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Brief Research Communication

No Interaction Between the Serotonin Transporter Polymorphism (5-HTTLPR) and Childhood Adversity or Recent Stressful Life Events on Symptoms of Depression: Results From Two Community Surveys

P. Chipman,[1]* A.F. Jorm,[1,2] M. Prior,[3] A. Sanson,[4] D. Smart,[5] X. Tan,[6] and S. Easteal[6]

[1]*Centre for Mental Health Research, Australian National University, Canberra, Australia*
[2]*ORYGEN Research Centre, University of Melbourne, Melbourne, Australia*
[3]*Department of Psychology, University of Melbourne, Melbourne, Australia*
[4]*Department of Paediatrics, University of Melbourne, Melbourne, Australia*
[5]*Australian Institute of Family Studies, Melbourne, Australia*
[6]*John Curtin School of Medical Research, Australian National University, Canberra, Australia*

In this study we investigated interactions between the 5-HTTLPR genotype and environmental risk factors (G × E) on symptoms of depression in two large Australian community samples of adolescents and young adults. We postulated that a significant interaction between the 5-HTTLPR genotype and environmental risk factors of childhood adversity or stressful life events on symptoms of depression would be observed in subjects with at least one short allele (s/l or s/s) compared with subjects with no short alleles (l/l). We did not find significant G × E interactions between the 5-HTTLPR genotype and recent stressful life events or childhood adversity on symptoms of depression in our sample populations. However, we did find adolescents aged 17–18 years homozygous for the long allele (l/l) and exposed to persistently high levels of family adversity over a 6-year period were at a greater risk of depression than subjects with the same genotype exposed to no or persistently low levels of family adversity. This interaction should be interpreted cautiously due to the small number of depressed subjects in the sample with persistently high levels of family adversity.
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KEY WORDS: 5HTTLPR; polymorphism; gene–environment interaction; depression

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INTRODUCTION

The serotonin transporter (5-HTT) protein is encoded by a gene with a functional polymorphism (5-HTTLPR) in its promoter region consisting of a 44-base pair (bp) insertion or deletion resulting in long (l) and short (s) alleles [Heils et al., 1996]. In vitro studies show that the long allele variant has about three times the transcriptional activity of the short allele variant [Heils et al., 1996; Lesch et al., 1996]. In 1996, Lesch et al. [1996] reported a significant association between anxiety-related personality traits and the short allele of the 5-HTTLPR genotype in a predominantly Caucasian population.

Over the ensuing decade consistent replication of the initial results of Lesch et al. [1996] has not been forthcoming with subsequent published studies reporting conflicting findings. However, results from three recent independent meta-analyses suggest that a positive association between the 5-HTTLPR genotype and anxiety-related personality traits can be demonstrated provided an appropriate assessment instrument is used to assess the trait [Schinka et al., 2004; Sen et al., 2004, 2005; Schinka, 2005; Munafò et al., 2005a, 2005b]. Furthermore, Caspi et al. [2003] have suggested that inconsistent results among studies might indicate that the effects of the 5-HTTLPR genotype on personality and mood are conditional on exposure to environmental risk factors. These authors found that the 5-HTTLPR genotype significantly moderated the effect of life events on depression in young Caucasian adults although the genotype alone was not directly associated with depression [Caspi et al., 2003]. The effect of stressful life events on self reports of symptoms of depression, diagnosis of major depression, and suicidal ideation or attempt was significant in individuals with at least one short allele (s/s or s/l) but not in those homozygous for the long allele (l/l). The reported interaction between the 5-HTTLPR genotype and stressful life events on depression has now been replicated by Wilhelm et al. [2006]. In contrast, no evidence supporting an interaction between the 5-HTTLPR genotype and stressful life events on depression was found by Jorm et al. [1998] and Gillespie et al. [2005]. However, interactions

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*Correspondence to: P. Chipman, Centre for Mental Health Research, Australian National University, Canberra ACT, 0200, Australia. E-mail: pchipman@bigpond.net.au

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between the genotype and environmental stressors on psychological outcomes have been reported by Eley et al. [2004], Kaufman et al. [2004], Grabe et al. [2005], and Kendler et al. [2005].

