

Monoamine Oxidase A, Gender Differences, and Social Exclusion: Comment on "Eisenberger *et al.*"

To the Editor:

The association between monoamine oxidase A (MAOA) and antisocial behavior is not new (1,2). What is new is the notion that under certain conditions MAOA might be able to explain the link between these conditions and antisocial behavior in adulthood (3). A few studies have given support to this association and interaction effect (4–6), but the subject remains controversial (7).

With a very clever design, Eisenberger *et al.* (8) explored brain responses in healthy individuals differing in MAOA genotype in diverse situations of social exclusion. Their results are very interesting and are certain to stimulate more research on this topic. However, the study presents several problems that should be addressed more exhaustively in future research and should be taken into account in the evaluation of the article's conclusions.

Regarding MAOA, women might be heterozygous, whereas men have a straightforward genotype. This would not be an insurmountable obstacle if it were not for the amount of evidence showing strong gender differences in antisocial behavior. So, in this case gender is undoubtedly a moderator variable that produces misleading conclusions. Eisenberger *et al.* (8) chose a sample composed mainly of women, on the basis that heterozygous women show intermediate patterns of neural activity between MAOA-L and MAOA-H (9). However, in the original study (9), the authors report these data at the end of supplementary data, using only MAOA-L and MAOA-H subjects for the main analysis. They even report a significant genotype \times gender interaction in some areas that are associated with antisocial behavior. But, from their results (9), we cannot infer that there is actual evidence for considering heterozygous women as a separate group, because there is too much variability within the groups.

There are other reasons for taking the authors' conclusions with caution. They use a composite index called "trait aggression" constructed by averaging and normalizing two independent scales. Trait aggression, however, is much more than the sum of two scores. Although closely related constructs, anger and aggression are not the same (10). A good choice would have been to use factor loadings resulting from a factor analysis of both scales. Additionally, a report of psychometric properties of this measure would have been appreciated; this is important because personality questionnaires have a larger measure error than neuroimaging or genotyping.

As the authors suggest briefly in the discussion, this lack of effect of gender could indeed be due to a lack of statistical power. But this might not be the only reason. We do not have information on the assumptions necessary to conduct an analysis of variance; the authors do not provide the confidence intervals of the correlations, and so on. We think that, before addressing different phenotypes, the role of gender differences regarding MAOA and antisocial behavior should be clarified. We should also mention the importance of replicating Caspi *et al.*'s results (3). When they have been replicated, it has been in the absence of heterozygous groups (4–6,11–15), whereas in samples comprising heterozygous individuals replication has failed (11,16). There are, however, a few studies comprising only hemizygous men that have also failed to replicate the results (17,18). There are other reasons that might suggest the existence of gender differences when processing emotional stimuli (e.g., 19).

So, we wonder whether gender differences would arise if only homozygous individuals were considered for the analysis.

We think that this would improve that excellent study and make an even fuller contribution to the understanding of biological processes that might lead to antisocial behavior. Finally, we note that the conclusions drawn from this article are tentative and should be taken as exploratory. Further research is needed with larger samples and designs that take gender and allele frequencies according to gender into account.

David Gallardo-Pujol

Department of Personality
Faculty of Psychology
University of Barcelona
Pg. de la Vall d'Hebron, 171
08035 Barcelona, Spain
E-mail: david.gallardo@ub.edu

Carlos García-Forero
Antonio Andrés-Pueyo
Albert Maydeu-Olivares

University of Barcelona

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