Journal of Affective Disorders 136 (2012) 189–193

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

Stressful life events and the serotonin transporter gene (*5-HTT*) in recurrent clinical depression

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ARTICLE INFO

Article history:
Received 9 August 2011
Received in revised form 17 September 2011
Accepted 18 September 2011
Available online 6 October 2011

Keywords:
Stressful life events
Unipolar depression
Recurrent
Serotonin transporter gene
Gene–environment interaction
5-HTTLPR

ABSTRACT

Background: An interaction between recent stressful life events (SLEs) and a serotonin transporter promoter polymorphism (*5-HTTLPR*) in depression has been inconsistently reported. Some of this variability may be due to a previous focus on sub-clinical depression, inclusion of individuals at the lower or upper ends of the age-span, or assumptions concerning the degree of dominance of the low expressing allele. Therefore, a large sample of patients with recurrent clinically diagnosed depression and controls screened for absence of depression was utilised to examine the moderating effect of each *5-HTTLPR* genetic model on the association between SLEs and severe depressive episodes.

Method: A sample of 1236 recurrent unipolar depression cases and 598 age-matched, never psychiatrically ill controls completed the List of Threatening Experiences Questionnaire to assess the number of SLEs experienced in the 6 months prior to the most severe depressive episode (cases) or interview (controls). DNA extracted from blood or cheek swabs was genotyped for the short (s) and long (l) alleles of *5-HTTLPR*.

Results: A greater number of SLEs were reported by cases than controls and this held across all genotypic groups. There was no main effect of *5-HTTLPR* on depression and no evidence of interaction between total SLEs and any of the *5-HTTLPR* genetic models. The results were the same for men and women.

Limitations: Utilisation of retrospective self-reported SLEs may have reduced the accuracy of the findings and the cross-sectional design prevents causal inference.

Conclusions: This study failed to find evidence of gene–environment interplay in recurrent clinical depression.

1. Introduction

Stressful experiences in childhood have consistently been shown to interact with a functional insertion/deletion polymorphism in the promoter region of the serotonin transporter gene (*5-HTTTLR*) to predict the presence of depression (Karg et al., 2011). However, the evidence for an interaction between this polymorphism and stressful life events in adulthood (SLEs) has been contradictory (Caspi et al., 2010; Munafò et al., 2009; Risch et al., 2009; Uher and McGuffin, 2010).

One potential reason for this inconsistency is that the phenotype examined has been too broadly defined (Uher

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doi:10.1016/j.jad.2011.09.016

and McGuffin, 2008), by utilising individuals with non-clinical depression (Lazary et al., 2008; Taylor et al., 2006) or those with only one depressive episode (Drachmann Bukh et al., 2009; Wilhelm et al., 2006). Indeed interactions with the *5-HTTLPR* have been hypothesised to be stronger amongst individuals suffering from chronic or recurrent clinical depression (Brown and Harris, 2008). Indeed, Uher et al. (2011) found an interaction between childhood maltreatment and the *5-HTTLPR* for persistent depression but not for single episodes of the disorder. However, the interactive effect of adult SLEs and the *5-HTTLPR* on chronic clinical depression has not yet been investigated. Additionally, as individuals with persistent depression place the highest burden on health services and the wider economy (World Health Organisation [WHO], 2006), it seems imperative that research should be focused on gaining a better understanding of what predicts recurrent depression to aid prevention of this longer-term disabling disorder.

Therefore, we sought to investigate the interaction between SLEs and the *5-HTTLPR*, utilising a large well-characterised sample of individuals with moderate to severe recurrent unipolar depression and controls purposely selected for having no personal or family history of psychiatric disorder. We also (i) limited our sample to individuals whose worst episode of depression occurred in early to mid-adulthood when this gene–environment interaction is expected to have its strongest effect (Uher and McGuffin, 2008); (ii) analysed all three genetic models (additive, dominant and recessive) as well as each *5-HTTLPR* genotype separately to ensure complete transparency of our results; and (iii) repeated our analysis stratified by gender as interaction effects have been found more consistently in women (Eley et al., 2004; Grabe et al., 2005; Hammen et al., 2010; Sjoberg et al., 2006). It was hypothesised that the short allele of the *5-HTTLPR* would moderate the effects of SLEs in predicting the most severe episode of depression and that this effect would be stronger in women.

2. Method

2.1. Participants

Individuals with recurrent unipolar depression and healthy controls were drawn from the Birmingham, Cardiff and London sites of the Depression Case–control (DeCC) multi-centre study (see Cohen-Woods et al., 2009). Additional controls from London were obtained from the Bipolar Affective Case–control study (BACCs; see Gaysina et al., 2009). These studies were 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 respondents to media advertisements. Patients must have experienced no less than 2 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 the ICD-10 (WHO, 1993). Exclusion criteria included: history of mania or hypomania, mood-incongruent psychosis, or a first or second-degree relative with bipolar or psychotic disorder. Controls were recruited through UK general medical practices across the UK (DeCC) or via internal emails at King's College London and newspaper advertisements (BACCs). Controls were excluded if they had a personal or first-degree relative with a history of psychiatric disorder. As number of SLEs has been demonstrated to be correlated with age at index period (Hosang et al., 2010), controls were only selected if their age at interview fell within 1 standard deviation either side of the mean age of patients at the time of their worst episode of depression (i.e. 24–49 years).

2.2. Measures

2.2.1. 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 most severe episode of depression. The CATEGO5 computerised scoring program provided DSM-IV or ICD-10 unipolar depression diagnoses.

2.2.2. Stressful life events

The List of Threatening Experiences Questionnaire (LTE-Q; Brugha et al., 1985) was used to record 11 SLEs that occurred 6 months before unipolar cases' most severe episode of depression and 6 months prior to interview for both cases and controls. The total score was collapsed into 0, 1 and 2 or more events due to the small number of participants reporting more than 2 events.

2.2.3. Current mood

Depressed 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 LTE-Q. A total score was obtained by summing all of the items, with higher scores indicating greater severity of depression. Controls that scored 10 or more on the BDI-II were excluded.

2.2.4. 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 ATGCCAGCACCTAACCCCTAATGT (forward) and GGACCGCAAGGTGGGCGGGA (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.

2.3. Analysis

Cuzick's non-parametric trend test was employed to investigate the effect of genotype (l/l: 2 long alleles; s/l: 1 short and 1 long allele; s/s: 2 short alleles) and SLEs on depression case status. The main effects and interaction between SLEs 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%