In our study, we investigated interactions between the 5-HTTLPR and environmental risk factors on symptoms of depression in adolescents and young adults in two large samples from the general Australian population.

MATERIALS AND METHODS

PATH20 participants came from the PATH Through Life Project, a large ongoing community survey concerned with the health and well being of people aged 20–24, 40–44, and 60–64 years who live in Canberra, Australia, or the neighboring town of Queanbeyan. The method for this survey has been described in detail previously [Jorm et al., 2003]. The results reported here are from 2,095 participants (52.1% female, 47.9% male) aged 20–24 years on 1 January 1999 who identified themselves as "Caucasian/White." Symptoms of depression and anxiety were assessed by the Goldberg Depression and Anxiety Scales [Goldberg et al., 1988], anxiety proneness in response to situational cues by the Behavioral Inhibition System component of the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) scales based on Gray's neuropsychological theory of anxiety [Carver and White, 1994], and neuroticism by the Neuroticism scale of the short form of the Eysenck Personality Questionnaire-Revised [Eysenck et al., 1985]. Stressful life events experienced over the 6 months immediately preceding interview were assessed by a 12-item list of threatening experiences [Brugha et al., 1985]. Childhood adversity up to the age of 16 years was assessed by a list of 17 adversities ranging from relatively common experiences such as mother, or mother figure, suffering from "nervous or emotional trouble or depression" to rare events such as "sexual abuse by a parent" [Rosenman and Rodgers, 2004]. Both recent stressful life events and childhood adversities were divided into five groups based on the number of events and adversities (none, one, two, three, and four or more).

The ATP is a longitudinal study of the psycho-social development of a representative sample of 2,443 children born in the Australian state of Victoria between September 1982 and January 1983 [Prior et al., 2000]. The results reported here are from a cohort of adolescents aged 15–16 years in 1998, and 17–18 years in 2000 on whom DNA had been collected for genotyping. Relevant data were available on 584 (50.6% females, 49.4% males) adolescents at age 15–16 years, and 544 (48.5% females, 51.5%) at age 17–18 years. While race was not recorded, information on the total number of children in the study for whom DNA was available showed that only one child had a parent who was likely to be of non-European background.

The methods used in this study have been previously described [Jorm et al., 2000]. Participating adolescents self-reported on depression using the Short Mood and Feelings Questionnaire (SMFQ) [Angold et al., 1995]. Subjects scoring greater than 10 were classified as depressed. The environmental risk factors for depression were the number of family stressors reported to have a negative effect on the family over the previous 12 months, and persistent family adversity over a 6-year period. The number of recent family stressors having a negative effect ranged from 0 to 5 at time points 1998 and 2000. As the number of subjects with two, three, four, or more stressors at both time points was small, subjects were dichotomized into those experiencing no or one family stressors and those experiencing two or more family stressors. Family adversity was assessed at five time points (1992, 1994, 1995, 1996, 1998) using a 6-item index consisting of unemployed father, father in unskilled occupation, many family moves, large family size, non-intact family, and high levels of family stress in the previous 12 months. Subjects with two or more items on this six-item index were considered to have high levels of family adversity, and subjects with two or more items on the index at two or more of the five time points were considered to have persistently high levels of family adversity.

In the PATH20 study, the effects of the interactions between the 5-HTTLPR genotype and environmental risk factors on the severity of depression were analyzed by binary logistic regression with sex being included in the models. The dependent variable was dichotomized for severity of depression (0 = Goldberg Depression Score <6; 1 = Goldberg Depression Score ≥6). The predictor variables for the models were sex (0 = female, 1 = male), 5-HTTLPR genotype (0 = s/s, 1 = s/l, 2 = l/l), recent stressful life events (from 0 = no events up to 4 = 4 or more events), childhood adversity (from 0 = no events up to 4 = 4 or more events), with the G × E interaction term being the product of the genotype and the relevant environmental risk factor. All predictor variables were entered simultaneously into the binary logistic analysis. In addition to investigating the effect of the G × E interaction on depression we also explored the effect of the interaction on anxiety (0 = Goldberg Anxiety <8; 1 = Goldberg Anxiety Score ≥8) using binary regression analyses including the same predictor variables as those used for depression. We also looked for associations between the 5-HTTLPR genotype and symptoms of anxiety, symptoms of depression, and anxiety-related personality traits using analysis of variance (ANOVA). Genotype frequencies were tested for Hardy–Weinberg Equilibrium by chi-square.

