et al., 1996). This famine was the consequence of a German-imposed food embargo during the end of World War II in the winter of 1944–45. A similar finding was reported in a study of the Chinese famine during 1959–1961, in which individuals who were prenatally exposed to famine conditions had an increased risk for schizophrenia (St Clair et al., 2005). It is plausible that this famine-associated increase in schizophrenia could be mediated by an altered intake in the amount of important nutrients such as methionine and folate.

In support of this hypothesis, another study using the Dutch Hunger Winter cohort (Heijmans et al., 2008) found that prenatal exposure to famine was associated with reduced methylation of *IGF2* six decades after famine exposure. The *IGF2* gene is one of the best-characterized imprinted genes, and plays a key role in the regulation of cellular proliferation and growth (Delaval et al., 2006). Postmortem studies indicate that brain weight in males is positively correlated with DNA methylation at *IGF2* (Pidsley et al., 2010) and, in turn, that decreased brain weight is associated with schizophrenia (Harrison et al., 2003). The dual association of reduced *IGF2* methylation with two factors previously associated with schizophrenia—exposure to famine and lower brain weight—offers compelling evidence that epigenetic mechanisms may play a key role through which the social environment affects the onset of this disorder. Of note, the methylation level associated with schizophrenia in *IGF2* (i.e. reduced methylation) contrasts with that observed for *RELN* (i.e. increased methylation); these contrasting patterns emphasize a complex picture whereby the nutritional alterations that have been directly (Tremolizzo et al., 2002) and indirectly (Heijmans et al., 2008) linked to methylation levels in these loci likely have opposing effects depending on the gene involved.

Major Depressive Disorder

Major depressive disorder (MDD) is a psychiatric disorder characterized by an all-encompassing depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two-week period. This mood must represent a change from the person's normal mood; social, occupational, educational or other important functioning must also be negatively impaired by the change in mood (Association, 1994). Major depressive episodes often follow psychosocial stressors including the death of a loved one, marital separation, divorce, and work-related stress. Features more distal to the individual have also demonstrated an association with depression, with, for example, poor quality of the built environment (Mair et al., 2008), lower socioeconomic status (Galea, Ahern, 2007) and urban residence (Kim et al., 2004) all showing evidence for a positive association with this disorder.

The potential role of epigenetics in MDD has been well illustrated via animal studies. The hypothalamic-pituitary-adrenal axis and hippocampus are among the major endocrine systems and brain regions, respectively, involved in coordinating short-term responses to stress and MDD. Work in rodents has documented epigenetic alterations in the hippocampus with relevance to MDD. For example, adult offspring of rats born to mothers displaying lower licking and grooming show increased anxiety and reduced expression of glucocorticoid receptors within the hippocampus (Szyf et al., 2005). Similarly, a greater expression of the glucocorticoid receptor gene has been demonstrated in offspring of high licking and grooming mothers (Liu et al., 1997). These environmental effects appear to be mediated by DNA methylation changes in the promoter region of the glucocorticoid receptor gene (*NR3C1*) (Weaver et al., 2004). Similar effects have been reported in humans. Oberlander and colleagues (Oberlander et al., 2008) investigated the association between prenatal exposure to maternal mood and the methylation status of a CpG-rich region of the *NR3C1* locus in newborns and hypothalamic-pituitary-adrenal stress reactivity at age three months in humans. Increased third trimester depressed maternal mood was associated with a site-specific increase in *NR3C1* methylation in infants and with increased infant cortical stress reactivity at 3 months. The association may indicate a potential epigenetic process that links antenatal maternal mood and altered hypothalamic-pituitary-adrenal stress reactivity during infancy.

