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

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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.

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Contributors.

P McGuffin and A Farmer designed the study and wrote the protocol. Profs Craig, Craddock, Farmer, Korszun, McGuffin and Owen and Drs I Jones and L Jones were involved in the management of the study and the data collected. S Cohen-Woods, G Powell-Smith and M Tropeano oversaw appropriate storage of the tissue samples and undertook genotyping. G Hosang, S Cohen-Woods and R Keers assisted with data cleaning and management of the database. R Uher provided advice on statistical analysis and interpretation of the findings. HL Fisher undertook the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest.

Anne Farmer and Peter McGuffin have received consultancy fees and honoraria for participating in expert panels from pharmaceutical companies including Lundbeck and GlaxoSmithKline. All other authors declare that they have no conflicts of interest.

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.

Keywords

Stressful life events; unipolar depression; recurrent; serotonin transporter gene; gene-environment interaction; *5-HTTLPR*

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-HTTLR*) 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 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; Sjöberg 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.

Method

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).

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

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.

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.

Genotyping—A 25ml 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 ATGCCAGCACCTAACCCTAATGT (forward) and GGACCGCAAGGTGGGCGGGA (reverse). The products were run on 2.5-3% agarose gel at 100mV for one hour. Genotyping was conducted blind to depression status and life events.

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% confidence intervals (CI). These analyses were adjusted for age at index period (most severe episode for cases; interview for controls) and repeated separately by gender. Regression censored at a minimum value of 0 was employed to assess main and interactive effects between SLEs in the 6 months prior to interview and *5-HTTLPR* genetic models on total current BDI-II score amongst cases. This analysis was adjusted for the cases' age at interview.

Results

Data were available on 1236 recurrent unipolar depression cases and 598 age-matched controls (334 from DeCC and 264 from BACCS). The majority of cases were women ($n=844$, 68.3%) and their mean age at interview was 47.5 years ($SD=12.3$; 20-82 years). The unipolar cases had an average onset of depression at 23.3 years ($SD=11.7$) and their mean age at the start of their most severe depressive episode was 36.7 ($SD=12.2$). Controls also tended to be women ($n=354$, 59.2%) and their mean age at interview was 36.8 years ($SD=8.1$; 24-49 years).

The *5-HTTLPR* genotypes were in Hardy-Weinberg equilibrium amongst both cases ($X^2=0.014$, $p=0.908$) and controls ($X^2=1.402$, $p=0.317$). There was no difference in the distribution of genotypes between depressed cases and controls ($z=-0.12$, $p=0.904$). Recurrent unipolar cases reported significantly more SLEs in the 6 months prior to their worst depressive episode than controls in the 6 months prior to interview ($z=14.34$, $p<0.001$). This difference remained when the unipolar cases with severe levels of depression at the time of reporting (BDI-II score ≥ 29 ; $n=358$, 29.0%) were excluded ($z=10.57$, $p<0.001$) suggesting that current mood did not substantially bias reports of SLEs. There was no significant difference in the number of SLEs reported by genotype amongst cases ($z=-0.48$, $p=0.634$) or controls ($z=-0.14$, $p=0.889$).

Table 1 presents the main and interactive effects of SLEs and *5-HTTLPR* on presence of recurrent unipolar depression. The number of SLEs reported in the 6 months prior to the index period was significantly associated with greater risk of severe depression even after adjustment for age at index period. This association was evident amongst all *5-HTTLPR* genotypic groups. No main effects were found for any of the *5-HTTLPR* genetic models nor were there any significant interactions with SLEs.

Finally, the effects of SLEs and *5-HTTLPR* on severity of current depression amongst the unipolar cases were investigated (Table 2). There was a main effect of number of SLEs in the 6 months prior to interview on BDI-II score and this held across all *5-HTTLPR* genotypes. No main genetic effect was evident. No significant interactions between SLEs and any of the *5-HTTLPR* genetic models were found. All findings remained unchanged when the analysis was stratified by sex (results not shown).

Discussion

This large sample of well-characterised individuals with recurrent unipolar depression and age-matched controls selected for lifetime absence of psychiatric disorder failed to provide evidence of an interaction between *5-HTTLPR* and SLEs in severe clinical depression. This lack of interaction was apparent for both recurrent unipolar depression and severity of depressed mood at time of interview amongst the cases, as well as for both men and women.

The lack of interaction between SLEs and *5-HTTLPR* is contrary to many previous studies but consistent with two meta-analyses that found no replicable evidence of interaction (Munafò et al., 2009; Risch et al., 2009). Therefore, one potential explanation for the current findings is that there is actually no interaction between SLEs and *5-HTTLPR* in recurrent depression. Alternatively, this study may have failed to detect an interaction due to a lack of power, utilisation of brief self-report measures (Uher and McGuffin, 2010), the focus on SLEs that only occurred within a short period (compared to Caspi et al., 2003), or because childhood adversity is driving the effect (Brown and Harris, 2008). Moreover, the lack of a gender difference in the current study may be due to the age of our participants and the inclusion of only severe clinical depressive episodes.

