Interactions Between Life Stressors and Susceptibility Genes (5-HTTLPR and BDNF) on Depression in Korean Elders

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Background: It has been reported that the functional polymorphism in the serotonin transporter gene linked promoter region (5-HTTLPR) modifies the association between stressful life events (SLEs) and depression in child, adolescent, and adult populations. We sought to replicate this finding in elders and, additionally, to test modifying effects of the brain-derived neurotrophic factor (BDNF) val66met polymorphism.

Methods: In 732 Korean community residents ages 65+, diagnosis of depression (Geriatric Mental State Schedule), information on SLEs, and genotypes for 5-HTTLPR and BDNF val66met were ascertained. Of those without depression at baseline, 521 (88%) were followed up 2.5 years later. Interactions between SLEs and the two genotypes were investigated for both prevalent depression at baseline and incident depression at follow-up.

Results: Significant interactions of SLEs with both 5-HTTLPR and BDNF genotypes were observed on risk of depression after adjustment for age, gender, education, and disability. A significant three-way interaction between 5-HTTLPR, BDNF, and SLEs was also found. The same findings were observed for predictors of incident depression in the prospective analysis.

Conclusions: These findings suggest that environmental risk of depression is modified by at least two genes and that gene–environment interactions are found even into old age.

Key Words: Aged, brain-derived neurotrophic factor, depression, gene–environment interaction, life stress, serotonin transporter

Both adverse psychosocial conditions, such as stressful life events (SLEs), and genetic predisposition are important in the etiology of depression (Levinson 2006; Paykel 2003). Many studies have highlighted the potential importance of gene–environment interactions. Individuals with family history of depression are recognized to be more vulnerable to the depressogenic effects of SLEs than those without (Phelan *et al.* 1991; Pollit 1972). In a community study of female twins, the risk of major depression after SLEs was increased in those with greater genetic liability (Kendler *et al.* 1995). Recently, specific genes have been implicated. The serotonin transporter (5-HTT) gene has attracted particular attention. There is a biallelic polymorphism in the 5-HTT gene linked promoter region (5-HTTLPR) with short (*s*) and long (*l*) alleles. The *s* allele reduces the transcriptional activity of the 5-HTT gene promoter resulting in decreased 5-HTT expression (Heils *et al.* 1995) and therefore has been hypothesized to be a risk factor for depression (Anguelova *et al.* 2003). In the context of gene–environment interaction, individuals with the *s* allele of the 5-HTTLPR polymorphism exhibited more depression and suicidality in relation to SLEs than those with the *l* allele (Caspi *et al.* 2003). This finding has been replicated in child (Kaufman *et al.* 2004), adolescent (Eley *et al.* 2004), and adult (Jacobs *et al.* 2006; Kendler *et al.* 2005; Taylor *et al.* 2006) populations. However, negative findings have also been reported (Gillespie *et al.* 2005; Surtees *et al.* 2006). This line of investigation has not been pursued in elders, although biopsychosocial origins of late-life depression have been hypothesized to extend into late-life (Blazer and Hybels 2005) and a study of elders who had all been subject to a traumatic event (hip fracture) found associations between the 5-HTTLPR *s* allele and subsequent depression (Lenze *et al.* 2005).

Another more recent candidate etiological gene for depression is the brain-derived neurotrophic factor (BDNF) gene. This is located on chromosome 11p14.1 and has several polymorphic markers. These include the single nucleotide polymorphism (SNP) at nucleotide 196 (G/A), which results in an amino acid substitution (valine to methionine) at codon 66 (val66met, dbSNP number: rs6265) of the proBDNF molecule. This SNP affects intracellular processing and secretion of BDNF, and the met allele is associated with reduced BDNF activity (Egan *et al.* 2003). The met allele might confer increased vulnerability to depression after SLEs, but interactions between the two have not thus far been investigated. A three-way interaction between BDNF, 5-HTTLPR, and maltreatment was found to be associated with depression in children (Kaufman *et al.* 2006), but this has not been investigated in an adult population.

