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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 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.

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Keywords

Childhood maltreatment; unipolar depression; recurrent; serotonin transporter gene; gene-environment interaction; *5-HTTLPR*

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; Brown et al., 2008; Brown & 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 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.

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Method

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 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 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.

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.

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.

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 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).

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 ATGCCAGCACCTAACCCCTAATGT (forward) and GGACCGCAAGGTGGGCGGGA (reverse). The products were run on 2.5-3% agarose gel at 100mV 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 [2

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long alleles]: 33%; s/l [1 short and 1 long allele]: 48%; s/s [2 short alleles]: 19%) were in Hardy-Weinberg equilibrium (X^2=0.192, p=0.662).

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).

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 effects of the *5-HTTLPR* genetic models on recurrent depression (additive: Adj.RD=−0.011, 95% CI −0.75-0.054, p=0.749; recessive: Adj.RD=−0.112, 95% CI −0.228-0.003, p=0.056; dominant: Adj.RD=0.055, 95% CI −0.42-0.151, p=0.267). There was also no significant difference in the overall severity of maltreatment reported by genotype amongst cases (z=1.41, p=0.158) or controls (z=0.08, p=0.935).

Table 1 presents the main effects of each form of maltreatment and their interactions with *5-HTTLPR* on presence of recurrent unipolar depression. All forms of childhood maltreatment were significantly associated with greater risk of recurrent depression even after adjustment for gender. These differences remained when the unipolar cases with severe levels of depression at the time of reporting (BDI-II score >=29: n=72, 31.7%) were excluded (overall: Adj.RD=0.271, 95% CI 0.206-0.336, p<0.001; EA: Adj.RD=0.251, 95% CI 0.194-0.307, p<0.001; PA: Adj.RD=0.136, 95% CI 0.040-0.231, p=0.005; SA: Adj.RD=0.105, 95% CI 0.025-0.185, p=0.010; EN: Adj.RD=0.187, 95% CI 0.126-0.249, p<0.001; PN: Adj.RD=0.264, 95% CI 0.205-0.323, p<0.001) suggesting that current mood did not substantially bias reports of childhood maltreatment. The proportion of participants with recurrent depression for each level of childhood maltreatment severity by *5-HTTLPR* genotype is visually displayed in Figure 1. Significant interactions were found for overall maltreatment severity, sexual abuse and physical neglect with both additive and recessive *5-HTTLPR* genetic models. However, only interactions with sexual abuse remained significant when a Bonferroni correction for multiple testing was applied (p=0.05/18=0.003). No interactions were demonstrated for the other forms of maltreatment.

Discussion

This sample of well-characterised individuals with recurrent unipolar depression and controls selected for lifetime absence of psychiatric disorder provided preliminary evidence of interaction between severity of childhood maltreatment and the *5-HTTLPR* in relation to recurrent depression. Specifically, the strongest interactions were found between sexual abuse and *5-HTTLPR*, under both additive and recessive genetic models. Weaker

interactions were demonstrated for physical neglect but these did not remain statistically significant after correction for multiple testing. These findings extend previous reports of interactions between *5-HTTLPR* and undifferentiated childhood maltreatment on persistent depression (Brown et al., under review; Uher et al., 2011).

Given that a previous analysis of this sample found no interactions between adult stressful life events and the *5-HTTLPR* (Fisher et al., 2012), the current findings are also in keeping with the proposition that the *5-HTTLPR* specifically moderates the effects of adversity that occurs in childhood (Karg et al., 2011; Uher and McGuffin, 2008, 2010). The greater aetiological importance of an early gene-environment interaction seems biologically plausible as the neural circuits involved in affective regulation, and that are impacted upon by the *5-HTTLPR*, mature during childhood and adolescence (Kobiella et al., 2011; Lenroot and Giedd, 2006). Additionally, the specificity of the gene-environment interaction found is consistent with previous reports for depressive symptoms, which suggest a stronger interactive effect of sexual abuse and the *5-HTTLPR* than for other forms of maltreatment (Aguilera et al., 2009; Cicchetti et al., 2007) and may point to excessively heightened stress levels following exposure to this type of maltreatment. Furthermore, the greater moderating effect of the s/s genotype, suggested by the significant additive and recessive *5-HTTLPR* interactions, was also reported by Uher et al. (2011) in relation to persistent depression. However, it is also possible that exposure to stressful events in both childhood and adulthood may interact with the *5-HTTLPR* to further increase the risk of experiencing recurrent depression. Unfortunately we did not have sufficient power in this sample to investigate this potential three-way interaction but it should be considered in future larger studies.