One limitation is the reliance upon cross-sectional retrospective self-report of depression and SLEs. However, studies have demonstrated that depressive symptoms do not result in exaggeration of retrospectively recalled stressful events (Brewin et al., 1993; Fisher et al., 2011) and when severely depressed cases were removed from our analysis the greater preponderance of SLEs in the depression group remained. Additionally, severe depressive episodes are likely to be the most memorable (Kendler et al., 1993) and self-reports are comparable to contemporary hospital records (McGuffin et al., 1986). Nonetheless, for some individuals there was around 10 years between the occurrence of their worst depressive episode and interview, potentially reducing the accuracy of the findings.

Another limitation is that patients were not systematically recruited; however the sample was broadly comparable to more systematically collected series (Kessler et al., 1993) and it seems unlikely that this would have resulted in an excess of cases with an unusually large number of life events during the index period. Nevertheless, it is not possible to extrapolate the findings to other ethnic groups. There were also insufficient participants to assess population stratification, though the inclusion of only Caucasian individuals from England and Wales may have minimised this potential bias. Additionally, we did not take into account the single nucleotide polymorphism (SNP) rs25531 within the repeats region of the *5-HTTLPR* as most comparable studies have only utilised bi-allelic genotypes. Moreover, the functionality of this SNP has been questioned (Huezo-Diaz et al., 2009), it may not index a greater proportion of biological variation (Clarke et al., 2010), and as the minor allele frequency of this SNP is low it is unlikely to have substantially affected our results. However, taking into account the functional second intron (STin2) SNP in future investigations may be warranted (Huezo-Diaz et al., 2009).

In conclusion, this large study of recurrent unipolar depression failed to extend evidence of an interaction between the *5-HTTLPR* and SLEs in depression to severe episodes of clinically diagnosed depression. These results require further exploration in similarly well-characterised samples, ideally with more objective assessments of stressors over longer periods.

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Table 1

Effects of stressful life events in the 6 months prior to most severe depressive episode (cases) or interview (controls), *5-HTTLPR* genetic models and their interactions on presence of recurrent unipolar depression.

	Adjusted RD ^a	95% CI		P
		Lower	Upper	
<i>Main effects</i>				
Stressful life events				
Overall (N=1834)	0.208	0.182	0.234	<0.001
l/l genotype (N=606)	0.198	0.151	0.245	<0.001
s/l genotype (N=884)	0.232	0.197	0.268	<0.001
s/s genotype (N=344)	0.160	0.095	0.225	<0.001
Additive genetic model	−0.009	−0.044	0.025	0.594
Recessive genetic model	−0.018	−0.081	0.045	0.573
Dominant genetic model	−0.009	−0.060	0.042	0.737
<i>GxE interactions</i>				
Additive model x SLEs	−0.010	−0.047	0.028	0.615
Recessive model x SLEs	−0.058	−0.129	0.012	0.104
Dominant model x SLEs	0.015	−0.041	0.072	0.593

^a Adjusted for age at most severe depressive episode (cases) or interview (controls). *5-HTTLPR*, polymorphism in promoter region of serotonin transporter gene. CI, confidence interval. GxE, gene by environment interaction. l/l, homozygous for long allele. *p*, probability of result being due to chance. RD, risk difference. s/l, heterozygous. SLEs, stressful life events. s/s, homozygous for short allele.

Table 2

Effects of stressful life events in the 6 months prior to interview for recurrent unipolar depression cases, *5-HTTLPR* genetic models and their interactions on total BDI-II score of current depression.

	Adjusted beta ^a	95% CI		P
		Lower	Upper	
<i>Main effects</i>				
Stressful life events				
Overall (N=1236)	2.379	1.502	3.256	<0.001
l/l genotype (N=406)	2.762	1.202	4.322	0.001
s/l genotype (N=603)	2.024	0.773	3.276	0.002
s/s genotype (N=227)	2.544	0.520	4.568	0.014
Additive genetic model	−0.678	−1.693	0.338	0.191
Recessive genetic model	−0.611	−2.446	1.224	0.514
Dominant genetic model	−1.090	−2.603	0.424	0.158
<i>GxE interactions</i>				
Additive model x SLEs	−0.205	−1.460	1.050	0.748
Recessive model x SLEs	0.329	−1.917	2.576	0.774
Dominant model x SLEs	−0.631	−2.515	1.253	0.511

^a Adjusted for age at interview. *5-HTTLPR*, polymorphism in promoter region of serotonin transporter gene. beta, regression coefficient censored with a lower limit of 0. BDI-II, Beck Depression Inventory – Second Edition (Beck et al., 1996) assesses severity of depressed mood over 2 weeks prior to interview. CI, confidence interval. GxE, gene by environment interaction. l/l, homozygous for long allele. *p*, probability of result being due to chance. s/l, heterozygous. SLEs, stressful life events. s/s, homozygous for short allele.