5-HTTLPR x stress hypothesis: is the debate over?

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Letter to the Editor

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We read with great interest the impressive meta-analysis by Culverhouse *et al*.,[1] the largest and most comprehensive study to investigate whether *5-HTTLPR* genotype modifies the association between stress and depression. Their findings based on 31 studies totaling 38 802 individuals of European ancestry, do not support the interaction hypothesis between *5-HTTLPR* genotype and stress (childhood maltreatment, broad life stress) on depression (lifetime or current). The authors also examined the possible effects of sex and age (as both a covariate, and investigating specifically the 21-30 age group), as well as genetic models (dominant, recessive), but again failed to find strong evidence of an interaction. The findings of this meta-analysis contrast with the original report that *S* allele carriers of *5-HTTLPR* compared to *LL*, had an increased risk of depression following a stressful event.[2]

In a subsample of participants from the ESPRIT study (included in this meta-analysis), we recently published findings investigating the impact of both extrinsic (recent stressful events) and intrinsic (diurnal cortisol secretion) stress indicators on current depression.[3] Consistent with meta-analysis findings, stressful events were significantly associated with a more than two-fold increased risk of depression in 334 elderly participants and the interaction term between stress and *5-HTTLPR* genotype was not significant. Examining *5-HTTLPR* genotypes separately however, we found evidence for neuroendocrine heterogeneity of late life depression with differential stress-related susceptibility. *LL* participants (N=88) appeared highly vulnerable to stressful events (OR=6.45, 95%CI=1.82-22.9, p=0.004), yet among *SS* individuals (N=82), only morning cortisol appeared as a biological correlate for depression (OR=4.09, 95%CI=1.03-16.2, p=0.04).[3] The larger group of *SL* heterozygotes (N=164) appeared more resilient to both extrinsic (OR=2.26, 95%CI=0.80-6.34, p=0.12) and intrinsic stress-related factors (OR=0.89, 95%CI=0.41-1.92, p=0.77 for morning cortisol). Past major depression was also a risk factor for current depression only in *LL*. Hence, *SS* participants appeared to have a cortisol-related neuroendocrine vulnerability to depression (that could be referred as "endogenous depression"), *LL* homozygotes were more reactive to stressful events ("reactive depression") and more likely

to have recurrent depression, while the *SL* heterozygotes appeared more resilient to both types of factors, despite double the number of participants compared with the homozygote subgroups.

Although our data require replication, they add to the findings by Culverhouse *et al.*, and the broader debate. They may help account for the lack of strong evidence supporting the interaction hypothesis.[1] While none of our findings are compatible with a linear/additive allelic model, hypothalamic-pituitary-adrenal (HPA) axis dysregulation and psychological load (stressful events and past major depression) suggest opposite recessive models, and resilience reflects heterosis. Indeed, a heterosis effect has been found in up to 50% of all gene association studies[4] and has already been reported with *5-HTTLPR* in a variety of psychiatric phenotypic expressions.[5] It may explain the conflicting findings reported in association studies on depression depending on allele grouping and an arbitrary choice of a genetic model. Such heterozygote advantage could be based on an inverted U-shaped response curve in which either too little or too much gene expression is deleterious, with optimal gene expression occurring in heterozygotes.

Culverhouse *et al.* should be commended for their attempts to rule out other factors which may explain the divergence in prior study findings, including those of previous meta-analyses. However there are other explanations which were not explored and could also play a role, such as interactions with other genes or variants, causing a hidden stratification of the sample such that the depression phenotype would be associated with either one set of homozygotes or the alternate homozygote set.[4] Twin studies show a high heritability of morning cortisol (60%).[6] Gene x gene x environment interactions have been reported between *5-HTTLPR* and *BDNF*.[5] Exploring epistatic effects of genes involved in corticosteroid signaling could be a promising approach, but obviously very large studies would be needed.

Age may also be an important factor to consider, and was adjusted for in the models by Culverhouse *et al.* However, most studies involved adolescents or young adults with only two studies specifically including older adults; the Esprit study and the Heart & Soul study of

outpatients with coronary heart disease.[1] As a consequence, they could only perform sub-group analysis in a specific age group (early adulthood, 21-30 years).[1] Age has however, frequently been evoked as a potential explanation for the inconsistent findings regarding the associations between *5-HTTLPR* and depression[5] or stress reactivity.[7] In older adults, a switch from the *S* allele to the *LL* genotype has been reported for the risk of mental and physical distress with an increasing number of chronic diseases.[8] Hence, severe stressors may indicate underlying traumatization, psychobiologically distinct from the "regular" stress and may be associated with the subsequent development of posttraumatic stress disorder (PTSD). Consistent with this hypothesis, we have also recently shown in this subsample a specific association between *LL* homozygote and susceptibility to re-experiencing, the main clinical symptom of PTSD.[9] The influences of serotonergic neurotransmission on HPA-axis regulation, and the link between serotonergic signaling and *5-HTTLPR* genotype, and with HPA axis functioning, have been largely documented from both animal studies and healthy human exposed to laboratory stress. Rarely have such associations been examined in the older adult population. Hence, further exploring of the interplay between neuroendocrine, genetic, and environmental factors could provide nosologic insights with clinical implications. Whether the differential stress-related susceptibility reported in our work concerns only late-life depression and elderly people, who are more likely to accumulate stressful experiences and HPA axis dysregulation[10], remains to be addressed.

While clearly complex, this area warrants further investigation given the potential for better treatment targets and most importantly patient outcomes. Individuals with a sensitive genotype who are vulnerable to develop depression following adverse experiences may be more likely to benefit from psychological therapy, whereas depressed carriers of an environmentally insensitive genotype may be more likely to require a pharmacological modification of the pathological process. Up until now however, clinical trials based on HPA activation by stress and response to corticosteroids in complement of serotonergic antidepressant have produced contrasting findings. Antiglucocorticoid augmentation therapy appeared inefficient in adult

patients with chronic treatment-resistant depression but efficacious in patients not selected for treatment resistance.[11] Individual neuroendocrine heterogeneity in depression may help provide an explanation for clinical heterogeneity in response to treatments; *LL* homozygotes being more likely to have previous major depressive episodes and thus to experience resistant depression, but clearly more work is required.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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