With data from a community study of an older Korean population, we examined the roles of SLEs, 5-HTTLPR, and BDNF polymorphisms in association with depression. The objectives of this investigation were: 1) to replicate and extend to elders the findings from child and younger adult populations that suggest modifying effects of 5-HTTLPR polymorphism on the associations between SLEs and depression, and 2) to test modifying effects of BDNF polymorphism on these associations.

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Methods and Materials

Sample and Measurements

This analysis was carried out on data from a prospective community-based study of late-life psychiatric morbidity carried out in Kwangju, South Korea from 2001 to 2003, in collaboration with the 10/66 International Research Program on Dementia in Developing Countries (Prince *et al.* 2003). All participants gave written formal informed consent at each examination. This study was approved by the Chonnam National University Hospital Institutional Review Board.

Cross-sectional data were analyzed from a survey of a geographically defined population carried out in 2001. The sampling procedure and measurements have been described previously (Kim *et al.* 2004a, 2004b). In brief, 732 community residents ages 65 or over identified from national residents registration lists within two areas of Kwangju, South Korea were examined. Examinations included a fully structured diagnostic interview for depression; assessment of SLEs; blood samples for 5-HTTLPR and BDNF genotypes; and formal assessment of disability, cognitive function, and demographic characteristics.

Depression was assessed with the community version of the Geriatric Mental State (GMS) diagnostic schedule (GMS B3) (Copeland *et al.* 1986). This is a fully structured diagnostic instrument in wide international use with an accompanying computerized algorithm. The GMS B3 was translated into Korean according to a formal standardization process (Kim *et al.* 2003). As in other studies, a "stage one" (non-hierarchical) confidence level of 3 or above in the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) algorithm was used to define depression of clinical significance (encompassing both severe and moderate depression).

The instrument used in this study to ascertain SLEs was the List of Threatening Events (LTE) (Brugha *et al.* 1985), designed to detect events carrying significant long-term threat and of particular salience for depression. Nine SLEs over the previous year are enquired about: serious illness (self), serious illness (close relative), bereavement (immediate family), bereavement (other relative or close friend), marital separation, end of relationship, problem with close friend or relative, and theft or loss. Positive responses were totaled to generate a summary scale and, because of the skewed distribution, were divided into four groups (0, 1, 2, 3+). The SLEs over the previous year were ascertained from interview with the participant and with their family informants where possible (available for 41.7% of participants at baseline and 53.6% of those followed up). The validity of this instrument in aging adults has been previously established (Prince *et al.* 1997).

For genotyping, DNA was extracted from venous blood with standard procedures. Polymerase chain reaction (PCR) and the PCR-based restriction fragment length polymorphism assays were performed following previously published protocols with slight modification (Edenberg and Reynolds 1998; Proschel *et al.* 1992). Briefly, for the 5-HTTLPR genotype, a PCR product was amplified with primers (5′-GGCGTTGCCGCTCTGAATGC-3′, 5′-GAGGGACTGAGCTGGACAACCA-3′) flanking the region containing the gene variation. The PCR conditions consisted of a 5-min denaturation step at 94°C, 40 cycles of 30-sec denaturation at 94°C, 30 sec annealing at 63°C, and 60 sec extension at 72°C, and a final 10-min extension step at 72°C. The PCR products were separated by electrophoresis in a 3% agarose gel stained with ethidium bromide and visualized by UV transillumination. The different genotypes were defined by the specific bands. For BDNF genotyping, the primer sequences used were the forward primer 5′-ACTCTGGAGAGCGTGAATGG-3′ and the reverse primer 5′-ACTACTGAGCATCACCCTGGA-3′. The amplification conditions were pre-denaturation at 95°C for 5 min, followed by 40 cycles consisting of denaturation at 95°C for 30 sec, 62°C for 30 sec, and 72°C for 30 sec, and post-elongation at 72°C for 5 min, with a final maintenance step at 4°C. The PCR products were digested at 37°C with the corresponding restriction enzyme (*Eco*72I), and gel electrophoresis was used to detect the 196G (val: 99 and 72 base pair [bp] fragments) and 196A (met: 171 bp fragment) alleles. The genotypes were categorized as "*s/s*," "*s/l*," and "*l/l*" for the 5-HTTLPR and as "val/val," "val/met," and "met/met" for the BDNF (Supplements 1 and 2).

