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Editorial

The promoter of the serotonin transporter genotype, environment and depression: A hypothesis supported?

The article by [Uher et al. \(2011\)](#) in this issue of the *Journal* re-examines the role of gene–environment interaction involving the short allele in the promoter of the serotonin transporter genotype (5-HTTLPR) in the etiology of major depression. The importance of the original paper in 2003 by Caspi and colleagues is widely accepted, and the current paper promises to be a significant elaboration. It takes account of further data from the Dunedin cohort and an additional one of UK women, and examines a new hypothesis concerning gene–environment interaction involving childhood maltreatment identified in the original report: that the interaction relates to the *persistence* of adult depression rather than its *onset*. It is a change in focus that has significant public health implications.

The research to be discussed employed two ways of measuring persistence. The hypothesis tested by Uher and colleagues in the current paper arose from research in London dealing with whether or not an onset depression takes a *chronic course* lasting at least 12 months ([Brown and Harris, 2008](#)). The present authors by contrast take account of the presence of depression across four 12-month periods in adulthood separated by 2 years or more. *Persistent* depression is defined as its presence at any two assessment windows and is compared with *single-episode* depression. Therefore persistent depression includes not only chronic, but recurrent cases. I will provisionally accept the authors' assumption that the two approaches overlap sufficiently to test a hypothesis that arose from the London research. I assume therefore that *persistence* is broadly equivalent to *chronic*, and *single-episode* to *non-chronic depression*. However, the approaches are not equivalent and I will comment on this later.

The original [Caspi et al.](#) article documented contributions to gene–environment interaction from both childhood maltreatment and adult negative life events, although the role of the latter is not considered in the current paper. Since the publication of their paper evidence has emerged that such events may not contribute to gene–environment interaction. This would considerably simplify the task of developing a coherent etiological model. Evaluating this evidence is complicated by the fact that the original report dealt with events

occurring in a 5-year period, while almost all subsequent publications have employed a much shorter period, influenced by research showing that only events occurring within a year of onset, and usually a much shorter period, play a role ([Brown, 1989](#)). An article by [Wilhelm et al. \(2006\)](#) dealing with the gene–environment interaction reported in the original Caspi et al. article is of particular interest as it considered both 5-year and 1-year periods. This led to a paradoxical result. Interaction was confirmed using the 5-year index, but not, as might have been expected for the shorter period. A recent meta-analysis also concludes that recent events make only a marginal contribution to gene–environment interaction ([Risch et al., 2009](#)). One explanation for Wilhelm et al.'s finding is that because childhood maltreatment is associated with a doubling of negative adult life events, the 5-year index serves as a marker of such maltreatment but makes no aetiological contribution itself. This possibility was confirmed by data from a UK non-genetic study of women using investigators to rate the likely degree of threat of events ([Brown, 1989](#)), and a measurement based on the SCAN ([Wing et al., 1990](#)) to assess depression. While both were associated with childhood maltreatment only negative events occurring fairly close to onset played a role in onset with a 5-year index making no contribution ([Brown and Harris, 2008](#)).

By contrast systematic reviews of subsequent research have confirmed that childhood maltreatment, the other risk factor considered in the original report, does contribute to gene–environment interaction ([Karg et al., 2011](#); [Uher and McGuffin, 2008, 2010](#)). The current paper takes a further step. Depressive onsets are not considered. Instead it takes account of the radically different course that a depressive episode can take and the possibility that only persistent depression is involved in gene–environment interaction. This hypothesis arose from a puzzling finding concerning chronic depressive episodes in three non-genetic studies dealing with women. One was a retrospective study of a population sample covering adulthood as a whole ([Brown et al., 2007a](#)). Two others were prospective and dealt with whether onsets of depression occurring in a 12-month period took a chronic course — one a population sample ([Brown and Moran,](#)

1994) and the other a patient series (Brown et al., 1994). All the studies explored the long-term influence of childhood maltreatment using the Childhood Experience of Care and Abuse (CECA) instrument based on an interview dealing with physical and sexual abuse, and neglect (Bifulco et al., 1994). Findings concerning depressive onsets were as expected. Childhood maltreatment was associated with a doubling of the risk of onset with this mediated by risk factors close to onset such as life events, low self-esteem and level of emotional support. In other words the effect of such maltreatment on onset was entirely *indirect*.

