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Brief report

Interaction between specific forms of childhood maltreatment and the serotonin transporter gene (5-*HTT*) in recurrent depressive disorder

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ABSTRACT

Background: There is inconsistent evidence of interaction between stressful events and a serotonin transporter promoter polymorphism (5-*HTTLPR*) in depression. Recent studies have indicated that the moderating effect of 5-*HTTLPR* may be strongest when adverse experiences have occurred in childhood and the depressive symptoms persist over time. However, it is unknown whether this gene–environment interaction is present for recurrent depressive disorder and different forms of maltreatment. Therefore, patients with recurrent clinically diagnosed depression and controls screened for the absence of depression were utilised to examine the moderating effect of 5-*HTTLPR* on associations between specific forms of childhood adversity and recurrent depression.
Method: A sample of 227 recurrent unipolar depression cases and 228 never psychiatrically ill controls completed the Childhood Trauma Questionnaire to assess exposure to sexual, physical and emotional abuse, physical and emotional neglect in childhood. DNA extracted from blood or cheek swabs was genotyped for the short (*s*) and long (l) alleles of 5-*HTTLPR*.
Results: All forms of childhood maltreatment were reported as more severe by cases than controls. There was no direct association between 5-*HTTLPR* and depression. Significant interactions with additive and recessive 5-*HTTLPR* genetic models were found for overall severity of maltreatment, sexual abuse and to a lesser degree for physical neglect, but not other maltreatment types.
Limitations: The cross-sectional design limits causal inference. Retrospective report of childhood adversity may have reduced the accuracy of the findings.
Conclusions: This study provides support for the role of interplay between 5-*HTTLPR* and a specific early environmental risk in recurrent depressive disorder.

1. Introduction

The potential aetiological role of an interaction between stressful experiences and a functional insertion/deletion polymorphism in the promoter region of the serotonin transporter gene (5-*HTTTLR*) in depression has sparked a great deal of debate and an array of inconsistent findings (Caspi et al., 2010; Munafò et al., 2009; Risch et al., 2009; Uher and McGuffin, 2010). However, stressful events occurring in childhood have been shown more consistently than those limited to adulthood to interact with the 5-*HTTLPR* to predict the presence of depression (Brown and Harris, 2008; Karg et al., 2011; Uher and McGuffin, 2008, 2010). This makes more biological sense as serotonin is thought to impact upon the neural circuits underlying affective regulation which mature during childhood and adolescence (Kobiella et al., 2011; Lenroot and Giedd, 2006). Therefore, these networks are likely to be more vulnerable to disruption from stressful events early in life (Sibille and Lewis, 2006).

Furthermore, interactions between early adversity and the 5-*HTTLPR* have been hypothesised to be stronger amongst individuals suffering from chronic or recurrent clinical depression (Brown and Harris, 2008) as a stronger direct effect has been found between childhood maltreatment and persistence rather than onset of depression (Brown et al., 1994; 2008; Brown and Moran, 1994). Indeed, recent studies have supported this proposition. Uher et al. (2011) reported a significant interaction between childhood maltreatment and the 5-*HTTLPR* in predicting persistent depression but not single depressive episodes using two different longitudinal cohorts. This study was unable though to determine whether persistent depression involved chronic and/or recurrent episodes. Subsequently, the 5-*HTTLPR* has been

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shown to moderate the association between adverse childhood experiences and any chronic episode of depression (Brown et al., under review). However, it remains unknown whether this gene–environment interaction is also involved in recurrent depression. Moreover, whereas these two studies did not differentiate between types of maltreatment, previous findings for sub-clinical depressive symptoms (Aguilera et al., 2009; Cicchetti et al., 2007) suggest that interactions with the 5-*HTTLPR* may be stronger for childhood sexual abuse than other forms of childhood adversity.