Disability was assessed by the Korean version of the World Health Organization Disability Assessment Schedule II (WHODAS II) (Kim *et al.* 2005). Cognitive function was evaluated by the Korean version of the Mini-Mental State Examination (MMSE) (Park and Kwon 1990). Demographic data on age, gender, and education were recorded.

Further prospective analyses were carried out on a subsample of 521 participants without depression at baseline who were re-examined in 2003 (83% follow-up rate, mean (SD) follow-up period 2.4 (.3) years). The follow-up examination has been described in detail previously (Kim *et al.* 2006). In brief, depression was identified in an identical manner with the same instrument, and SLEs over the previous year were also reassessed.

Analyses

Associations between SLE score, 5-HTTLPR, and BDNF genotypes and depression were measured initially by univariate analyses (χ^2 tests) and then further analyzed with multivariable logistic regression models adjusted for disability, cognitive function, and demographic characteristics. The main effects of SLEs and genotypes in these models were investigated (entering these as ordinal variables), together with all possible two- and three-way interactions between the two genotypes and SLE score. These procedures were repeated in the follow-up sample. Statistical analyses were carried out with SPSS 12.0 software (SPSS, Chicago, Illinois).

Results

Of 732 participants at baseline, case-level depression was present in 101 (13.8%). Frequencies of SLEs and 5-HTTLPR/BDNF genotypes in the sample are displayed in the first column of Table 1. These are compared between those with and without depression in the second through fifth columns of Table 1. Depression was significantly associated with increased numbers of SLEs. Although associations between depression and the two genotypes were in the directions anticipated, these were not significant. In addition (further data not shown), depression was significantly associated with worse disability ($p < .001$), lower cognitive function ($p = .006$), and female gender ($p = .004$) but was not associated with age ($p = .095$) or education ($p = .321$). No deviation from the Hardy–Weinberg equilibrium was observed for either genotypes [$\chi^2 = 1.72$ and .66 for 5-HTTLPR and BDNF genotypes in the total sample, respectively; all $p > .05$].

Prevalence rates of depression by SLE score and genotypes are displayed in Figure 1. For the 5-HTTLPR genotypes, the association between SLE score and depression was significant in *s/s* homozygotes [$\chi^2 = 20.5$, $p < .001$] and *s/l* heterozygotes [$\chi^2 = 6.55$, $p = .010$] but not in *l/l* homozygotes [$\chi^2 = .56$, $p = .454$]. For

Table 1. Frequencies of Stressful Life Events and Genotypes in the Baseline Sample

Source	Total Sample (n = 732)	No Depression (n = 631)	Depression (n = 101)	X^2 (linear)	p
Stressful life events (%)					
0	206 (28.1)	193 (30.6)	13 (12.9)	26.4	< .001
1	281 (38.4)	245 (38.8)	36 (35.6)		
2	184 (25.1)	151 (23.9)	33 (32.7)		
3+	61 (8.3)	42 (6.7)	19 (18.8)		
5-HTTLPR (%)					
s/s	386 (52.7)	333 (52.8)	53 (52.5)	.82	.365
s/l	250 (34.2)	209 (33.1)	41 (40.6)		
l/l	96 (13.1)	89 (14.1)	7 (6.9)		
BDNF (%)					
val/val	184 (25.1)	158 (25.0)	26 (25.7)	1.20	.274
val/met	406 (55.5)	358 (56.7)	48 (47.5)		
met/met	142 (19.4)	115 (18.2)	27 (26.7)		

5-HTTLPR, serotonin transporter gene linked promoter region; BDNF, brain-derived neurotrophic factor.

the BDNF genotypes, the association between SLE score and depression was significant in met/met homozygotes [χ^2 = 16.6, p < .001] and val/met heterozygotes [χ^2 = 6.95, p = .008] but was not in val/val homozygotes [χ^2 = 3.68, p = .055].