Recent work suggests that depression is associated with higher methylation levels in the 5-hydroxytryptamine transporter (*5-HTT*, or *SLC6A4*) gene (Olsson et al., 2010; Philibert et al., 2008), a transporter for serotonin released under the parasympathetic excitation (Lechin & van der Dijs, 2009). Genetic studies suggest that carriers of the short allele of the *5-HTT* promoter polymorphism exhibited more depressive symptoms than individuals homozygous for the long allele under high stress conditions (Caspi et al., 2003). However, these results have been controversial, with some recent meta-analytic studies finding no evidence for gene-environment interactions (Munafo et al., 2009; Risch et al., 2009) while other studies have found an increased risk for depression among those with other alleles or genotypes (Chipman et al., 2007; Sjoberg et al., 2006; Uddin, Koenen et al., 2010). These mixed findings may be due, in part, to unmeasured epigenetic variation at the *SLC6A4* locus. Recent work suggests that the joint action of methylation and genotype at this locus influences risk for depression, such that increased risk for this disorder occurs only among individuals with both high *5-HTT* methylation and the *s* allele at the *5-HTTLPR* locus (Olsson et al., 2010). Recent work in non-human primates also suggests that higher *SLC6A4* methylation interacts with early life social experiences (i.e. maternal separation) to increase stress reactivity (Kinnally et al., 2010); and that, in humans, child abuse is associated with higher *SLC6A4* methylation (Beach et al., 2010). Both maternal separation and child abuse are known risk factors for depression in later life (Afifi et al., 2008; Kendler et al., 1992; Roy, 1985). The association of these known risk factors with increased DNA methylation at the *SLC6A4* locus thus provides an additional example of how epigenetic processes may mediate social exposures in a manner salient to psychopathology.

Post-traumatic Stress Disorder

PTSD is unique among psychiatric disorders because it includes an explicit requirement of an exposure to a potentially traumatic event. The three major symptom domains of this illness include reexperiencing a traumatic life event along with avoidance of reminders of the trauma, emotional numbing, and increased arousal (Association, 1994). Examples of potentially traumatic events include war-related events, natural or human-made disasters, severe automobile accidents, physical assault, sexual assault or violence, threats with weapons, serious accidents, being diagnosed with a life-threatening illness, and the unexpected death of loved ones. The longevity of effects due to potentially traumatic events

implies the participation of dynamic biological processes in addition to any permanent genetic predisposition. There is accumulating evidence that indicates the involvement of the hypothalamic-pituitary-adrenal function and epigenetic process with PTSD, which is highly comorbid with MDD (Koenen et al., 2008).

A recent genome-scale study (Uddin, Aiello et al., 2010) investigated epigenetic signatures associated with PTSD among individuals who were participants of a prospective epidemiologic study in Detroit, the Detroit Neighborhood Health Study. The lifetime and 12-month prevalences of PTSD among the participants were more than twice that previously reported in United States (Kessler & Wang, 2008), and exposure to assaultive violence in the Detroit survey sample far exceeded that reported for suburban communities, but was similar to levels reported in other major U.S. urban areas (Breslau et al., 2004). This work assessed the correlation between number of potential traumatic events and methylation levels at over 27,000 CpG sites covering more than 14,000 genes. Compared to PTSD-unaffected individuals, PTSD-affected individuals showed nearly six times as many genes with significant negative correlations and nearly seven times as many genes with significant positive correlations between methylation level and number of potential traumatic events. In addition, significant differences were noted in the biological pathways that characterized those with vs. without lifetime cases of PTSD (Figure 2).

Additional work on this cohort suggests that, as with depression, methylation of the *SLC6A4* locus plays an important role in risk for PTSD. More specifically, the effect of cumulative traumatic burden on risk for PTSD is modified by methylation levels at the *SLC6A4* locus: individuals with exposure to a greater number of potentially traumatic events are at higher risk of PTSD, but only at lower *SLC6A4* methylation levels; at higher methylation levels, these same individuals are protected against this disorder (Koenen et al., 2011). Given that exposure to potential traumatic events is known to vary by social contextual factors, such as inner city vs. suburban residence (Breslau et al., 2004), these PTSD-related epigenetic differences provide further evidence for the role of epigenetic processes as mediators, and moderators, of social context on mental health.

Anorexia nervosa

Anorexia nervosa is an eating disorder marked by extremely low body weight and persistent fear of weight gain (Association, 1994). Anorexia nervosa is prevalent in industrialized societies, in which there is typically little anxiety regarding food availability and in which thin body image is considered attractive (Bulik et al., 2007). Immigrants from cultures in which the disorder is rare who emigrate to cultures in which the disorder is more prevalent may develop anorexia nervosa as thin-body ideal are assimilated (Association, 1994). Anorexia nervosa is unique among psychiatric disorders because of the effect of ideal and cultural pressure on human psychiatric condition.

