Stressful life events, 5-HTT genotype and risk of depression†

STANLEY ZAMMIT and MICHAEL J. OWEN

Summary Studies of how genetic and environmental exposures interact may be essential for understanding the aetiology of complex psychiatric disorders. In this issue of the Journal an Australian study reports evidence of such an interaction on risk of depression. We discuss findings in this field in the context of the limitations inherent in studies of gene–environment interactions.

Declaration of interest MJ.O. is a consultant to GlaxoSmithKline and has received honoraria for academic talks from Eli Lilly, AstraZeneca and GlaxoSmithKline.

The processes underlying psychiatric disease are clearly extremely complex. Studies of how genes and environment interact and affect vulnerability to risk of disease are likely to contribute substantially to our understanding of these processes. The study by Wilhelm et al (2006, this issue) adds to a growing body of literature suggesting that the effects of stressful life events on risk of depression may be dependent on variation at the 5-HTTLPR locus of the serotonin transporter (5-HTT) gene. The study of gene–environment interactions, although clearly important, is beset with a number of potential problems, and we discuss these findings within this context.

GENE–ENVIRONMENT INTERACTIONS

A situation where risk from an environmental exposure varies according to genotype or where genotype effect varies according to environment is known as gene–environment interaction, or effect modification. Studies of genetic effects stratified by environmental exposures, or vice versa, may increase our ability to find evidence of risk or protective factors for disease, and increase understanding of pathophysiology. They may also allow more accurate estimation of effect sizes within population subgroups, and – although difficulties in implementing change in high-risk groups are substantial – may allow for specific targeting of interventions in the future.

Studies of interactions need to be approached with caution for a number of reasons. First, sub-analyses inevitably result in more statistical tests and consequently increased likelihood of type I errors. Second, the smaller numbers of events within comparison groups lead to reduced statistical power, which will only be offset in the presence of a strong interaction effect. Third, evidence for statistical interaction does not provide direct evidence of biological interaction. Evidence of statistical interaction depends on the mathematical model used and, as the null hypothesis is that joint exposure effects on outcome are as described by the model, rejecting this hypothesis has less clear biological meaning than for the study of main effects (Clayton & McKeigue, 2001).

S-5HTT, STRESSFUL LIFE EVENTS AND DEPRESSION

Evidence for an interaction between 5-HTTLPR genotype and adult depression was first reported in the Dunedin birth cohort (Caspi et al, 2003). Presence of the short (‘s’) allele of 5-HTTLPR reduces in vitro gene transcription and transporter activity compared with the long (‘l’) allele, resulting in increased synaptic levels of serotonin. In this study, presence of stressful life events was associated with an increase in risk of depression in heterogeneous individuals and in those homozygous for the ‘s’ allele, but not in ‘l/l’ homozygotes. Five studies have since reported similar deleterious effects of adverse events on depression, modified by the underlying genotype at this locus (studies 2–6 in Table 1). In these studies the interaction effect was in the same direction as the original finding, although it was only observed in women in two of the studies. Some of these results, however, are difficult to explain biologically. For example, Sjoberg et al (2005) reported interactions between 5-HTTLPR genotype and various adversity measures on risk of depression, but the interaction effects observed were in opposite directions in men and women. Although gender-specific effects are compatible with some observations from animal models, opposite effects of genetic modification of stress on depression risk between genders seems biologically less plausible.

In this issue Wilhelm et al report an interaction between genotype and stressful life events on risk of depression, with increased risk present in ‘s/s’ and ‘s/l’ but not ‘l/l’ phenotypes (Wilhelm et al, 2006, this issue). Adverse events appear to protect against depression in the ‘l/l’ group, although it is not clear whether the confidence intervals here are compatible with a null effect. Interestingly, a similar trend is observed in other studies that have reported an interaction, although an opposite effect of adversity on depression risk across genotypes seems biologically unlikely.

SUPPORTING EVIDENCE

In rhesus macaques interactions between rearing experience and rh5-HTTLPR (analogous to the human polymorphism) have been described for a number of potential depression-related outcomes (Barr et al, 2003). These findings probably require further replication, and lack of a clear pattern in the interactions reported for adrenocorticotrophic hormone and cortisol response to stress complicates interpretation of some results. Nevertheless, these studies provide a fascinating insight into possible advances to be gained from future research in this field. Other support for effect modification of stress by 5-HTT genotype comes from neuroimaging studies, where amygdala hyperreactivity in response to fearful stimuli has been reported in individuals with ‘s’ alleles compared with ‘l/l’ homozygous individuals in a number of studies (for example, see Hariri et al, 2005).
EVIDENCE AGAINST

Surtees et al (2005), in the largest and most high-powered study to date examining this relationship, found no evidence of an interaction between genotype and adverse experiences in childhood or adulthood on risk of depression. In men, an interaction was observed for childhood adversity, but this was in the opposite direction to that reported by Caspi et al (2003). Another study, by Gillespie et al (2005), also failed to find evidence of interaction. Moreover, a non-significant trend for increased depression in 'll' homozygous individuals who had experienced more stressful life events was again in the opposite direction to the findings reported by Caspi and colleagues.