The idea that chronic depressive episodes rather than new onsets might be involved in the gene–environment interaction arose from a very different set of findings. In one of the two studies dealing with the general population childhood maltreatment was associated with a four-fold greater risk of a chronic episode occurring in a 12-month period compared with two-fold for depressive onset (Brown and Moran, 1994), with a comparable order of difference in the other dealing with adulthood as a whole (Brown et al., 2008). For the present argument the critical finding is that when proximal risk factors, such as life events and current interpersonal difficulties, and distal risk factors, such as early pregnancy, were taken into account, childhood maltreatment made a substantial *direct* contribution to whether a depressive episode took a chronic course. This contribution was more or less equal to that from all other psychosocial factors. A similar picture emerged from a third study dealing with psychiatric patients with the additional finding that neither clinical characteristics nor personality disorder contributed to risk of a chronic course (Brown et al., 1994). It was this substantial *direct* effect on the risk that an episode would take a chronic course that prompted the hypothesis about its importance for elucidating gene–environment interaction. The presence of a direct effect in all three studies had to be taken seriously even though it was inexplicable in terms of psychosocial experience occurring after childhood maltreatment. Data from molecular genetics suggested a partial explanation might be that the interaction of serotonin transporter activity and childhood maltreatment disrupts the formation of neural networks critical for normal adult function. In other words the critical gene–environment interaction does not take place at the time of an adult onset (Brown and Harris, 2008).

Sibille and Lewis (2006) discuss the involvement of the short allele in the promoter of the serotonin transporter genotype in early development in the light of human and animal research, and in a reference to the original Caspi et al. paper suggest that the relevant gene–environment interaction might involve both early experience and adult life events. However, their general argument for the long-term significance of early brain development is more coherent if the contribution of adult life events is omitted.

To sum up: the hypothesis concerning the involvement of chronic episodes in the gene–environment interaction identified by Caspi et al. (2003) and tested in the current paper stemmed from three studies showing a substantial direct link of childhood maltreatment with chronic episodes not mediated by other psychosocial risk factors. Gene–environment interaction taking place in childhood would help to explain such a puzzling effect. Evidence that adult life events play little or no role in such interaction is also consistent with a long-term perspective. The presence of early interaction would also make it

easier to accept that childhood maltreatment may have a long-term influence via early development irrespective of the involvement of the short allele in the promoter of the serotonin transporter genotype or other polymorphisms. Relevant changes in brain development are yet to be established, but are not unlikely in the light of animal research (Sibille and Lewis, 2006). It should perhaps be added that lack of a contribution by adult life events to gene–environment interaction would in no way conflict with the fact that they provoke the majority of depressive onsets (Brown, 1989) and in doing so influence the number of episodes in a population that can potentially take chronic course.

This conclusion concerning childhood does not necessarily rule out that the promoter of the serotonin transporter genotype may also interact with the current adult environment. However, given aversive events do not appear to be of importance, it is more likely to result from interplay with protective factors such as level of emotional social support. This would be consistent with the idea that the genetic contribution of the s allele increases sensitivity to positive as well as negative stimuli (Belsky et al., 2009; Homberg and Lesch, 2011; Uher, 2008). Another possibility is that a different polymorphism acting in adulthood may be involved. There is, for example, evidence that the val/val allele of the brain-derived neurotrophic factor (BDNF) reduces risk of a depressive onset (Kaufman et al., 2006), and this might in turn reduce the risk of a chronic course arising from changes in brain development so far discussed.

The current article raises three more specific questions: i) The non-genetic studies discussed earlier dealt only with women, but there are hints that gender may be relevant (e.g. Sjöberg et al., 2006). ii) As noted earlier the index of persistent depression used by Uher et al. is based on presence of depression at two or more points in time. While it is likely to be substantially correlated with chronic episodes lasting at least 12 months there will be exceptions. For instance, ‘single-episodes’ not considered ‘persistent’ will at times last 12 months or longer; and some classified as ‘persistent’ will involve only recurrent non-chronic episodes. More research will be needed to sort this out, bearing in mind there is no reason why the multiple episodes should not at times be the result of the gene–environment interaction envisaged for chronic episodes. iii) The time period involved during development needs further study. Interview-based measures such as the Childhood Experience of Care and Abuse instrument (CECA) appear to be reasonably accurate (Brown et al., 2007b), but are unable to deal with experience during the early years of infancy. This is not necessarily a threat to current findings as such early maltreatment is likely to be fairly highly correlated with later adverse childhood experience. It is also worth bearing in mind that for maltreatment to have a long-term effect it may usually have to extend for a substantial period in childhood or adolescence (Brown, 2006).

The stunning technical achievements of molecular genetics have been linked with frequent failures to replicate findings. Research following the original Dunedin study has been no exception. But there are grounds for cautious optimism about the results of the current Uher et al. paper. Shortcomings in design and measurement have certainly played a part in non-replications of the original findings of Caspi and

colleagues (Brown and Harris, 2008; Uher and McGuffin, 2010) and in addition the role of adult life events in depressive onset appears likely to have been a diversion. It is therefore possible that some version of the present findings will remain and even become clearer as measurement improves and research develops. The results are also relevant for a key epidemiological question. The two population enquiries of women discussed earlier found that around a quarter of depressive onsets had taken a chronic course with the result that around half of all depressive episodes present in a 12-month period had lasted at least 12 months (Brown et al., 2007a). The life-span perspective of the current paper promises to increase interest in the formidable public health implications of the link of early maltreatment with such chronic depressive episodes.

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