The interaction between stress and genetic factors in the etiopathogenesis of depression

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The presence of a genetic component to depression has been established by family, twin and, to a lesser extent, adoption studies. Family studies have shown that first-degree relatives of patients with depression have on average three times the risk of depression of those without a family history of the disorder (1), but at least one study of clinically ascertained narrowly defined depression estimated the risk in siblings to be nearly ten times the risk in controls' siblings (2). A systematic meta-analysis including data from five twin studies reported an average heritability estimate of 37% (1), but a clinically based twin study provided an estimate of over 70% (3).

Genetic association studies have mainly focused on neurotransmitter and hypothalamic-pituitary-adrenal (HPA) axis related genes (4,5). Although almost 200 genes have been investigated through this type of "candidate gene" approach, only a few findings have been replicated (6), with seven candidate genes explored by meta-analysis yielding statistically significant results (5HTTLPR, APOE, DRD4, GNB3, HTR1A, MTHFR and SLC6A3) (6).

Since a landmark publication in 2007 of a genome-wide association study (GWAS) of seven common diseases, one of which was bipolar disorder (7), association studies of major depression have also taken a GWAS approach. Unfortunately this has been less successful so far than in other common psychiatric disorders, including Alzheimer's disease, bipolar disorder and schizophrenia. A recent mega-analysis conducted on eight GWAS included 18,759 unrelated individuals (9,240 major depressive cases and 9,519 controls) and analyzed more than 1.2 million single nucleotide polymorphisms (SNPs). No SNPs achieved the stringent criteria that have now become the standard for declaring genome-wide significance ($p < 5\times10^{-8}$) (8).

Thus, despite substantial heritability, there has been a failure to robustly identify genetic variants that contribute to depression. Plausible explanations include heterogeneity (diagnostic, etiological or both), the existence of multiple tiny genetic effects that require even larger samples, and failure to take into account gene interplay with environmental factors.

The association between stress and depression is strong and compelling, with consistent evidence that life stressors influence the onset and clinical course of depression (9). On the other hand, not everyone who experiences such events develops the disorder and not everyone who becomes depressed appears to have a precipitating life event.

Methodological issues regarding stress assessment have been repeatedly discussed. First, there is the question of using a time consuming standardized interview versus a quicker checklist method. Research has consistently confirmed that semi-structured interviews are more accurate and effective than simple questionnaires (10). Second, there is the problem of direction of causality: is the subject's mental state influencing the event (or how it is reported) or is the event really precipitating depression? Researchers have tried to tease out events that are truly independent of the patients' own actions and mental state. Acute life events have been most consistently found to precede the onset of a depressive episode compared with chronic and distal events (11), but early life stress, specifically adverse childhood experiences (emotional, physical or sexual) have been shown to increase the risk of depression in adulthood and even in old age (12,13). Indeed, life events occurring long before the onset of depression have little or no relationship with adult depression once childhood maltreatment is controlled for (14).

One of the first attempts to study the effects of life events within a familial context used a semi-structured interview, the Life Events and Difficulties Schedule (LEDS) (9), and resulted in the provocative finding that not only did the relatives of depressed subjects have an increased rate of depression, but also they appeared to have an elevated rate of threatening events (15). Subsequent work with twins suggested that there is actually a modest but significant heritable component to self-reported life events (16) and a genetic correlation between self-reported life events and depressive symptoms in adolescents (17). However, this genetic effect is probably only characteristic of self-reported life events assessed by a questionnaire, since parental reports of life events occurring in the same adolescents showed no evidence of heritability. Furthermore, the phenomenon of familiarity of LEDS-detected threatening life events in relatives of depressed patients was shown to be explained by shared events, for example illness in a parent affecting both members of a sibling pair (2). This whole question of how life events are detected and defined has recently attracted renewed interest in the context of studies of gene-environment interaction.

Gene-by-environment interaction (GxE) studies aim to detect whether there are genetic influences affecting individual differences in response to the environment. The first GxE study of depression focusing on a specific genetic variant was reported by Caspi et al in 2003 (18). They found

that a functional polymorphism in the serotonin transporter linked polymorphic region (5-HTTLPR) moderates the effect of environmental factors (childhood maltreatment and stressful life events) on the risk of depression. Individuals carrying one or two copies of the relatively low-expressing short allele (s) had a higher risk of depression after being exposed to stressful life events or childhood maltreatment than homozygous for the long allele (l) (18).

Subsequently, there have been more that fifty studies trying to replicate Caspi's findings, and the results have been somewhat contradictory (4,19), with two "negative" meta-analyses (20,21) receiving much attention. However, Uher and McGuffin (22) have noticed a significant systematic effect of how life events were assessed, with negative studies being the ones that used subjective self-report measures. The most recent and complete meta-analysis, including 54 studies, has found strong evidence that 5-HTTLPR does indeed moderate the relationship between depression and adversity, particularly childhood maltreatment and specific objectively measurable stressors (23).

There is also support from recent data that interactions with 5-HTTLPR are stronger amongst individuals with chronic or persistent forms of depression (14,24,25). A recent study has also confirmed the presence of an interaction between 5-HTTLPR and various forms of childhood maltreatment (26). Currently, an ambitious large scale meta-analysis is underway, attempting to provide a definitive exploration of adversity, depression and 5-HTTLPR and including data from 35 independent groups and at least 33,761 individuals (27).

There is also emergent work suggesting that the s allele of the 5-HTTLPR polymorphism may confer a differential sensitivity to the environment, which may be either beneficial or negative (28). For example, a study of preschool children indicated that homozygotes for the 5-HTTLPR s allele were more vulnerable to depression at high stressful live events exposure, but showed reduced rates of depression at low stressful events exposure, appearing to benefit from a better environment (29). Furthermore, there is preliminary evidence that children with anxiety or depression respond more positively to psychological treatments if they carry the 5-HTTLPR s allele (30).

5-HTTLPR has become a forerunner for a whole range GxE interaction studies in mood disorders that are focusing on other candidates (19,31). Furthermore, epigenetic modifications, specifically DNA methylation, have been found in genes involved in GxE interactions, suggesting that these interactions could be mediated by epigenetic mechanisms (19,32). Recent studies implicate epigenetic mechanisms as an important link between early life adversity and sensitivity to stressful life events in adulthood (33). There is also emerging evidence that such interactions are not limited to unipolar depression. For example, a functional variant in the gene encoding brain derived neurotrophic factor (BDNF) may moderate the effect of adversity preceding onset of episodes in patients with bipolar disorder (34).

Until now, GxE studies have focused on candidate genes and, although the genome wide genotyping technology has been available for a while, no gene-environment wide interaction studies (GEWIS) have been conducted in psychiatric disorders so far. GEWIS face two major challenges: the availability of environmental data and statistical power (19). The other major problem is that the largest analysis to date by the Psychiatric Genomics Consortium, including nearly 20,000 individuals, failed to find any genome-wide significant hit (8). Therefore, we can predict that extremely large samples will be needed to detect GxE interactions that withstand the statistical stringency needed in genome-wide studies. Nevertheless, such efforts are ongoing and one of the highly welcome benefits of the post-genomic era in psychiatric genetics is the now universal acceptance that real advances can only be made by consortia that apply global standards of both scientific method and practical collaborative spirit.

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