In the ATP study, interactions between the 5-HTTLPR genotype and exposure to recent family stress on depression in the cohort at age 15–16 years (1998) and 17–18 years (2000) were analyzed by binary logistic regression. In both age groups, depression based on SMFQ score was the dependent variable (0 = not depressed, 1 = depressed), and the predictor variables were sex (0 = female, 1 = male), 5-HTTLPR genotype (0 = s/s, 1 = s/l, 2 = l/l), recent family stress (0 = no or one family stressors, 1 = two or more family stressors), and the G × E interaction term was the product of the genotype and recent family stress. Binary logistic regression was also used to analyze the interaction between the 5-HTTLPR genotype and longitudinal exposure to persistent family adversity (0 = time points <2; 1 = time points ≥2) on depression. All predictor variables were entered simultaneously into the binary regression analyses.

In both PATH20 and ATP participants, genomic DNA was isolated using QIAamp blood kits (QIAGEN, Hilden, Germany) from buccal epithelial cells obtained using cotton swabs. Polymerase chain reaction (PCR) primers and conditions were as described by Heils et al. [1996]. The method used for visualization of the PCR products in the ATP study has been described previously [Jorm et al., 2000].

Genomic DNA from some PATH20 samples was primarily amplified using the method previously described for the ATP study while some was amplified with *Phi*29 DNA polymerase (Genomiphi DNA Amplification Kit; GE Healthcare Life Sciences, Little Chalfont, UK) according to the manufacturer's protocol. The primers used for PCR were stpr5 (5′ GGC GTT GCC GCT CTG AAT GC 3′) and stpr3 (5′GAG GGA CTG AGC TGG ACA ACC AC 3′). PCR reactions mixture consisted of 20 μl volume, using 2 μl of DNA, 2 μl of 10× PCR buffer, 2 μl of 2 mM dNTPs, 0.8 μl of 25 mM $MgCl_2$, 0.5 μl of 10 μM of each primer, Taq DNA polymerase, and ddH_2O to make a total volume of 20 μl. The PCR conditions were a cycle of pre-denaturation at 95°C for 3 min, 35 cycles of denaturation at 95°C for 30 sec, annealing at 61°C for 30 sec and extension at 72°C for 1 min. Extension in the final PCR cycle reaction was at 72°C for 7 min followed by 25°C for 5 min. PCR products were separated by

TABLE I. Binary Logistic Regression Analyses for Predictor Variables of Sex, 5-HTTLPR Genotype, Recent Stressful Life Events or Childhood Adversity Scores, and Gene × Environment Interaction on Depression in the PATH20 Study

Sex			Recent stressful life events (E)			5-HTTLPR genotype (G)			Gene (G) × Environment (E)		
β	SE	*P*	β	SE	*P*	β	SE	*P*	β	SE	*P*
−0.470	0.126	<0.001	0.548	0.081	<0.001	0.006	0.164	0.973	−0.034	0.062	0.584

Sex			Childhood adversity (E)			5-HTLLPR genotype (G)			Gene (G) × Environment (E)		
β	SE	*P*	β	SE	*P*	β	SE	*P*	β	SE	*P*
−0.373	0.125	0.003	0.398	0.070	<0.001	−0.039	0.128	0.761	−0.027	0.053	0.613

Depression (No: N = 1,756, Yes: N = 338); Sex (Female: N = 1,091, male: N = 1,003); 5-HTTLPR genotype (s/s: N = 435, s/l: N = 971, l/l: N = 688); Recent stressful life events (0 events: N = 559, 1 event: N = 522, 2 events: N = 437, 3 events: N = 255, 4 or more events: N = 321); Childhood adversity (0 events: N = 909, 1 event: N = 478, 2 events: N = 236, 3 events: N = 149, 4 or more events: N = 322).

electrophoresis (130 V for 2.5 hr; 2.5% agarose gel) and visualized with ethidium bromide staining. Alleles were designated as short (484 bp) and long (528 bp) by visual inspection in comparison with fragments of known size.