A logistic regression analysis was carried out to examine further the effects of main covariates and effect modification (interaction) for depression as the dependent variable. All factors were entered as ordinal variables with Wald statistics analyzed against 1 *df*. In a model adjusted for age, gender, education, cognitive function, and disability, the following factors were statistically significant: SLEs (Wald 17.2, p < .001), SLEs × 5-HTTLPR (Wald 6.69, p = .010), SLEs × BDNF (Wald 16.1, p < .001), and SLEs × 5-HTTLPR × BDNF (Wald 6.38, p = .012). There were no significant effects of either gene alone (Wald statistics for 5-HTTLPR and BDNF: .78 [p = .378] and .05 [p = .822], respectively), and there was no significant gene × gene effect modification (Wald .54, p = .461).

The three-way effect modification was positive, indicating greater than expected effect modification by each allele on the SLE-depression association if the other risk allele was present. For example, the prevalence rates of depression for people with 3 or more life events and the BDNF met/met genotype were as follows: 0% for those with the 5-HTTLPR *l/l* genotype, 20.0% for those with the *s/l* genotype, and 70.0% for those with the *s/s* genotype. For people with the 5-HTTLPR *s/s* genotype and 3 or more life events, prevalence rates of depression were 22.2% and 16.7%, respectively, for those with the BDNF val/val and val/met genotype.

Of the 521 participants without baseline depression, "incident" depression at follow-up was present in 63 (12.1%). Frequencies of SLEs and 5-HTTLPR/BDNF genotypes in the followed sample and associations with depression were near-identical to those in the baseline sample (data not shown). Incident depression was significantly associated with increased numbers of SLEs but not directly with the two genotypes. Incidence rates of depression by SLE score and genotypes are summarized in Figure 2. For the 5-HTTLPR genotypes, the association between SLE score and depression was significant in *s/s* homozygotes [χ^2(1) = 10.4, p = .001] but not in heterozygotes [χ^2 = 1.79, p = .18] or *l/l* homozygotes [χ^2 = .77, p = .38]. For the BDNF genotypes, the association between SLE score and depression was significant in met/met homozygotes [χ^2 = 7.26, p =

