CORRESPONDENCE

Brain-Derived Neurotrophic Factor, Serotonin Transporter, and Depression: Comment on Kaufman *et al.*

To the Editor:

Brain-derived neurotrophic factor (BDNF) and serotonin transporter (SERT) have recently been implicated in depression (Caspi *et al.* 2003; Kaufman *et al.* 2004) and depression-like behavior in animals (Berton *et al.* 2006). A recent study has examined BDNF/SERT genes interactions in depressed children, reporting that a combination of met-BDNF allele with two short SERT alleles was associated with higher depression in maltreated children (Kaufman *et al.* 2006). The effect was magnified in children with reduced social support, suggesting its protective role in depression (Kaufman *et al.* 2006). Although their interesting findings outline the important role of BDNF–SERT interplay in vulnerability to depression, our understanding of these results might benefit from further discussion.

Although a role for SERT in depression has been generally accepted (Kaufman *et al.* 2004), there are conflicting data on the role of BDNF in depression, with both antidepressant and pro-depressant effects described (see discussion in Berton *et al.* 2006). Likewise, there is a lack of understanding of the exact role of BDNF–SERT interaction in emotional behavior in animal models. Although heterozygous BDNF knockout mice have unaltered anxiety and depression (MacQueen *et al.* 2001), Rios *et al.* (2001) reported high anxiety and altered serotonergic tone in conditional BDNF mutants. Our recent study (Ren-Patterson *et al.* 2005) in double BDNF(+/−)SERT(−/−) knockout mice showed that loss of a single BDNF allele exacerbates the anxiety phenotype of SERT mutants. This situation parallels clinical trials of Kaufman *et al.* (2004, 2006) and suggests that anxiety domain might also be involved in BDNF–SERT interplay (Murphy *et al.* 2003). Although both depressed and nondepressed maltreated children might be affected by posttraumatic stress, other subtypes of anxiety might also be involved in this study, such as social anxiety. Collectively, this might counter the beneficial effects of social support. Moreover, assessing social support by summing the number of positive support categories reported by each child might be confounded by a depression-related predisposition to name fewer positive categories. Therefore, social support data from multiple informants (as the authors used for maltreatment) could help corroborate. It also seems appropriate to make associations with general trauma instead of maltreatment specifically, because all maltreated children were removed from their homes (which might have been as stressful as the initial abuse/neglect).

Sociability might also factor into this study. For example, introversion (autistic-related phenotype) in some maltreated children might lead to their insensitivity to social support, regardless of their depression. Notably, both anxiety and autism have been linked to BDNF (Lang *et al.* 2005; Miyazaki *et al.* 2004) and SERT (Murphy *et al.* 2003; Ren-Patterson *et al.* 2005, Ren-Patterson et al, in press; Sutcliffe *et al.* 2005). Therefore, a parallel analysis of anxiety and/or sociability phenotypes might provide further insights into BDNF–SERT interactions.

We also note that both BDNF (Alonso *et al.* 2005; Dempster *et al.* 2005; Monteggia *et al.* 2004) and SERT (Koponen *et al.* 2004; Payton *et al.* 2005) are implicated in memory and learning, raising the possibility that these genes influenced cognitive functions in the study of Kaufman *et al.* (which might be important, because recurrent negative cognitions often lead to increased depression).

Finally, Kaufman *et al.* sampled depressed children, whose depression might differ from that of adults, adding further complexity to the problem. From this point of view, comparing emotional responsivity in children versus adults as well as using relevant adult and neonatal animal models of stress might be necessary. For example, higher depressiveness and reduced hippocampal BDNF levels (both corrected by antidepressant medications) were reported in rodents with early-life maternal separation (MacQueen *et al.* 2003), similar to recent studies in nonhuman primates (Bennett *et al.* 2002). Thus, the use of biological psychiatry approaches to parallel animal and human data might promote our understanding of complex gene–gene and gene–environment interactions.