RESULTS

In the PATH20 study, the allele frequencies in the Caucasian population (n = 2,095) were 56.1% for the long allele (l) and 43.9% for the short (s) allele. The genotype frequencies were l/s 46.3% (n = 971), l/l 32.9% (n = 689), and s/s 20.8% (n = 435) and were not in Hardy–Weinberg Equilibrium; $\chi^2 = 7.34$, df = 1, $P = 0.007$. There was no significant difference between the genotype frequencies in males and females. No significant associations between the 5-HTTLPR genotype and anxiety-related personality traits, anxiety symptoms or depressive symptoms were observed in the ANOVAs.

No significant G × E interactions between the 5-HTTLPR genotype and recent stressful life events or childhood adversity on the severity of depression (or anxiety) were observed in the binary logistic analyses. However, significant main effects were seen for sex, recent stressful life events, and childhood adversity on depression (and anxiety) in these analyses. The results for binary logistic regression for the depression outcome are found in Table I.

In the ATP study, subjects were a cohort aged 15–16 years in 1998 and 17–18 years in 2000 from a sample of 674 participants genotyped for the 5-HTTLPR polymorphism. The allele frequencies in the 674 participants genotyped for 5-HTTLPR polymorphism were 58.0% for the long allele (l) and 42.0% for the short allele (s). The genotype frequencies in these participants were l/s 50.8% (n = 342), l/l 32.6% (n = 220) and s/s 16.6% (n = 112), and the frequencies were in Hardy–Weinberg Equilibrium: $\chi^2 = 1.17$, df = 1, $P = 0.279$. There were no significant differences between the genotype frequencies in the male and female subgroups. No significant G × E interaction was observed between the 5-HTTLPR genotype and recent family stressors on depression in the cohort when aged 15–16 years (n = 584) in 1998, or aged 17–18 years (n = 544) in 2000. Significant main effects were seen for sex but not for recent family stressors or the 5-HTTLPR genotype. The results are summarized in Table II.

However, a significant G × E interaction was observed between the 5-HTTLPR genotype and persistent family adversity on depression in the cohort when aged 17–18 years (n = 592) in 2000 ($P = 0.007$), but not when aged 15–16 years (n = 568) in 1998 ($P = 0.215$). Significant main effects were seen for sex but not for family stressors or the 5-HTTLPR genotype. The results are summarized in Table III.

In the 17–18 year olds, participants homozygous for the long allele had an approximately fourfold increased risk of depression if they had been exposed to persistently high levels of adversity over the previous 6 years compared with those with this genotype and persistently low levels of family adversity. In contrast, the 17–18 year old participants homozygous for the short allele had an approximately two fold lower risk of depression when exposed to persistently high levels of adversity compared with those with this genotype exposed to persistently low levels of family adversity, while the risk of depression in heterozygous participants was similar in those experiencing either high or low levels of persistent family adversity. The interaction data are plotted in Figure 1.

However, in the 17–18 year olds there was only a small number of participants with persistently high levels of family adversity who were depressed (s/s n = 1/15, s/l n = 6/46, l/l n = 7/19). The comparable numbers for 17–18-year-old participants with depression and persistently low levels of family adversity were 12/82 (s/s), 30/252 (s/l), and 14/154 (l/l). The

TABLE II. Binary Logistic Regression Analyses for Predictor Variables of Sex, 5-HTTLPR Genotype, Recent Family Stressors, and Gene × Environment Interaction on Depression in the ATP Study Cohort When Aged 15–16 (1998) and 17–18 (2000)

	Cohort aged 15–16 (1998 analysis)			Cohort aged 17–18 (2000 analysis)		
	β	SE	*P*	β	SE	*P*
Sex	1.185	0.266	<0.001	0.739	0.278	0.008
Family stress (E)	0.166	1.415	0.906	0.415	0.786	0.598
5-HTTLPR (G)	−0.014	0.183	0.941	−0.056	0.208	0.788
Interaction (G × E)	−0.116	0.948	0.903	0.141	0.595	0.812

