Correspondence

No Replication of Genotype Effect of 5-HTTLPR on Cortisol Response to Social Stress in Larger Adolescent Sample

To the Editor:

In the March 2010 issue of Biological Psychiatry, Way and Taylor (1) reported that the serotonin transporter promoter polymorphism was associated with the cortisol response to psychosocial stress in a population sample of 182 healthy adults (aged 18–35 years). We compliment Way and Taylor for including different versions of the social stress test in their study design to reveal a dose response effect of social evaluative treat. Combined analyses of the negative and positive evaluative conditions (N = 118) indicated that individuals homozygous for the short version (S) of the 5-HTTLPR displayed stronger cortisol responses than those carrying a long version (L; the SL and LL genotypes). In follow-up analyses, only cortisol responses obtained in the negative evaluative condition were significantly associated with 5-HTTLPR genotype.

Although tempting, we feel that the results reported by Way and Taylor could be explained as a false-positive finding as well. Way and Taylor concluded that the S allele is consistently associated with increased cortisol responses to social stress paradigms and referred to the studies of Gotlib et al. (2) and Jabbi et al. (3). The studies of Gotlib et al. and Jabbi et al. were performed in mixed, rather small samples that mainly consisted of patients with major depression or subjects with a positive family history of depression. At least three other (published) studies found no main effect of 5-HTTLPR genotype on the cortisol response (4–6). These publications might have crossed the Way and Taylor publication because of the delay between acceptance and actual publishing of these studies, and Way and Taylor are therefore not to blame for not having included these references.

The publications of Way and Taylor, Alexander et al., Armbruster et al., and Wüst et al., reminded us of our own data. We examined the moderation of cortisol responses to social stress by 5-HTTLPR genotype in a 4-times larger (n = 518) adolescent sample (mean age = 16.12 years, SD = .59, all Dutch ancestry, 47.2% girls). We used the Groningen Social Stress Test, which was inspired by the Trier Social Stress Task (7) and the child version of the Trier Social Stress Task (8). Participants had to deliver a 6-min speech about their lives and perform difficult mental arithmetic in front of a video camera and a test assistant. They were told that their videotaped performance would be judged on content of speech and the use of voice and posture; it would then be ranked by a panel of peers after the experiment. The test assistant watched the performance critically and showed no empathy or encouragement. A detailed description of the Groningen Social Stress Test can be found in Bouma et al. (9).

We analyzed the data in a similar way to which it was done by Way and Taylor but found no effect of 5-HTTLPR genotype on the cortisol response to the social stress test (F [6, 515] = .57, p = .68). As mentioned by Way and Taylor, the lack of inclusion of the A/G single nucleotide polymorphism (SNP; rs25531) in the long version of the promoter region is a limitation of their study. The conversion from an A to a G results in lower expression of the gene, comparable to the S allele (10). This SNP is available in our data set, but including it (Lg considered as S) in the analyses did not change the effects (F [6, 515] = 1.06, p = .38).

Of all studies on the main effect of the 5-HTTLPR genotype on the cortisol response to a social stress task conducted so far, our study has by far the largest sample size. Indeed, to detect a medium effect (f = .25) (11) of a gene with allele frequency = .4 (comparable to the frequency of the S allele) at α = .05, a sample size of at least n = 258 is necessary (12).

We investigated the association between the 5-HTTLPR and the cortisol response to the social stress test in summer 2008. We found no significant main effects and gave low priority to publishing this null finding because we expected it would be difficult to have it accepted for publication by a high-impact journal. This story, although not an example of good scientific practice, illustrates the point Shridharan and Greenland (13) recently made in the Archives of Internal Medicine: publication bias exists throughout the scientific process.

Findings until now indicate that the serotonergic neurotransmission is complex, which makes it plausible that the presence of an individual common polymorphism such as the 5-HTTLPR will not have much influence on cortisol responses to a social stress task. Given the robustness of our nonreplication and the other three recent nonreplications, we hypothesize that the finding reported by Way and Taylor is a false positive.

The research in this Correspondence is part of the TRacking Adolescents’ Individual Lives Survey (TRAILS). Participating centers of TRAILS include various departments of the University Medical Center and University of Groningen, the Erasmus University Medical Center, Rotterdam, the University of Utrecht, the Radboud Medical Centre—Nijmegen, and the Parnassia Bavo group, all in the Netherlands. Principal investigators are Prof. Dr. J. Ormel (University Medical Center Groningen) and Prof. Dr. F.C. Verhulst (Erasmus University Medical Center). TRAILS has been financially supported by various grants from the Netherlands Organization for Scientific Research NWO (Medical Research Council Program Grant No. GB-MW 940-38-01; ZonMW Brainpower Grant No. 100-001-004; ZonMw Risk Behavior and Dependence Grant Nos. 60-60600-98-018 and 60-60600-97-118; ZonMw Culture and Health Grant Nos. 261-98-710; Social Sciences Council Medium-Sized Investment Grant Nos. GB-MaGW 480-01-006 and GB-MaGW 480-07-001; Social Sciences Council Project Grants Nos. GB-MaGW 457-03-018, GB-MaGW 452-04-314, GB-MaGW 452-06-004; NWO Large-Sized Investment Grant No. 175.010.2003.005); the Sophia Foundation for Medical Research (Projects 301 and 393), the Dutch Ministry of Justice (WODC), and the participating universities. We thank all the adolescents, their parents, and their teachers who participated in this research and to everyone who worked on this project and made it possible.

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