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The interaction between child maltreatment, adult stressful life events and the 5-*HTTLPR* in major depression

Robert A. Power [a,*], Lucy Lecky-Thompson [a], Helen L. Fisher [a], Sarah Cohen-Woods [a], Georgina M. Hosang [a], Rudolf Uher [a,b], Georgia Powell-Smith [a], Robert Keers [a,c], Maria Tropeano [a], Ania Korszun [c], Lisa Jones [d], Ian Jones [e], Michael J. Owen [e], Nick Craddock [e], Ian W. Craig [a], Anne E. Farmer [a], Peter McGuffin [a]

[a] MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK
[b] Department of Psychiatry, Dalhousie University, Halifax, NS, Canada
[c] Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Centre for Psychiatry, London, UK
[d] Department of Psychiatry, School of Clinical & Experimental Medicine, University of Birmingham, Birmingham, UK
[e] MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK

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ABSTRACT

Both childhood maltreatment and adult stressful life events are established risk factors for the onset of depression in adulthood. However, the interaction between them can be viewed through two conflicting frameworks. Under a mismatch hypothesis stressful childhoods allow 'adaptive programming' for a stressful adulthood and so can be protective. Only when childhood and adulthood do not match is there a risk of behavioural problems. Alternatively, under the cumulative stress hypothesis we expect increased risk with each additional stressor. It has also been suggested that an individual's genetic background may determine the extent they undergo adaptive programming, and so which of these two hypotheses is relevant. In this study we test for an interaction between exposure to childhood maltreatment and adult stressful life events in a retrospective sample of 455 individuals, using major depression as the outcome. We also test whether this interaction differs by genotype at the 5-*HTTLPR*, a candidate for an individual's plasticity to adaptive programming.

Early maltreatment and stressful life events in adulthood interacted to produce increased risk for depression over each individually ($p = 0.055$). This supports the cumulative stress hypothesis over the mismatch hypothesis, at least with respect to severe environmental risk factors. This effect was not altered by 5-*HTTLPR* allele, suggesting there was no difference by genotype in adaptive programming to these events. We suggest that the apparent additional vulnerability to stressful events of those who have experienced maltreatment has clinical relevance, highlighting the importance of providing support beyond the immediate aftermath of maltreatment into adulthood.

1. Introduction

Child maltreatment (such as abuse or neglect) has long been associated with increased risk of psychopathology in adulthood, including depression (Edwards et al., 2003; Mazure, 1998; Windle et al., 1995), and presents a major social burden. Adult stressful life events (e.g. bereavement and divorce) also predict risk for the onset of depression (Brown and Harris, 1989; Monroe et al., 1999; Paykel et al., 1980) and triggering depressive episodes (Hosang et al., 2012). However, the interaction between these two types of adversity is far from simple. In a recent review of the topic, Nederhof and Schmidt (2012) described two conflicting models, the cumulative stress hypothesis and mismatch hypothesis, for explaining the interactions between early and adult stressors, and proposed a study design for differentiating them.

The cumulative stress hypothesis states that disease risk increases as adversity accumulates through life, the more traditional view for which there is considerable evidence e.g. (Brown et al., 2008; Kendler et al., 2004; McLaughlin et al., 2010). The mismatch hypothesis stipulates that individuals are primed to undergo "adaptive phenotypic programming" during development, in order to best match their adult phenotype with the predicted

* Corresponding author.
E-mail address: robert.r.power@kcl.ac.uk (R.A. Power).

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environment (Frankenhuis and Del Giudice, 2012). In this case, a stressful childhood leads to developmental changes to prepare for a stressful adulthood. In contrast to the cumulative risk hypothesis, in the mismatch hypothesis individuals are more likely to experience disease if the early environment is different from the later adult environment; when the predicted programming and experienced environment are not in agreement. Here, one might imagine an individual adapted for low levels of stress responding poorly to adversity. Alternatively, an individual adapted for high levels of stress but encountering none may experience an apparent excess of anxiety or paranoia relative to their stress free environment. A recent review of animal models testing the mismatch hypothesis highlighted numerous examples in agreement with the model, but also many that were not (Schmidt, 2012).

One potentially confounding factor is that individuals have been predicted to differ genetically in their ability to experience adaptive programming and susceptibility to the environment (Belsky et al., 2009). Those who are genetically very susceptible to programming are more likely to follow the mismatch hypothesis (so called 'plastic' individuals), whereas those with no genetic susceptibility to programming do not undergo the initial adaptation and so the adverse effects of stress will accumulate. An individual's burden of 'plasticity polymorphisms' may therefore determine whether they respond according to the mismatch or the cumulative hypothesis, and may explain some of the conflicting results to date. One such genetic plasticity factor is a polymorphism within the promoter region of the serotonin transporter gene (5-*HTTLPR*), a candidate for plasticity suggested by Nederhof and Schmidt and previously found to interact with environmental risk factors for depression (Caspi et al., 2003; Eley et al., 2004; Fisher et al., 2013; Karg et al., 2011; Schmidt, 2012; Taylor et al., 2006; Uher et al., 2011).