1998 Analysis: Depressed (No: N = 504, Yes: N = 80); Sex (male: N = 301, female: N = 283); 5-HTTLPR (s/s: N = 97, s/l: N = 303, l/l: N = 184); Family stressors (0 or 1: N = 548, 2 or more: N = 36); Interaction (G × E) = product of family stressors and genotype. 2000 Analysis: Depressed (No: N = 478, Yes: N = 66); Sex (male: N = 269, female: N = 275); 5-HTTLPR (s/s: N = 92, s/l: N = 288, l/l: N = 164); Family stressors (0 or 1: N = 504, 2 or more: N = 40); Interaction (G × E) = product of family stressors and genotype.

TABLE III. Binary Logistic Regression Analyses for Predictor Variables of Sex, 5-HTTLPR Genotype, Persistent Family Adversity, and Gene × Environment Interaction on Depression in the ATP Study Cohort When Aged 15–16 (1998) and 17–18 (2000)

	Cohort aged 15–16 (1998 analysis)			Cohort aged 17–18 (2000 analysis)		
	β	SE	*P*	β	SE	*P*
Sex	1.194	0.266	<0.001	0.906	0.277	0.001
Family adversity (E)	0.477	0.631	0.450	−1.291	0.820	0.115
5-HTTLPR (G)	0.077	0.191	0.688	−0.292	0.207	0.159
Interaction (G × E)	−0.718	0.579	0.215	1.555	0.572	0.007

1998 Analysis: Depressed (No: N = 511, Yes: N = 81); Sex (male: N = 304, female: N = 288); 5-HTTLPR (s/s: N = 98, s/l: N = 308, l/l: N = 186); Family adversity (0–1 times: N = 506, 2 or more times: N = 86); Interaction (G × E) = product of family stressors and genotype. 2000 Analysis: Depressed (No: N = 498, Yes: N = 70); Sex (male: N = 280, female: N = 288); 5-HTTLPR (s/s: N = 97, s/l: N = 298, l/l: N = 173); Family adversity (0–1 times: N = 488, 2 or more times: N = 80); Interaction (G × E) = product of family stressors and genotype.

overall prevalences of depression in the 17–18 year old participants irrespective of exposure to high or low levels of family adversity were 13.4% (s/s), 12.1% (s/l), and 12.1% (l/l).

DISCUSSION

The major strength of our study is replication of non-significant findings for G × E interactions between the 5-HTTLPR genotype and recent stressful life events on depression in two large geographically separate community samples from a Caucasian population of adolescents and young adults. These results are similar to those previously reported from a sample of adults aged 18–79 years (n = 759) from the same geographically located population as the PATH20 participants [Jorm et al., 1998]. The limitations of our study include the failure of the genotype frequencies in the PATH20 participants to demonstrate HWE, the absence of longitudinal data on stressful life events, and the lower statistical power in the ATP study to demonstrate a significant interaction between the genotype and stressful life events if in fact one exists.

The departure of the genotype frequencies from HWE in the PATH20 sample may be a chance occurrence or a result of genotyping error. All genotype results were checked independently by three people, but we cannot rule out the possibility that all three were biased in the same way in making their calls. Alternatively it may be due to differential amplification of alleles during either PCR or whole genome amplification by multistrand displacement (MDA). PCR bias does not seem likely, as there is no indication of it in the ATP sample. MDA, however, was performed on the PATH20 sample, but not on the ATP sample. This procedure can lead to genotyping error for length polymorphisms due to amplification bias [Dickson et al., 2005]. Other explanations such as natural selection and population mixing seem highly unlikely based on the extent of differential mortality required in the case of the former and the relatively homogeneous nature of our sample in the case of the later. Although the genotype frequencies in PATH20 were not in HWE they were similar to those observed in other Caucasian populations [Caspi et al., 2003; Gillespie et al., 2005; Olsson et al., 2005; Surtees et al., 2006; Wilhelm et al., 2006]. We consider that the observed departure from HWE is unlikely to have affected our overall finding of no significant G × E interactions in the PATH20 sample.