A number of studies have revealed that epigenetic mechanisms may contribute to eating disorders including anorexia nervosa. Atrial natriuretic peptide (ANP), one of the volume and appetite regulating hormones, has an important role in anorexia nervosa. Elevated plasma levels of ANP have been reported in women suffering from anorexia nervosa (Ohashi et al., 1988). In contrast, reduced mRNA expression of the ANP locus has been reported in female anorexia nervosa patients along with a significant increase in ANP promoter region methylation in a subset of anorexia- and bulimia-nervosa patients exhibiting purging behavior (Frieling et al., 2008). Explanations have been proposed to account for the contrasting patterns associated with anorexia nervosa provided by the protein data (detection of increased ANP levels in plasma) and the mRNA data (reduced ANP gene expression), including ANP activation of nitric oxide, which increases the activity of some DNA methyltransferases through inflammatory processes (Hmadcha et al., 1999), which are

known to contribute to anorexia (Gautron & Laye, 2009), and a decrease in enzymes that degrade ANP among patients with eating disorders (Frieling et al., 2008; van West et al., 2000). Although these explanations require further verification, the combined protein, mRNA and methylation level data do indicate that dysregulation of ANP is associated with anorexia nervosa, and suggest that hypermethylation of the ANP gene promoter may provide a mechanism that contributes to the development of this disorder. More generally, anorexia nervosa also provides a possible example of how epigenetic processes may mediate the effect of the image of ideal body and cultural background on dietary behavior.

Substance Dependence

Alcohol dependence is characterized by tolerance, withdrawal, inability to stop drinking, and continued drinking despite serious psychological or physiological problems. The use of alcohol in families, religious practices and preferences, and access to liquor stores, can affect the likelihood that alcohol problems will develop (Association, 1994).

Similar to the above-described studies of anorexia nervosa, alterations of the promoter-related DNA methylation of ANP precursor genes has been demonstrated in patients with alcohol dependence (Hillemacher, T., Frieling, H., Luber et al., 2009). Elevated DNA methylation within the promoter of alpha synuclein, which also play a key role in anorexia nervosa (Frieling et al., 2007), was found in peripheral mononuclear cells in patients with chronic alcoholism when compared with healthy controls (Bonsch et al., 2005). Common mechanisms may therefore be at work among eating disorders and alcohol consumption.

Aggravated alcohol withdrawal symptoms may plausibly be associated with epigenetic mechanisms. Changes in methylation occurring in early alcohol withdrawal have been identified in the promoter region of the subunit of NMDA receptor (*NR2B*) (Biermann et al., 2009), the dopamine transporter gene (*DAT*) (Hillemacher, Frieling, Hartl et al., 2009) and *HERP* (Homocysteine-induced endoplasmatic reticulum protein) (Bleich et al., 2006) among the patients with alcohol dependence. These changes in methylation profile are concordant with the occurrence of the aggravated withdrawal symptoms (Biermann et al., 2009).

Drug addiction is also a substance dependence that may be mediated in part by epigenetic mechanisms. Drug addiction is defined as a behavioral syndrome characterized by compulsive drug seeking and loss of control over drug intake regardless of medical illness, engaging in criminal activity, and other adverse consequences. Youth living in the most disadvantaged neighborhoods were likely to have a moderately high exposure opportunity to be offered cocaine compared to youth living in more advantaged neighborhoods (Crum et al., 1996), suggesting a window in which social contextual influences may exert influences on mental health that may again be mediated by epigenetic processes. The long-lasting effects of relapse to drug use may be accounted for by stable change in cellular function leading in turn to stable changes in neuronal plasticity (Malvaez et al., 2009).

Chronic exposure to cocaine does increase histone H3 acetylation at the locus of the brain-derived neurotrophic factor (*BDNF*) promoter (Kumar et al., 2005). Malvaez and colleagues have shown that histone deacetylase inhibition, which facilitates the extinction of fear-related memories, can also facilitate the extinction of drug-seeking behavior in a manner that significantly attenuates reinstatement (Malvaez et al., 2010). Thus, it may be possible that epigenetic mechanisms may modulate memory processes leading to extinction of memories associated with fear as well as extinction of drug-seeking behavior.