One limitation is the relatively small sample size which may have reduced our power to detect significant interactions for other forms of maltreatment. It is also possible that we did not find any other interactions due to exclusion of controls that had a first-degree relative with a psychiatric disorder. Parents with mental health problems are more likely to maltreat their children (Taylor et al., 1991) and thus our study design may have resulted in under-detection of the more commonly parent-perpetrated forms of maltreatment amongst controls and potentially reduced our power to detect significant interactions. Another limitation is that we relied on retrospective self-reports of depression and childhood maltreatment. However, severe depressive episodes are arguably the most memorable (Kendler et al., 1993) and self-report agrees well with contemporary hospital records (McGuffin et al., 1986). Furthermore, 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 severity of childhood maltreatment in the depression group remained. Therefore, the use of retrospective self-reports is likely to have had only a minimal impact on these results.

Although patients in the current study were not systematically recruited, they are broadly comparable to more systematically collected series (Kessler et al., 1993) and it seems unlikely that cases with an unusually high severity of childhood maltreatment would have been recruited. We were also unable to include a group who had experienced only a single depressive episode and thus could not test whether the interaction between childhood maltreatment and *5-HTTLPR* was stronger for recurrent versus single episode depression. There were also too few participants to stratify analysis by gender and this warrants future investigation as some previous studies on depression onset have reported interactions only amongst women (Eley et al., 2004; Hammen et al., 2010). Additionally, to be consistent with the prior studies of persistent depression we did not take into account the single nucleotide polymorphism (SNP) rs25531 within the repeats region of the *5-HTTLPR*. As this SNP has a low minor allele frequency, excluding it is unlikely to have substantially

affected our results. However, future studies might usefully take into account the functional second intron (STin2) SNP (Huezo-Diaz et al., 2009).

In conclusion, this study extended findings of interactions between childhood maltreatment and the *5-HTTLPR* to clinically diagnosed recurrent depression and demonstrated a particularly strong interaction for sexual abuse. These results require replication in larger, similarly well-characterised samples, ideally with prospective assessments of maltreatment.

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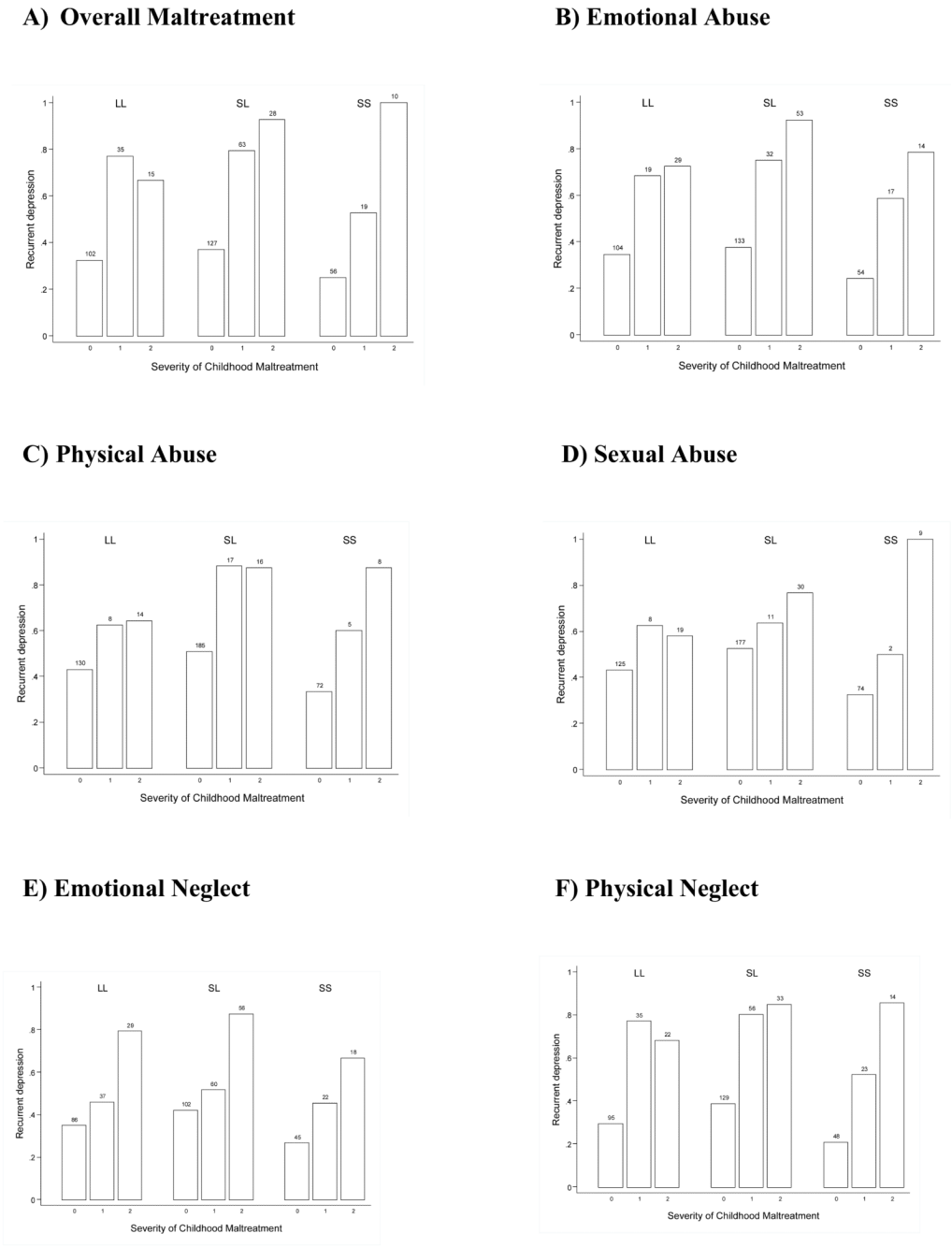

