Correspondence

Biological Psychiatry

Tripping Over the Same Stone

To the Editor:

Recently, in a large, 6-year follow-up controlled study, Abé *et al.* (1) found abnormal cortical thinning between study time points in subjects with bipolar disorder (BD). Moreover, they found that subjects who were being treated with lithium seemed to be "protected" from some of these anatomical changes. These findings are in line with those of other studies, which also support a neuroprogressive mechanism for BD and neuroprotective effects for lithium (2). This would seem to be both good news (we all hope that lithium's neuroprotective effects operate at the clinical level) and bad news (BD would appear to be a neuroprogressive disorder).

However, this study suffers from a serious methodological issue: it has not adequately controlled for the potential detrimental effects that antipsychotics may have on brain structure (3,4). This is critical, as it makes it impossible to adequately determine whether the structural changes in question are due to the mechanisms of the disease itself (such as the hypothetical neuroprogression) or are a consequence of antipsychotic treatment. Similarly, it also makes it impossible to determine whether the differences found in patients treated with lithium are due to the neuroprotective effect that has been proposed for this drug or to the fact that subjects treated with lithium are usually less exposed to antipsychotics.

The failure to consider the possible effects of antipsychotic treatment in a large and complex study such as Abé *et al.*'s is even more striking in light of the fact that in one of the few previous similar studies, the correlation found between loss of gray matter and exposure to antipsychotics was twice as strong as that found for the disease's chronicity (5). This raises the question of why, having expended the considerable effort required to carry out a longitudinal study, such a simple yet important variable was not adequately controlled for?

Since Alois Alzheimer first discovered a neuroanatomical substrate for the disease that bears his name, psychiatry has struggled, sometimes desperately, to achieve the same with some of our most emblematic disorders. Over a decade ago, neuroprogression was both the hope and the "paradigm" in the field of schizophrenia disorders, and neuroprotective effects were being proposed for novel antipsychotics (6). However, two strong arguments have weakened this hypothesis. First, prospective studies could not demonstrate that the cognitive deficit of patients with schizophrenia increased progressively (7). Second, and more disturbingly, it came to light that exposure to antipsychotics explained the decrease in brain volume found in cohort studies of people affected by these disorders at least as well as recurrence and chronicity did (4,8).

In recent years, the idea of neuroprogression has entered the field of BD with remarkable strength. In a relatively short time, neuroprogression hypotheses have gone from being simple theoretical proposals to being the conceptual foundation of the most influential treatment guidelines for BD (9). This has occurred without taking into account both the methodological problems discussed above and the fact that the latest meta-analysis of prospective cognitive studies in BD has found that the cognitive deficits of this population tend to be static and may even decrease over time (10). In light of this, it would be prudent to take to heart the lessons learned previously in the field of schizophrenias and to not trip again over the same stone.

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