Implications of existing work for epigenetics and epidemiology

Understanding the epigenetic consequences of social exposures stands to transform social and psychiatric epidemiology. As dynamic mechanisms by which external experiences translate into physical and psychological outcomes, epigenetic processes can serve as a bridge between the epidemiology of social environments and the biological sciences (Rutten & Mill, 2009). However, there is currently scant direct evidence for clear epigenetic mediation of environmental exposures in psychiatric disorders, and, moreover, there is currently no consensus as to the most appropriate way to evaluate these associations (Foley et al., 2009). The preliminary findings in psychiatric epigenetics, reviewed here through the lens of social epidemiology, need carefully employed replication studies and further refinement of methodological approaches.

The field of epigenetic epidemiology is in its infancy and, as such, there remain several methodological issues pertinent to its use in psychiatric and social epidemiology. For example, the issues of subjective diagnostic paradigms, sample size to achieve adequate power, accessibility of epigenetic marks from live human samples, interpretation fallacy from the mixture of measurement levels, and the improper linear modeling of nonlinear relationships all need to be resolved as the field advances. The accessibility of epigenetic marks is a particularly relevant issue for psychiatric epidemiology, as repeated sampling of the same individuals will be required to discern cause vs. effect of the disease in question. While analysis of postmortem brain tissue can provide valuable insight into the epigenetic profile of the target organ in mental illness, postmortem studies have the same limitation as cross sectional studies, i.e. the inability to discern which epigenetic alterations occur as a cause vs. as a consequence of disease onset. Although methods have been proposed to more precisely identify causal relationships between epigenetic patterns and disease, for example Mendelian randomization (Relton & Davey Smith, 2010), it is clear that the use of peripheral tissues such as blood or saliva will be required for population-based longitudinal data collection that will allow us to draw robust causal inferences about observed associations between epigenetic marks and disease onset in representative populations. Several studies using such tissues have been conducted, in order to assess the extent of intra- and inter-individual variation in epigenetic patterns over time (Bjornsson et al., 2008; Talens et al., 2010; Wong et al., 2010). Results provide evidence of stability in DNA methylation within individuals over time (Talens et al., 2010); the extent of this intraindividual correlation varies across loci (Bjornsson et al., 2008; Talens et al., 2010; Wong et al., 2010). Age-related epigenetic changes have also demonstrated tissue-specific effects in animal models of aging, with some tissues (e.g. liver) and genomic regions (e.g. gene bodies) showing more pronounced changes in DNA methylation than others (e.g. adipose tissue and intergenic regions) (e.g. Thompson et al., 2010). Preliminary work suggests this issue exists in peripheral human tissues as well, with some loci demonstrating high intra-individual correlations of DNA methylation levels over time in DNA derived blood but not buccal cells (Talens et al., 2010). Identifying and controlling for age-related changes will thus be an important consideration in longitudinal studies of peripheral epigenetic marks associated with psychiatric illness.

Despite the problems of sample tissue accessibility, one compromise is to use more accessible tissue sources like lymphocytes, which may not completely reflect those in generally inaccessible tissues such as brain and neurons. There is increasing evidence from other disorders that many epigenetic alterations are not only limited to the affected tissue or cell type but can also be detected in other tissues - this may be the case for environmentally induced changes where exposure occurs throughout the body (Rutten & Mill, 2009). Indeed, lymphocytes have been flagged as a potential neural probe due, in part, to the existence of receptors for neurotransmitters that are expressed on both neurons and lymphocytes,

including glucocorticoid receptors and GABA receptors (Gladkevich et al., 2004). Further research is needed to confirm that epigenetic patterns in the accessible tissues will reflect those of the real tissue of interest. Given the challenges inherent to undertaking large-scale epidemiologic studies in living populations, additional work assessing the utility of psychopathology-associated epigenetic signatures that are observed only in peripheral tissues may also be warranted.

