# Correspondence

Biological Psychiatry

## Reply to: Tripping Over the Same Stone

### To the Editor:

Commenting on our longitudinal study of brain structural changes in bipolar disorder (BD) (1), Strejilevich and Quiroz (2) raised the important issue of potential effects of medication use. Certain drugs may affect brain structure. Therefore, we controlled for current medication use at follow-up and baseline. These analyses did not indicate that our findings were confounded by antipsychotic drug use.

However, our naturalistic study precludes causal inferences as to what causes the observed cortical thickness decline. It is particularly challenging to distinguish between structural changes resulting from the natural course of BD and changes that are due to medication. This is because drug use is confounded by indication: persons with a more severe—and potentially progressive—disorder might both receive more drug treatment and feature more pronounced structural changes. We did not have data on cumulative drug use, but collecting fine-grained data on medication use would not solve this problem, which is a general limitation of observational studies. For the same reason, results obtained after statistical control for medication use should be treated with caution, as this may, in fact, control for the trait of interest (e.g., controlling for antipsychotic use might control for psychotic symptoms and associated brain changes). To adequately investigate medication effects on brain structure, randomized placebo-controlled clinical trials are required.

Notably, our study aimed to overcome the limitations of cross-sectional studies that cannot distinguish between static premorbid conditions and cortical changes over time. Our longitudinal observational study found an accelerated cortical decline in patients with BD. Although neuroprogression is one potential explanation of our findings, our results neither provide evidence of the underlying cause nor suggest that all patients are affected. Thus, it cannot be excluded that exposure to antipsychotic drugs might have an (additive) effect on cortical decline in BD. The same applies to other drug types. In the absence of randomized clinical trials, our findings need to be appraised against the backdrop of collateral evidence of long-term changes in, for instance, cognitive functioning and other biomarkers.

Finally, we dispute that discovering that BD is a neuroprogressive disorder would be "bad news," as Strejilevich and Quiroz suggest. On the contrary, revealing the true nature of a disorder is essential for treatment development, and no stone should be left unturned until the underlying mechanisms are fully understood.

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The authors report no biomedical financial interests or potential conflicts of interest.

### Article Information

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### References

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2. Strejilevich SA, Quiroz D (in press): Tripping over the same stone. Biol Psychiatry.

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