Cautionary Note: Complex (Dys)function of the Serotonin Transporter

To the Editor:

Reduced binding to the serotonin transporter (5-HTT) in unaffected relatives of patients with manic–depressive illness has been recently reported as a hint of a putative trait marker for the disease by Leboyer et al (1999). We offer a few comments and views on this.

First, the fashion by which individuals in the population differ from each other for some parameters indicative of 5-HTT function (i.e., transporter level and 5-HT uptake) can be predicted on the basis of their genotype at the 5-HTT–linked polymorphic region (5-HTTLPR; Greenberg et al 1999; Nobile et al 1999), with subjects who are carriers of the s variant exhibiting reduced transcription and a dominant effect (or codominant effect, according to different studies; Goldman 1996) for this allele. Apparently, the Leboyer et al (1999) data were processed under the uncontrolled assumption that 5-HTTLPR genotypes and allele frequencies were under the Hardy–Weinberg equilibrium among control subjects. With such a small sample, however, casual deviations from Hardy–Weinberg equilibrium among control subjects. With such a small sample, however, casual deviations from Hardy–Weinberg equilibrium leading to overrepresentation of l/l homozygotes are possible.

Second, several parameters of 5-HT function follow predictable seasonal variations, and it was unspecified whether appropriate procedures were adopted to control for this potential source of bias.

Third and foremost, levels of platelet imipramine binding and 5-HT content found among unaffected relatives of patients with bipolar disorder were lower than among control subjects (Leboyer et al 1999), and taken as indirect evidence of an excess of carriers of the s allele in the former group. This reasoning may be flawed, not only because it is based on a second-order hypothesis. Although several studies report diminished indices of 5-HT functionality among depressed patients, as compared with euthymic control subjects, up until recently none had controlled for the possible effect of 5-HTTLPR polymorphisms. By finding decreased platelet 5-HT uptake in depressed drug-naive children compared with nondepressed peers, we (Nobile et al 1999) have shown that such group effect can in fact be sustained by the homozygote depressed carriers of the l variant, whereas heterozygotes and s/s homozygotes may have normal indices of 5-HT functionality during depression.

Consistently, differential response to selective serotonin reuptake inhibitors in adult depressed patients can be predicted according to their genetic setup at the 5-HTTLPR (Smeraldi et al 1998), and by measuring 5-HTT protein availability in vivo with [123I]β-CIT single photon emission computed tomography, Heinz et al (2000) found reduced availability only in l/l-homozygous patients with alcoholism, as compared with control subjects.

Although we are at an early and tentative stage, these data together suggest that, at least in subjects who develop symptoms of depression and alcoholism, the function of the 5-HTT becomes affected for l/l-homozygous subjects, whereas the same may not be true for s/s homozygotes and heterozygotes. Future studies may address this issue in terms of possible epigenetic/epistatic mechanisms.

We therefore note that analyzing 5-HT functionality in patients with depression and in their relatives without 5-HTTLPR genotyping can be misleading. Incidentally, the grand average of group effect found by studies that compared indices of 5-HT functionality in depressed patients and normal control subjects fits well with the rough 30% frequency of subjects with an l/l genotype predicted by the Hardy–Weinberg equilibrium.

Follow-up studies of 5-HT indices after remission from depression in patients characterized for their 5-HTTLPR genotypes are lacking, and reassessments in depressed children after recovery in our study are still under way. Assessing unaffected relatives from multiplex families of patients with mood disorders (Leboyer et al 1999) can be a further, valuable strategy when appropriate genotyping is added. It is still conceivable that l/l-homozygous relatives without depression may have lowered 5-HT functionality, which would be a more robust hint of a trait marker. But this remains to be demonstrated.

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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 variation in 5-HT parameters is irrelevant: it is well-known that the power of genetic analysis of psychiatric disorders. Illness. This alternative phenotypic strategy may greatly enhance 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 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