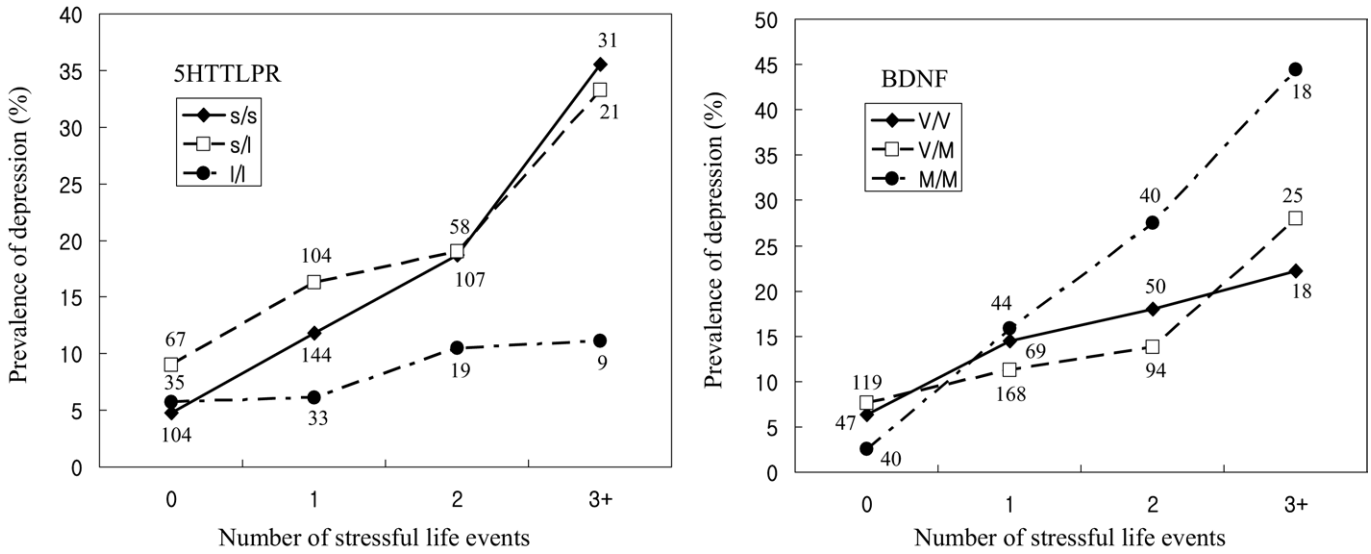

Figure 1. Prevalance of depression according to stressful life events, serotonin transporter gene linked promoter region (5-HTTLPR), and brain-derived neurotrophic factor (BDNF) genotypes in the baseline sample. Cell sizes are given for each genotype/stressful life event combination.

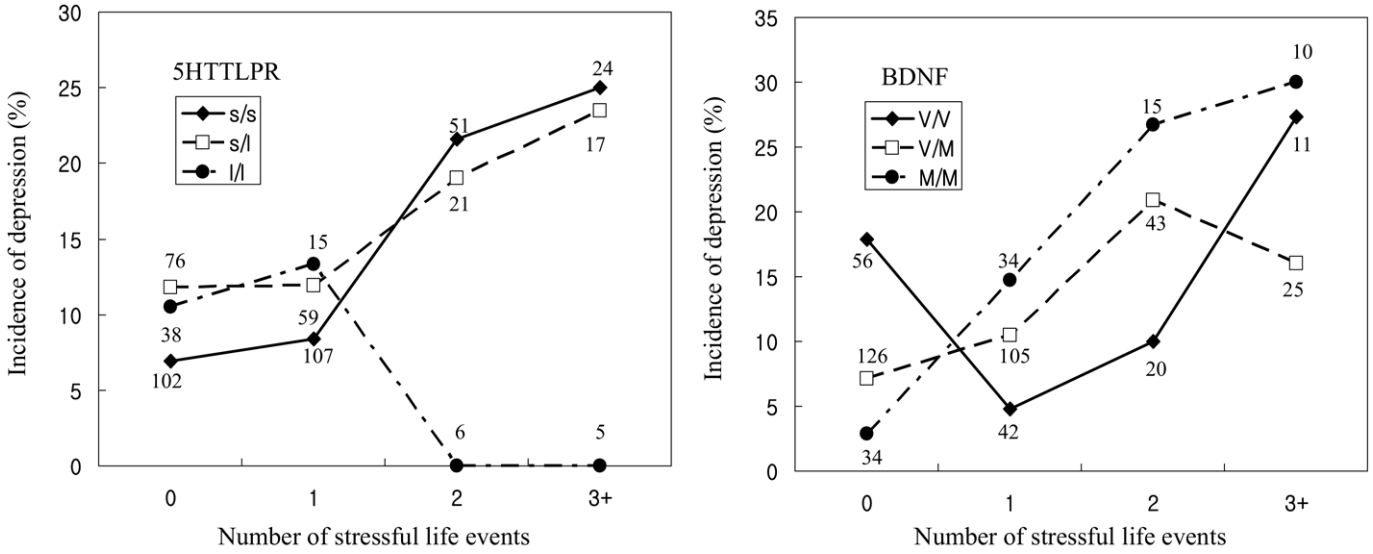

Figure 2. Incidence of depression according to stressful life events, serotonin transporter gene linked promoter region (5-HTTLPR), and brain-derived neurotrophic factor (BDNF) genotypes in the follow-up sample without baseline depression. Cell sizes are given for each genotype/stressful life event combination.

.007] and val/met heterozygotes [$\chi^2 = 5.19$, $p = .023$] but not in val/val homozygotes [$\chi^2 = .01$, $p = .967$]. In a logistic regression model identical to that summarized earlier for prevalent depression, the following factors were statistically significant: SLEs (Wald 8.68, $p = .03$), SLEs × BDNF (Wald 10.1, $p = .001$), and SLEs × 5-HTTLPR × BDNF (Wald 3.88, $p = .049$). The SLEs × 5-HTTLPR effect modification term was of borderline significance (Wald 3.13, $p = .077$) in this model.