Here we seek to follow Nederhof and Schmidt's (2012) proposed study design to test the cumulative risk model and the mismatch model in explaining major depression, including an attempt to incorporate an individual's genetic susceptibility to adaptive programming. We use reported levels of childhood maltreatment and stressful life events prior to interview/depressive episode as markers for early and adult stressors, respectively. As well as looking at their interaction in the whole sample, we also test stratifying by genotype at the 5-*HTTLPR* which, as mentioned, has been explored as a candidate for gene–environment interactions including within this sample (Fisher et al., 2013, 2012). To our knowledge, this will be the first human study incorporating genotypic data into a test of the mismatch hypothesis. A finding in support of either the cumulative stress or mismatch hypothesis has relevance to how individuals who have experienced childhood stress are likely to be affected by adult stress and risk of depression.

2. Methods

2.1. Participants

Individuals with recurrent unipolar depression and healthy controls were drawn from the Cardiff and London sites of the Depression Case–Control (DeCC) multi-centre study (Cohen-Woods et al., 2009). This study was approved by the local University and NHS Ethics Committees at each site and all participants provided written informed consent. Patients were identified through psychiatric clinics, hospitals, general medical practitioner surgeries, and media advertisements. Patients must have experienced at least two episodes of depression of at least moderate severity, separated by 2 or more months of remission, as defined by DSM-IV (American Psychiatric Association, 1994) and/or ICD-10 (World Health Organisation, 1993). All participants were aged 18 or over and had parents and grandparents of white European origin. Exclusion criteria were a history of mania or hypomania, mood-incongruent psychosis, and a first or second- degree relative with bipolar or psychotic disorder. Controls were recruited through UK general medical practices and excluded if they had a personal or first-degree relative with a history of any psychiatric disorder.

2.2. Measure of child maltreatment

Self-reported abuse or neglect during childhood, defined as until age 17, was recorded using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). The CTQ is a 28 item questionnaire widely used in clinical and general population samples and has good psychometric properties (Bernstein et al., 2003; Scher et al., 2004). Here we used a dichotomous variable to differentiate those who had experienced abuse or neglect from those who had not. This used a cut-off score of 8 or more for the sexual abuse, physical abuse or neglect subscales; a cut-off of 10 for emotional abuse; and a cut-off of 15 for the emotional neglect subscale. If an individual's scores exceeded any of these cut-offs, they were deemed to have experienced childhood maltreatment (Fisher et al., 2013).

2.3. Measure of stressful life events

The List of Threatening Experiences Questionnaire (LTE-Q) (Brugha et al., 1985) was used to record 11 stressful life events that occurred 6 months before cases' most severe episode of depression or 6 months prior to interview for controls (see Hosang et al., 2010). Each event was rated on a scale of zero (not present) to 3 (severe) and in this analysis, only severe events were counted. As in the measure of childhood maltreatment, the measure of stressful life events was dichotomized into those with any severe events and those with none (Fisher et al., 2012).

2.4. Genotyping

A 25 ml sample of whole blood was collected from cases at the time of interview and six cheek swabs were obtained from controls by mail. Polymerase chain reaction (PCR) was performed on the samples to amplify a 419 base-pair product for the l-allele (16-repeat) and a 375 base-pair product for the s-allele (14-repeat) of the 5-*HTTLPR* (Gelernter et al., 1997). The primer sequences were TGCCAGCACCTAACCCCTAATGT (forward) and GGACCGCAAGGTGG GCGGGA (reverse). The products were run on 2.5–3% agarose gel at 100 mV for 1 h. Genotyping was conducted blind to depression status and life events, and is described in previous publications (Fisher et al., 2013).

2.5. Analysis

In a logistic regression model we tested for each combination of stressors (childhood maltreatment only, adult stressors only, or both) against those who had no stressors, with depression as the outcome. We also tested whether an additive interaction between the dichotomous variables for childhood maltreatment and adult stressful life events was predictive of depression, using a binomial regression. Analyses were corrected for sex and age at assessment. Lastly, we tested to see if the direction of effect for these analyses differed depending on genotype at the 5-*HTTLPR*, using a dominant model for carriers of the short allele. We tested for normality of residuals and heteroscedasticity, and to account for the latter in some regressions we checked the results were consistent when robust standard errors were used. All analyses were carried out in STATA (StataCorp., 2011).