As this review illustrates, there is growing evidence that epigenetic alterations offer a plausible mechanism by which social environments are translated into human psychiatric consequences. The recognition that most illnesses are the result of a joint contribution from both endogenous and exogenous factors suggests that non-psychiatric diseases are also likely to have epigenetic etiologies that may reflect aspects of the social environment. Epidemiological data will be useful to provide indirect evidence of epigenetic effects on human health by highlighting the mechanistic link between the social environment and psychiatric disorders and providing an umbrella under which variation in genetics, behavior, nutrition, stress, psychiatric conditions may be more fully accounted for. Many important questions in this nascent area of research remain to be addressed. For example, what effect sizes can we expect to observe in associations between a quantitative trait such as DNA methylation and complex psychiatric illness? Significant (albeit average) intraindividual age-related changes ranging from 14% to 72% have been reported based on DNA methylation assays conducted on peripheral tissues (Bjornsson et al., 2008), but it is not yet known if comparable effect sizes will be found in longitudinal, population-based studies of mental illness. Small-scale pilot studies of carefully selected, existing biobanked samples that have accompanying information on psychiatric phenotypes, as well as individual- and macrosocial-level environmental exposures, may be warranted. Such studies would permit a thorough characterization of the causal and/or mediating epigenetic changes involved in psychiatric illness, while also providing some parameters on the effect sizes that may be reasonably expected.

Despite these and other challenges, there is growing momentum to include epigenetic data into future epidemiologic studies of psychiatric illness and other complex diseases. The Human Epigenome Project is currently underway, which aims to identify, catalogue and interpret genome-wide DNA methylation patterns of all human genes in all major tissues ("Moving AHEAD with an international human epigenome project," 2008). Introducing epigenetic measures into epidemiologic investigations will help to expand research into human health and disease by providing insight into the dynamic biological process by which the social environment gets “under the skin”.

Research Highlights

- Social determinants of mental illness have long been recognized, yet biologic pathways linking the two have remained unclear.
- Epigenetic dysregulation offers a plausible mechanism by which an adverse social environment results in poor mental health.
- Here we review studies suggesting that epigenetic changes translate exogenous stressors into psychopathological outcomes.
- Evidence pertaining to schizophrenia, MDD, PTSD, anorexia nervosa and substance dependence is reviewed.
- Implications for future work incorporating epigenetic measures into epidemiologic studies are discussed.

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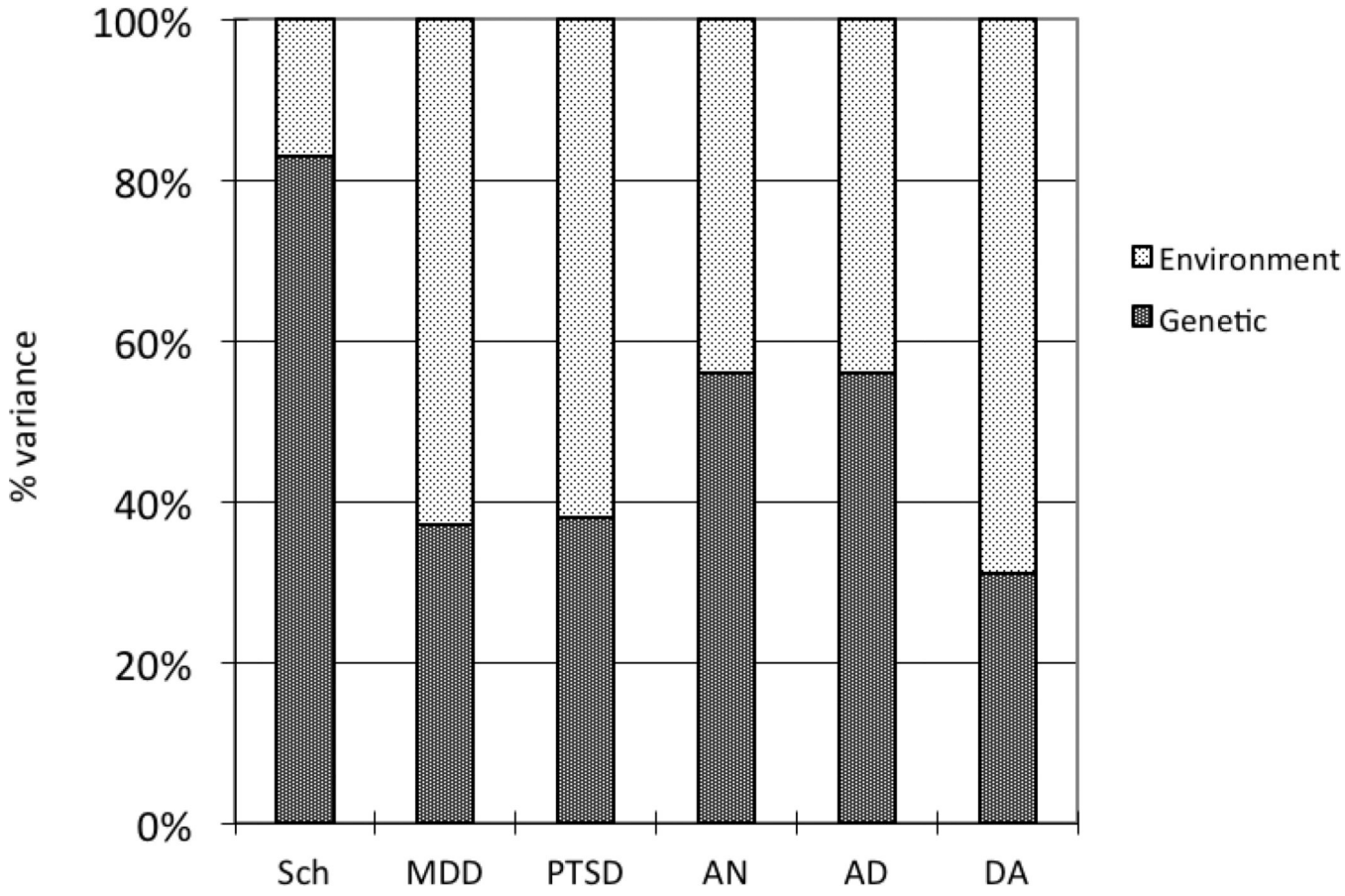