WEIGHING UP THE EVIDENCE

Although the studies to date have examined different depression and environmental stress measures, and employed different study designs and genetic models, most find evidence for a gene–environment interaction from both multiplicative as well as linear statistical models. However, the two largest studies to date find no evidence to support such an interaction, although issues regarding study design as well as temporal sequence and validity of measures are also important to consider when summarising findings across studies. Nevertheless, studies of interactions tend to be relatively low-powered, and as initial findings tend, on average, to be overestimates of true effect sizes, larger samples than those used in the original study are usually required for replication. Given that there is evidence of interaction from a number of studies with fairly small sample sizes, but no small negative studies, as can be seen in Table 1, it seems likely that publication bias is occurring, making interpretation of the evidence more problematic.

### Table 1  Summary of studies examining the relationship between serotonin transporter (5-HTT) genotype, stressful life events and depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Depression measure</th>
<th>Stress measure</th>
<th>Evidence of G × E interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspi et al (2003)</td>
<td>847</td>
<td>MD, depressive symptoms, suicidality</td>
<td>SLE, childhood maltreatment</td>
<td>Yes</td>
</tr>
<tr>
<td>Eley et al (2004)</td>
<td>377</td>
<td>High score on MFQ</td>
<td>Family environment risk</td>
<td>Yes, in females only</td>
</tr>
<tr>
<td>Kaufman et al (2004)</td>
<td>101</td>
<td>MFQ score</td>
<td>Childhood maltreatment</td>
<td>Yes</td>
</tr>
<tr>
<td>Kendler et al (2005)</td>
<td>549</td>
<td>MD</td>
<td>SLE</td>
<td>Yes</td>
</tr>
<tr>
<td>Sjoberg et al (2005)</td>
<td>180</td>
<td>Depressive symptoms</td>
<td>Four different categories</td>
<td>Yes</td>
</tr>
<tr>
<td>Grabe et al (2005)</td>
<td>1005</td>
<td>High BL̅38 score</td>
<td>Unemployment, chronic diseases</td>
<td>Yes, in females only</td>
</tr>
<tr>
<td>Gillespie et al (2005)</td>
<td>1091</td>
<td>MD, depressive symptoms, suicidality</td>
<td>Personal and network SLE</td>
<td>No</td>
</tr>
<tr>
<td>Surtees et al (2005)</td>
<td>4174</td>
<td>MD</td>
<td>Adult and childhood social adversity</td>
<td>No, except in 1 subgroup</td>
</tr>
<tr>
<td>Wilhelm et al (2006)</td>
<td>127</td>
<td>MD</td>
<td>SLE, 3 years and 1 year prior to MD</td>
<td>Yes, for 5-year SLE</td>
</tr>
</tbody>
</table>

BL̅38, modified von Zerssen complaint scale; G × E, gene–environment; MD, major depression; MFQ, Mood and Feelings Questionnaire; SLE, stressful life events.

**FUTURE DIRECTIONS**

In view of the above we believe it is sensible to be cautious in the interpretation of results from these studies. The consistency of findings from animal studies with these epidemiological observations suggests that the effects of stressful events might indeed be mediated by 5-HTTLPR genotype. If this can be confirmed by further adequately powered and well-designed studies, this will provide an intriguing base for further exploration and dissection of pathological mechanisms underlying depression. Guidelines for the study of gene–environment interactions suggest useful strategies as to how future studies may best be approached (Moffitt et al, 2005). Studies such as those discussed here and those reporting evidence for gene–environment interaction in other psychiatric disorders (Caspi et al, 2002, 2005) have all focused on reasonably well-supported candidate genes and environmental factors. Independent effects for most of these exposures are already established, and it is not yet clear to what extent these sorts of findings will influence our understanding of pathophysiology.

Interestingly, for most of these studies, a clear effect of genotype was only observed after stratification by environmental exposure, and recent meta-analyses provide only weak evidence, if any, of association between 5-HTTLPR and depression (Levinson, 2005). Consequently, it has been suggested that genome-wide scans for novel genes might profitably be based upon affected and unaffected samples selected for known exposure to an environmental pathogen for the disorder (Moffitt et al, 2005). This has inherent attractions where robust effects of specific environmental effects have been demonstrated. However, there are limitations. First, the number of environmental pathogens that have been clearly implicated in psychiatric disorders is small; it seems unlikely that the majority of risk genes for psychiatric disorders will interact with these few well-established pathogens, and the scope of such studies will thus be limited. Second, the unit costs of studies that include measurements of environmental exposures of sufficient quality will be great. Even though there should be gains in power to detect genes interacting with the candidate environmental exposure, it is not clear whether these will outweigh the increased cost per sample compared with necessarily larger studies of cases unselected for environmental exposure, where the unit costs are much lower. Population-based longitudinal studies that have both DNA as well as detailed environmental exposure data throughout the life course are ideally placed for such studies, and greatly improve the economic case for genetic studies of environmentally stratified samples.

The study of how genetic and environmental exposures interact on risk of disease...
may be an essential element to understanding complex disorders. However, the study of interactions requires a more cautious approach than studies of main effects, and evidence for modification of the effects of stress on risk of depression by 5-HTTLPR genotype is not yet robust. Although heralding much promise, the extent to which this fascinating area of research will enhance our understanding of psychiatric disease remains to be seen.

REFERENCES


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Access the most recent version at DOI: 10.1192/bjp.bp.105.020644

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