Monoamine Oxidase A, Gender Differences, and Social Exclusion: Response to Gallardo-Pujol *et al.*

To the Editor:

Thank you for the opportunity to respond to the letter by Gallardo-Pujol *et al.* concerning our article. We believe that they raise some important issues, but we also believe that their response is based on some misconceptions.

Gallardo-Pujol *et al.* expressed concern that choosing a sample that includes mostly women may lead to misleading conclusions when trying to understand the relationship between monoamine oxidase A (MAOA) and antisocial behavior. They explain that this is due to the fact that 1) only women can be heterozygous for the MAOA gene; and 2) women are less likely to show antisocial behavior. We are less worried about this concern for several reasons. First, our purpose in the article was to examine aggression, not antisocial behavior as discussed by Gallardo-Pujol *et al.* Aggression is a broader construct than antisocial behavior and has been shown to be just as prevalent among women as it is among men (1–3). Our measure of aggression and the task that we use to assess neural reactivity tap the kinds of aggression that do not show gender differences, and thus we feel that our inclusion of women in this study is appropriate. (Moreover, our sample is 59% female, not "mostly female" as stated by Gallardo-Pujol *et al.*)

In addition, when we rerun the analyses looking only at individuals (men and women) who are homozygous for the MAOA gene (low-activity MAOA [MAOA-L] or high-activity MAOA [MAOA-H]), our findings do not change. We still find that MAOA-H individuals show significantly higher levels of trait aggression, higher levels of trait interpersonal sensitivity, and greater dorsal anterior cingulate cortex (dACC) responses to social rejection than MAOA-L individuals (all p's $< .05$). In addition, we find no gene-by-gender interactions in predicting these outcome variables (all p's $> .47$). The fact that analyzing the data in this manner did not change the results is not surprising, in light of the group differences apparent in Figures 1, 2, and 3 of the original manuscript. Although these findings are reassuring, they are also based on small sample sizes ($n = 20$), and thus we did not feel it was appropriate to report them in the original article. As stated in the article, such results should be interpreted with caution until these findings are replicated in larger samples.

Gallardo-Pujol *et al.* also expressed concern regarding our measure of trait aggression; however, there is no generally agreed upon operational definition of aggression, and we stand by our composite measure as one appropriate operational definition. We agree that more research is needed on different operational definitions and subtypes of aggression, but we feel that we have made a good start on the problem by assessing a broad array of self-reported aggressive behaviors.

Last, our article was criticized for not replicating the gene-by-environment interaction found by Caspi *et al.* (4). It is unclear why this was mentioned, as our study was not a gene-by-environment interaction study. With respect to studies of gene-environment interactions, we would point Gallardo-Pujol *et al.* to a recent meta-analysis confirming the Caspi *et al.* findings (5), as well as a more recent study with a large sample that provides further support for these findings (6). This is a commonly replicated gene-by-environment interaction in psychiatry and it is important to know the potential neural mechanisms by which this polymorphism might be influencing responses to the environment, which we feel our study does. Our focus on aggression and our inclusion of women broadens the conclusions that can be drawn beyond previous studies. By utilizing a sample of healthy individuals (both men and women) who are free of major clinical or psychological problems, as we have done in our investigation, we can better understand how specific genetic polymorphisms relate to subclinical forms of aggressive behavior in a way that is not afforded in samples that include only those with clinical disorders.

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