Discussion

The principal findings of this study of community elders were as follows: 1) previous findings of effect modification between 5-HTTLPR genotype and SLEs on risk of depression were confirmed; 2) similar effect modification between BDNF val66met genotype and SLEs on risk of depression was identified; and 3) three-way effect modification between these two genotypes and SLEs on risk of depression was found. These findings were largely confirmed when the analysis was repeated in a follow-up study of participants without depression at baseline for the association between depression at follow-up and recent life events.

To our knowledge, this study is the first to report on effect modification between SLEs and 5-HTTLPR genotype for late-life depression in a community population and the first to report on an interaction between BDNF genotype and SLEs in an adult population. Strengths of our study were that depression was ascertained with a widely validated diagnostic schedule and that information on a variety of important risk factors was obtained by standardized assessment instruments. The polymorphisms were assayed specifically for this analysis and were two of only five genetic assays carried out to date on this sample (the other three assays having been carried out for potential associations with dementia: apolipoprotein E, aldehyde dehydrogenase 2, and methylenetetrahydrofolate reductase). An important limitation was that the onset of depression in relation to SLE occurrence was not ascertained; so, the direction of causal relationships between the two cannot be assumed. However, the prospective analysis of participants without depression at baseline confirmed the cross-sectional findings, providing support for the anticipated direction of causation, even though the precise timing of onset of depression could not be established within the follow-up period.

With respect to the 5-HTTLPR genotype, our sample had higher *s* allele (70%) and lower *l* allele (30%) frequencies compared with reports from Western populations (Caspi *et al.* 2003; Eley *et al.* 2004; Gillespie *et al.* 2005; Kendler *et al.* 2005) where the usual frequencies are 43%–47% (approximately) for the *s* allele and 53%–57% (approximately) for the *l* allele. However, the findings are consistent with reports from Korean (Ha *et al.* 2005) and other East Asian populations (Kato *et al.* 2005). Despite the ethnic differences in 5-HTTLPR genotype distribution, the findings from this study are very similar to previous results from different populations (Caspi *et al.* 2003; Eley *et al.* 2004; Kendler *et al.* 2005), in that the 5-HTTLPR polymorphism was not directly associated with depression but instead modified associations with SLEs. In a finding similar to previous studies, associations between SLEs and depression were most prominent in people with one or more copies of the *s* allele.

A three-way interaction between BDNF genotype, 5-HTTLPR genotype, and maltreatment has been previously found with respect to depression in childhood (Kaufman 2006). Our novel finding of modifying effects of BDNF val66met polymorphism on the association between SLEs and depression (as well as the three-way effect modification) in an elderly sample requires replication but suggests that several genes might underlie the well-recognized familial vulnerability to environmental stressors. The BDNF system is a logical source of candidate genes for depression, because BDNF is the most abundant neurotrophin in the brain and has survival-promoting actions on a variety of central nervous system functions (Angelucci *et al.* 2005). The met allele is associated with reduced BDNF activity compared with the val allele (Egan *et al.* 2003). However, evidence for an association between the met allele and depression is inconclusive (Levinson 2006). Although the BDNF val66met polymorphism might not be directly associated with depression, it

might—like 5-HTTLPR—modify the association between environmental stress and depression. There has been accumulating evidence on potential relationships between stress and BDNF. Animal models have indicated reduction in hippocampal BDNF expression (Smith *et al.* 1995) and atrophy of hippocampal BDNF neurons in response to stress (Magarinos *et al.* 1996). Downregulation of BDNF has been hypothesized as an important mediating pathway (Elkis 1995). With respect to the BDNF genotype, our sample had higher met allele (47%) and lower val allele (53%) frequencies compared with reports from Western populations (Kaufman *et al.* 2006; Zhang *et al.* 2006) where the usual frequencies are 17%–21% (approximately) for the met allele and 78%–87% (approximately) for the val allele. However, the findings are similar to reports from other Asian populations (Kunugi *et al.* 2004).

