Correspondence


Reply

To the Editor:

Battaglia et al based their comments on the fact that in our article (Leboyer et al 1999b) “we did not make any genotyping of the 5-HTTLPR.” They further suggest that we should have selected the unaffected relatives on the basis of their 5-HTTLPR genotypes. This suggestion is highly inappropriate according to the strategy we are using, which is the identification of peripheral vulnerability markers (“endophenotypes”) in nonaffected relatives of psychiatric patients (Leboyer et al 1998, 1999a, 1999b; Pierson et al, in press). Endophenotypes are traits, or covariates, that correlate with the main trait of interest and serve to define the trait or its underlying genetic mechanism more accurately. Endophenotypes may be biochemical, neurophysiologic, cognitive, and/or neuropsychologic markers. To fulfill the criteria for a marker trait, an endophenotype should be able to be measured in an objective fashion among clinically unaffected relatives of patients, should occur before the onset of illness, should be stable, and should be associated with an increased risk of clinical illness. This alternative phenotypic strategy may greatly enhance the power of genetic analysis of psychiatric disorders.

Their second concern regarding the potential bias of seasonal variation in 5-HT parameters is irrelevant: it is well-known that 5-HT function might change by less than 20% according to the season (Wirz-Justice 1988), whereas the differences of imipramine binding between unaffected relatives and control subjects we report is close to 60% for the Kd and 75% for the Bmax.

Their third comment is related to the fact that, having shown that unaffected relatives have lower platelet imipramine binding and 5-HT content, we say “this result was consistent with several reports of an association between bipolar disorder and the short allele of the 5-HTTLPR, although this result has not always been replicated.” The association with the s allele reported among bipolar patients in the literature is indeed coherent with reduced 5-HT uptake (Lesch et al 1996). One team (the authors of these criticisms) has reported that depressed children do not differ from control subjects with regard to paroxetine binding, although they carry the l/l genotype (Nobile et al 1999); however, this is in contradiction with the highly replicated observation of functional expression of the promoter (i.e., l/l and l/s being associated with high uptake and the s allele being associated with reduced uptake; Greenberg et al 1999).

In conclusion, we disagree with the assumption made by Battaglia and colleagues that it can be misleading to analyze 5-HT functionality in depressed patients and their relatives without 5-HTTLPR genotyping. Studying these two parameters (protein phenotype and genotype) separately only reflects the interest of performing two different research strategies independently (i.e., a biochemical versus a genetic association study). We strongly believe that, in this greatly controversial field, functional studies of proteins, as well as genetic case–control studies, are highly required. But as we said in our article, we are in the process of exploring the genotypes of another larger population of unaffected relatives, first to confirm our preliminary findings and second to explore blindly (without knowing the biochemical endophenotype) the different 5-HTT genotypes (Nakamura et al 2000).

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References