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Reply

To the Editor:

We appreciate Dr. Kalueff et al's thoughtful commentary of our paper. They are absolutely correct to note that there are contradictory data on the role of brain-derived neurotrophic factor (BDNF) in depression. As we discussed in our report, prior investigations examining the BDNF val66met polymorphism have reported opposite findings in association with depression and other traits, with the "val" allele associated with vulnerability in some studies (Lang *et al.* 2005), and the "met" allele designated as the "risk" allele in others (Jiang *et al.* 2005). Inconsistencies in prior investigations might be attributable to sampling and measurement issues or genetic heterogeneity, which can result from many sources, including differences in the ethnic composition of samples across studies. It might also relate to failure to take into account relevant gene × gene and gene × environment interactions.

In our sample, BDNF was not independently linked with depression. No increased risk for depression was associated with the "met" allele alone or in combination with a history of maltreatment. A gene × gene × environment (G × G × E) interaction was detected, such that the "met" allele of the BDNF gene was found to potentiate risk for depression associated with maltreatment and the presence of two short alleles of the serotonin transporter protein gene (SLC6A4) 5-HTTLPR variant (Kaufman *et al.* 2006).

As Dr. Kalueff *et al.* note, our finding of a BDNF-5-HTTLPR interaction is consistent with preclinical studies of BDNF knockout mice (Lyons *et al.* 1999). It is also consistent with results of studies of double mutant mice generated by breeding serotonin transporter protein gene knockout mice with BDNF heterozygous knockout mice. Compared with mice with knockouts in only one of these systems, double mutant mice show enhanced anxiety, elevations in stress hormones, and exaggerated deficits in serotonergic availability in the hypothalamus and hippocampus (Ren-Patterson *et al.* 2005).

Table 1. Results of Generalized Estimating Equation Analysis Examining the Effect of Maltreatment, 5-HTTLPR Genotype, BDNF Genotype: WALD Type 3 statistic (N = 198)

Source	*df*	Chi Square	*p* Value
Age	1	7.71	.007
Gender	1	.21	ns
Ancestral Proportion Score	1	5.23	.02
Maltreatment	1	4.96	.05
5-HTTLPR	2	4.26	ns
BDNF	1	1.50	ns
5-HTTLPR × Maltreatment	2	4.71	.07
BDNF × Maltreatment	2	3.38	.09

5-HTTLPR, a serotonin transporter polymorphism; BDNF, brain-derived neurotrophic factor.

Given the previously cited finding of enhanced anxiety in double mutant mice, Dr. Kalueff *et al.* recommended parallel analysis of depression and anxiety phenotypes to better understand the role of BDNF-5-HTTLPR interactions. At baseline, in addition to collecting depression data, the children in our study also completed the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher *et al.* 1997). The SCARED is a 41-item self-report anxiety measure used extensively in child psychiatry. The SCARED data were available for 198 subjects: 109 children who were removed from their parents' care within the past 6 months owing to reports of abuse and/or neglect, and 89 community control subjects with no history of maltreatment or exposure to intrafamilial violence. The 198 children were from 126 families with various numbers of sibs and half-sibs (range, 1–4) in each family. Subjects were a mean age of 9.3 (SD: 2.4), approximately one-half were female, and 28% of the children were European-American, 28% African American, 24% Hispanic, and 20% biracial. The "maltreated" and "comparison" groups were comparable in terms of age, gender, and ethnic composition ($p > .10$, all comparisons), and population structure was controlled for by means of ancestral proportion scores computed with genotypes from an ancestry informative marker set (Pritchard *et al.* 2000; Yang *et al.* 2005).

Maltreated children had significantly higher total anxiety scores than the demographically matched, low socioeconomic status community control subjects [$F = 5.80$, $p < .02$, Maltreated: 28.4 ± 15.9; Control subjects: 23.3 ± 12.6], although more than one-half of the children in both groups scored above the clinical cut off score of 14 on the SCARED. A Generalized Estimating Equation (GEE) analysis was used to examine predictors of children's anxiety scores, given familial correlations between subjects resulting from the inclusion of siblings in the sample. Age, gender, and ancestral proportion scores were entered as covariates and modeled together with 5-HTTLPR, BDNF, and maltreatment status to examine main effects and interactions. Results of this analysis are depicted in Table 1. Age and ancestral proportion scores were significant covariates in the model, and there was a main effect for maltreatment history. The 5-HTTLPR and BDNF were not significant, although the terms examining their interaction with maltreatment showed trends toward significance. The more robust G × E associations we observed in predicting depression in the children might be because: 1) the G × E variables we tested are more strongly associated with