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Reply to AA Palmer and DC Airey

Reply: Inappropriate Choice of the Experimental Unit Leads to a Dramatic Overestimation of the Significance of Quantitative Trait Loci for Prepulse Inhibition and Startle Response in Recombinant Congenic Mice

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Sir

In response to comments from Drs AA Palmer and DC Airey on our recent publication in Neuropsychopharmacology (Joober *et al*, 2002, 27, 765–781), we would like to acknowledge their objection to using animals in each line as inde-pendent observations, as well as the fact that this may increase type I error. However, as expressed both in the title and in the discussion section, we consider our results as provisional mapping that need to be further tested by linkage analyses.

The primary aims of our paper are to identify informative strains with regard to responses to startle and prepulse inhibition of startle (strains showing significantly lowered or enhanced responses when compared to their parental strains), and as many informative markers as possible to the traits of interest. The definitive proof of the involvement of these markers in the traits should be derived from an F2 linkage mapping analysis produced from the crosses between informative and parental lines. Markers that were associated with either PPI or startle response, in the provisional mapping experiment, will be privileged to be analyzed in the F2 mapping experiment. It is this step of analysis, which will either confirm or refute their involvement in the traits of interest.

We believe that at the initial stage of provisional mapping, it was preferable to identify as many associated markers as possible, even at the expense of some false positive results, rather than to miss any such candidate marker. Missing truly linked markers at this stage would be more costly than having a few false markers, as the latter would be easily refuted at the next stage of the analyses. We think that the analyses presented in our publication have offered a wide pattern of potential markers for these traits, which can be scrutinized further by our lab or any other group working with the same traits.

Furthermore, strain distribution patterns of the markers from the parental strains and the recombinant congenic lines are in complete agreement with our results. The markers that were significantly associated either with increased or decreased PPI segregated in the informative lines with their PPI values either significantly higher or significantly lower, when compared to their parental lines.

Finally, we performed an ANOVA using the lines' means as dependent variable, as suggested by Palmer and Airey. Results of this analysis, for the most promising markers implicated in PPI, are summarized in Table 1. The new analysis confirms the results published in the original paper. However, as expected, the p values achieve lower levels of significance with this analysis.

In conclusion, the results reported by Joober *et al*, although preliminary and requiring confirmation by further linkage mapping analyses, provide important leads toward QTL mapping for PPI in mice.

Table 1 Summary of ANOVAs Using the Line Means

Marker	Background	Average PPI for A/J allele (SD)	Average PPI for C57BL/6J allele (SD)	F ratio (df)	*P* value
D2Mit113	C57BL/6J	52.93 (6.14)	72.14 (10.78)	8.77 (1, 21)	0.0074
D3Mit189	C57BL/6J	48.87 (5.40)	71.61 (10.71)	8.53 (1, 21)	0.0081
D5Mit157	A/J	55.19 (8.95)	73.11 (6.18)	13.36 (1, 13)	0.0029
D7Mit117	C57BL/6J	45.05 (0.00)	70.75 (11.20)	5.03 (1, 21)	0.035
D11Mit67	C57BL/6J	98.36 (8.33)	83.92 (8.31)	7.87 (1, 21)	0.01
D16Mit70	A/J	73.81 (5.47)	83.89 (2.64)	9.19 (1, 13)	0.0096

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