Fig. 1. Proportion of individuals with recurrent depression by severity of different types of childhood maltreatment and serotonin transporter (*5-HTTLPR*) genotype.

The y axis shows the probability of reporting recurrent depressive episodes by severity of childhood maltreatment and *5-HTTLPR* genotype (LL, SL, and SS). Maltreatment severity is based on the Childhood Trauma Questionnaire (0 = None, 1 = Mild, 2 = Moderate or Severe), with a rounded average score of all domains for overall maltreatment (panel A), and individual domain scores for emotional abuse (panel B), physical abuse (panel C), sexual abuse (panel D), emotional neglect (panel E) and physical neglect (panel F). The number of individuals included in each subgroup is given above each bar.

Table 1

Main effect of different forms of childhood maltreatment and their interactions with each *5-HTTLPR* genetic model on presence of recurrent unipolar depression.

Type of maltreatment	Depressed cases	Unaffected controls	Adjusted RD[a]	95% CI		*p*
	n (%)	*n (%)*		Lower	Upper	
Overall Maltreatment (OM)			0.273	0.227	0.319	<0.001
None	94 (41.4)	191 (83.8)				
Mild	87 (38.3)	30 (13.2)				
Moderate/severe	46 (20.3)	7 (3.0)				
Additive model × OM			0.072	0.024	0.120	0.003
Recessive model × OM			0.098	0.022	0.175	0.012
Dominant model × OM			0.053	−0.058	0.164	0.347
Emotional Abuse (EA)			0.247	0.202	0.292	<0.001
None	99 (43.6)	192 (84.2)				
Mild	47 (20.7)	21 (9.2)				
Moderate/severe	81 (35.7)	15 (6.6)				
Additive model × EA			0.034	−0.031	0.098	0.305
Recessive model × EA			0.023	−0.102	0.149	0.714
Dominant model × EA			0.070	−0.032	0.172	0.180
Physical Abuse (PA)			0.180	0.117	0.242	<0.001
None	174 (76.7)	213 (93.4)				
Mild	23 (10.1)	7 (3.1)				
Moderate/severe	30 (13.2)	8 (3.5)				
Additive model × PA			0.049	−0.029	0.128	0.220
Recessive model × PA			0.083	−0.062	0.228	0.263
Dominant model × PA			0.090	−0.051	0.231	0.211
Sexual Abuse (SA)			0.134	0.073	0.195	<0.001
None	171 (75.3)	205 (89.9)				
Mild	13 (5.7)	8 (3.5)				
Moderate/severe	43 (19.0)	15 (6.6)				
Additive model × SA			0.119	0.063	0.175	<0.001
Recessive model × SA			0.218	0.130	0.306	<0.001
Dominant model × SA			0.091	−0.041	0.224	0.117
Emotional Neglect (EN)			0.219	0.170	0.268	<0.001
None	85 (37.4)	148 (64.9)				
Mild	58 (25.6)	61 (26.8)				
Moderate/severe	84 (37.0)	19 (8.3)				
Additive model × EN			−0.012	−0.082	0.058	0.729
Recessive model × EN			−0.036	−0.169	0.097	0.594
Dominant model × EN			−0.005	−0.111	0.100	0.919
Physical Neglect (PN)			0.256	0.209	0.303	<0.001
None	88 (38.8)	184 (80.7)				

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Type of maltreatment	Depressed cases	Unaffected controls	Adjusted RD[a]	95% CI		*p*
	n (%)	*n (%)*		Lower	Upper	
Mild	84 (37.0)	30 (13.2)				
Moderate/severe	55 (24.2)	14 (6.1)				
Additive model × PN			0.052	0.001	0.103	0.049
Recessive model × PN			0.102	0.001	0.203	0.048
Dominant model × PN			0.030	−0.073	0.134	0.566

[a]Adjusted for gender. *5-HTTLPR*, polymorphism in promoter region of serotonin transporter gene. CI, confidence interval. *p*, probability of result being due to chance. RD, risk difference.