The findings of both Caspi et al. [2003] and Wilhelm et al. [2006], suggest that G × E interactions between the 5-HTTLPR and stressful life events might be conditional on the duration of exposure to the stressors prior to the onset of depression. Exposures to environmental stressors of 12 months or less might be too short to result in significant G × E interactions with the 5-HTTLPR genotype. The potential importance of duration of environmental exposure is supported by our findings of a significant G × E interaction between long allele homozygosity (l/l) and persistently high levels of family adversity over a 6-year period on depression in adolescents when aged 17–18 years ($P = 0.007$). However, the involvement of the long allele (l/l) rather than the short allele (s/s or s/l) in the G × E interaction was opposite to that which we had hypothesized. Nevertheless, our findings are consistent with those of Surtees et al. [2006] who reported a significant

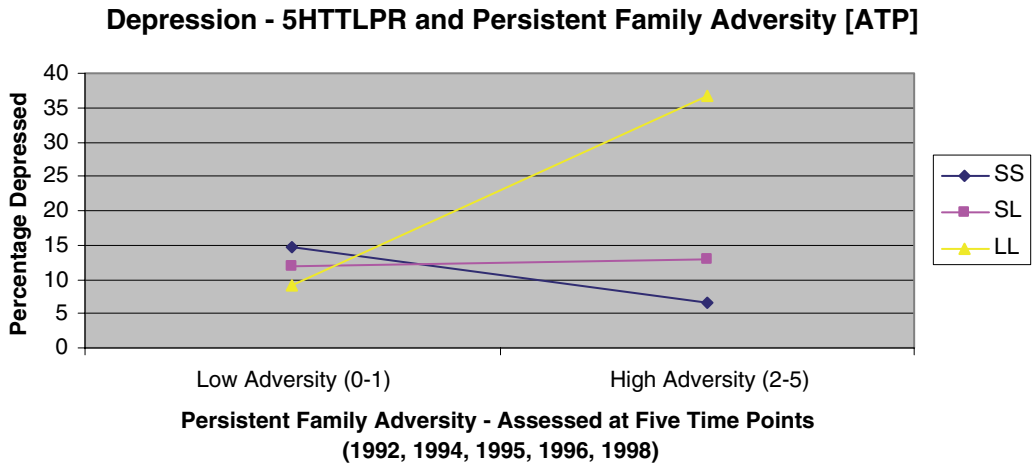

Fig. 1. Interaction between the 5-HTTLPR genotype and persistent family adversity [ATP]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

interaction between the l/l genotype and adverse experiences in childhood on past-year prevalent major depressive disorder in a large sample of English men with a mean age of about 60 years. Furthermore, in our 17–18-year-old participants there was evidence that those having the s/s genotype and persistently high levels of family adversity were less depressed than those with low levels of family adversity. This result suggests that the s/s genotype in these 17–18 year olds might have had a protective effect for the development of depression. The finding of a possible protective effect for the s/s genotype is consistent with that reported by Olsson et al. [2005] who found that increasing copies of the s allele in Australian subjects aged 14–24 years had a protective effect on persistent ruminative anxieties and binge drinking where the risk of insecure attachments was high.

Based on a simple binary logistic regression model it is likely that the PATH20 analysis is adequately powered to detect a significant interaction between the 5-HTTLPR genotype and stressful life events on depression while the ATP analysis is likely to be underpowered. In a simple binary logistic regression model, a sample size of about 1,300 subjects would be sufficient to provide a power of 80% to detect a small effect size for the G × E interaction (Odds Ratio 1.5), assuming a prevalence of depression 15% in the population from which the sample was drawn and an alpha of 0.05 (two-tailed).

In conclusion, our study failed to find significant G × E interactions between the 5-HTTLPR genotype and recent stressful life events on depression. We also failed to find significant interactions between the genotype and recent stressful life events on anxiety and between the genotype and childhood adversity on both depression and anxiety in the 20–24 year olds.

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