Figure 1.
Proportion of variance attributable to genetic and environmental effects according to twin studies of schizophrenia, MDD, PTSD, AN, AD, and DA.
Sch: Schizophrenia (Cardno & Gottesman, 2000); MDD: Major Depressive Disorder (Kendler & Prescott, 2007); PTSD: Post-traumatic Stress Disorder (Stein et al., 2002); AN: Anorexia Nervosa (Bulik et al., 2006); AD: Alcohol Dependence (Kendler & Prescott, 2007), DA: Drug Abuse (Tsuang et al., 1998)

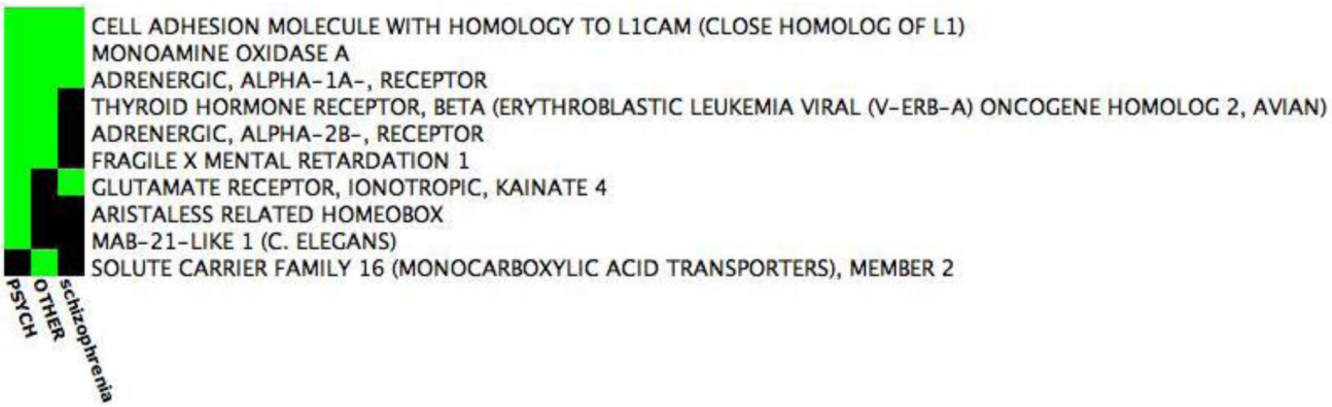

Figure 2.

Heat map of disease-related annotations (Huang da, Sherman, & Lempicki, 2009) associated with genes (n=167) in the uniquely unmethylated gene set among those without lifetime PTSD from Uddin (Uddin, Aiello et al., 2010). Results suggest a decrease in activity among genes known to play a role in schizophrenia and other psychiatric diseases in those with lifetime PTSD.

BLACK: Corresponding gene-disease association yet not reported.

GREEN: Corresponding gene-disease association positively reported.