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Negative results

5-HTTLPR genotype, stressful life events and late-life depression: No evidence of interaction in a French population

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Abstract

Modification of the effect of life events on risk of depression by a polymorphism in the serotonin transporter gene promoter (5-HTTLPR) has been reported in child, adolescent, adult and elderly populations. Replication attempted on data collected from 1421 individuals aged 65 and over from a French community study provided no evidence of a similar modifying effect. In the only analysis known to the authors to be carried out in an exclusively elderly, European population, this null finding remained consistent after restriction of analysis to prevalent or incident cases.

Keywords: Life stress; Serotonin transporter; 5-HTTLPR; Depression; Gene–environment interaction; Old age

1. Introduction

The common, 44 bp indel polymorphism in the serotonin transporter gene promoter (5-HTTLPR) has been found to modify the depressogenic effect of stressful life events, with the 5-HTTLPR "short" (s) allele of associated with increased, and the "long" (l) allele associated with reduced, influence (Caspi et al., 2003). This finding was recently replicated for late-life depression in Korea (Kim et al., 2007), but has not received further evaluation in an older community population or one where the functional influence of a recently identified SNP (rs25531) has been considered (Wendland et al., 2006).

2. Methods

In a French community sample of 1421 people aged 65+, recent (within 12 months) life-events were ascertained using a structured questionnaire and case-level depression was assessed using the MINI and CES-D schedules (Ritchie et al., 2004). 5-HTTLPR genotype was assayed from blood samples and recoded according to rs25531 status (Wendland et al., 2006). After two years, life events and depression were ascertained again using identical procedures. Interaction between life-events and 5-HTTLPR functional genotype was tested in binary logistic regression models with prevalent depression at baseline and incident depression at follow-up as the dependent variable.

3. Results

5-HTTLPR functional genotype and life event frequencies at baseline were ll = 24.1%, sl = 47.4% and ss = 28.5% and

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Table 1
Binary logistic regression analysis of the interaction between life events and 5-HTTLPR genotype, including influence of rs25531, in predicting depression

	Life events[a]			5-HTTLPR[b]			Interaction		
	β	S.E.	p	β	S.E.	p	β	S.E.	p
Prevalent at baseline									
MINI	1.47	.60	.01	.47	.38	.22	−.47	.27	.08
CES-D	.60	.23	.00	.04	.13	.76	−.08	.11	.47
Incident at 2-year follow-up[c]									
MINI	.19	1.01	.19	.19	.77	.81	−.18	.45	.70
CES-D	.64	.44	.14	.01	30	.97	−.04	.20	.82

[a] Entered as a three group ordinal variable (0, 1, 2+).
[b] Entered as a three group ordinal variable (ll, sl, ss).
[c] Only individuals who were not cases according to respective measures at baseline included in analysis.

0 = 40.3%, 1 = 34.8% and 2 or more = 24.9%, respectively. Case-level depression was present in 3.1% according to MINI and 29.2% according to CES-D at this time. Incident depression was present in 1.9% and 11.7% of the sample according to these instruments at follow-up. Results of the logistic regression analyses are displayed in Table 1. Stressful life-events were strongly associated with depression at baseline but not at follow-up. No main effect for 5-HTTLPR functional genotype or 5-HTTLPR functional genotype × life event interaction was evident for either depression measure or time point of assessment.

4. Discussion

In this sample of older people, we were not able to replicate the previously reported interaction between 5-HTTLPR and life-events as risk factors for depression. This outcome was unaffected by instrument used to identify depression, restriction of the analysis to incident cases or use of 5-HTTLPR genotype without reclassification according to rs25531 (see Supplementary material). Previously, two studies of the 5-HTTLPR × life event interaction for depression have focused on older participants: a European study with a 41–80 year age-range which not did not find an interaction (Surtees et al., 2006) and a Korean study with over 65's only which did (Kim et al., 2007). One possible explanation for the difference is the greater prevalence of the 5-HTTLPR s allele in the Korean sample (52.7% vs. 21.9% with an ss genotype), consistent with other East Asian populations. The Korean sample had also experienced more life events over the same time period (71.9% vs. 59.7% with >1 life event) and had a relatively high prevalence of the BDNF met allele that was found to be a modifying factor (Kim et al., 2007). It is possible that the relatively low number of risk factors leave the current analyses underpowered to detect an interaction. Another possibility is that the interaction is risk- rather than, or as well as, age-specific and is only apparent in comparatively high-risk environments. Exploration of this hypothesis could involve assessment of subjective experience of stressful events, as per Kendler et al. (2005). The 5-HTTLPR × life-event interaction is an important finding which has been well replicated. Our results suggest that, for late-life depression at least, there may be inter-population heterogeneity that should be considered when interpreting future studies.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2008.06.006.

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