There is evidence that the serotonin and BDNF systems might be linked at multiple intracellular and intercellular levels (Duman *et al.* 1997). For example, stress has been found to be associated with reductions in both Raphe serotonin transporter messenger RNA (mRNA) and hippocampal BDNF mRNA (Vollmayr *et al.* 2000). Brain-derived neurotrophic factor knockout mice have also been found to have brain serotonergic abnormalities (Lyons *et al.* 1999). A recent study of maltreated children found that those with the met allele of the BDNF gene and two short alleles of 5-HTTLPR had the highest depression scores (Kaufman *et al.* 2006). No direct interaction between the two genes was observed in the study presented here. However, gene–gene interactions, like direct gene effects, might only be observable in the presence of environmental stressors, and the significant three-way effect modification provides some evidence of this. Further research is required to confirm this association in other adult and elderly populations.

Previous studies of gene–environment interactions have focused on child or adolescent populations (Caspi *et al.* 2003; Eley *et al.* 2004; Kaufman *et al.* 2004). In adults, some studies have found significant associations (Jacobs *et al.* 2006; Kendler *et al.* 2005; Taylor *et al.* 2006), whereas other have not (Gillespie *et al.* 2005; Surtees *et al.* 2006). The negative findings from the large British EPIC (European Prospective Investigation into Cancer) population study reported by Surtees *et al.* (2006) are particularly important, because one of the suggestions for the failure to replicate the gene–environment interaction observed by Caspi *et al.* was that the EPIC sample was relatively old (ages 41–80 years). Our findings, in contrast, suggest that interactions between genetic predisposition and environmental stressors are still observable in old age. An important difference between our study and the EPIC study was in the method used to ascertain depression. In the EPIC study, restrictive major depression criteria were applied, whereas in our study a less restrictive category of depression was used, encompassing both moderate and severe levels of symptoms. Also, a fully structured diagnostic interview was used in our study specifically developed for ascertaining depression in elderly populations in whom DSM major depression criteria might not adequately characterize clinically relevant depressive syndromes. Comparing our results with those from the EPIC study, we found that prevalence rates of depression were higher in our study, which reflect the broader definition applied. Therefore it is possible that gene–environment interactions in older populations are more clearly observed with less restrictive criteria (i.e., they might apply to depressive syndromes that are not adequately measured by criteria developed for younger adult populations). The same reasons might underlie the difference between our findings and those of Gillespie *et al.* (2005), because DSM-IV criteria were also used in that study. The nature of the samples might also be relevant, because ours was an unselected community population compared with the twin-pair volunteer sample analyzed in the other study.

Other features of our study might also underlie the positive findings. Both risk genotypes (5-HTTLPR *s/s* and BDNF met/met) were relatively common in our sample (as with other East Asian populations), which will have increased the statistical power to detect associations. If the three-way gene–gene–environment effect modification is confirmed in other samples, then the effect of each risk genotype will have been increased by the relatively high frequency of the other modifying allele in our sample. It is also possible that other risk alleles have higher population prevalence rates, increasing the chances of detectable associations. Background environmental risk might also be raised. As can be seen from Table 1, adverse life events were commonly reported by participants with only just over one-quarter reporting no recent stressors. The strength of association between SLEs and depression was strong for both cross-sectional and prospective analyses (and consistent with that reported repeatedly from other research), which does not suggest that minor stressors were over-reported. Therefore it is possible that our positive findings are the product of a population with particularly high levels of genetic and environmental risk. The high prevalence rates of the 5-HTTLPR *s* allele and the BDNF met allele might have public health relevance in East Asian populations because of their high prevalence, but this requires further evaluation.

Although a view has traditionally been held that familial factors become less important in the etiology of depression in late life, genetic determinants of depression seem relatively stable across the lifespan (Gillespie *et al.* 2004). A recent study reported that there was no evidence for differences in the roles of genetic and environmental risk factors for major depression in birth cohorts spanning nearly 6 decades (Kendler *et al.* 2006). Life events, particularly bereavement, social isolation, physical illness, and economic loss, are considered to be important risk factors for late-life depression (Alexopoulos 2005). A biopsychosocial approach to evaluating the origins of late-life depression is heuristically valuable.

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Supplementary material cited in this article is available online.

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