Therefore, we sought to investigate the interaction between specific forms of childhood maltreatment and the 5-*HTTLPR*, utilising a well-characterised sample of individuals who had experienced at least two episodes of moderate to severe unipolar depression and controls purposely selected for having no personal or family history of psychiatric disorder. To ensure complete transparency, we also analysed all three genetic models (additive, dominant and recessive) in interaction with each form of maltreatment as there is no consensus concerning whether one or two 5-*HTTLPR* short alleles confer risk or indeed if there is a cumulative impact (Uher and McGuffin, 2008). We hypothesised that the short allele of the 5-*HTTLPR* would moderate the effect of childhood maltreatment in predicting recurrent depression and that this interaction would be stronger for sexual abuse than other maltreatment types.

2. Method

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 (see 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.

All participants were Caucasian, with parents and grandparents of white European origin, and aged 18 years or over. Patients were identified through psychiatric clinics, hospitals, general medical practitioner surgeries, and media advertisements. Patients must have experienced at least two episodes of unipolar depression of at least moderate severity and 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). Exclusion criteria were 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. Measures

Diagnosis. Cases were interviewed in person using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing et al., 1990). SCAN items were rated for the 4–6 week period of peak intensity within the two most severe episodes of depression. The CATEGO5 scoring program provided DSM-IV or ICD-10 diagnoses.

2.3. Childhood maltreatment

Self-reported emotional (EA), physical (PA), sexual (SA) abuse, emotional (EN) and physical (PN) neglect during childhood were recorded using the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003). The CTQ is widely used in clinical and general population samples and has good psychometric properties (Bernstein et al., 2003; Scher et al., 2004). Subscale scores were coded as none (0), mild (1), moderate (2) and severe (3) in accordance with the manual (Bernstein et al., 2003). An overall maltreatment score was also derived using a rounded average of the scores of all five subtypes. Prior to analysis the moderate (2) and severe (3) categories for each maltreatment type were combined due to the small numbers of participants in the latter category for some forms of maltreatment.

2.4. Current mood

Cases and controls completed the Beck Depression Inventory Second Edition (BDI-II; Beck et al., 1996) to ascertain their mood state at the time of completing the CTQ. A total score was obtained by summing up all of the items, with higher scores indicating greater severity of depression. Controls that scored 10 or more on the BDI-II were excluded. Cases scoring 29 or more were classified as severely depressed (Beck et al., 1996).

2.5. 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 ATGCCAGCACCTAACCCCTAATGT (forward) and GGACCGCAAGGTGGGCGGGA (reverse). The products were run on 2.5–3% agarose gel at 100 mV for one hour. In excess of 100 randomly selected samples were re-genotyped with an extremely low genotyping error rate being observed (0.26%); such individuals were excluded from further analyses. Genotyping was conducted blind to depression status and childhood maltreatment history and the 5-*HTTLPR* genotypes (l/l [two long alleles]: 33%; s/l [one short and one long allele]: 48%; s/s [two short alleles]: 19%) were in Hardy–Weinberg equilibrium ($X^2=0.192$, $p=0.662$).

2.6. Analysis

Analyses were conducted using Stata version 11.0. Cuzick's non-parametric trend test was employed to investigate the effect of genotype (l/l, s/l, s/s) on depression case status and maltreatment severity. The main effects and interaction between childhood maltreatment and 5-*HTTLPR* on the presence/absence of recurrent unipolar depression was examined using a generalised linear model with the binomial distribution and identity link function specified (Wacholder, 1986) to estimate risk differences (RD) and 95% confidence intervals (CI). These analyses were adjusted for gender. All three possible genetic models were tested—additive (0=l/l, 1=s/1, 2=s/s), dominant (0=l/l, 1=s/l or s/s) and recessive (0=l/l or s/l, 1=s/s).

3. Results

Data were available on 227 recurrent unipolar depression cases and 228 screened controls. The majority of cases were women ($n=163$, 71.8%), their mean age at interview was 45.4 years ($SD=12.7$; 20–82 years), and they had an average onset of depression at 23.2 years ($SD=11.0$). Controls also tended to be women ($n=137$, 60.1%) and their mean age at interview was 47.2 years ($SD=9.1$; 25–62 years).

There was no difference in the distribution of genotypes between depressed cases and controls ($z=-0.15$, $p=0.880$) and no main