LETTER TO THE EDITOR

The volumes of subcortical regions in depressed and healthy individuals are strikingly similar: a reinterpretation of the results by Schmaal et al.

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In their recent meta-analysis of magnetic resonance imaging data from 15 research samples worldwide, Schmaal et al. examined the structural differences of nine subcortical brain volumes between 1728 patients with major depressive disorder (MDD) and 7199 healthy participants. In the authors’ univariate analyses, none of the nine volumes was associated with depression severity, and only hippocampal volume was significantly decreased in MDD patients compared to controls, with the largest effect being observed in the recurrent MDD group (difference 1.4%, Cohen’s d 0.17). The study is the result of a huge collaborative effort, and we commend the authors on their insightful manuscript. However, as the results by Schmaal et al.1 (1119 recurrent MDD patients, 7040 controls, Cohen’s d = 0.17) leaves little hope to robustly distinguish between MDD and healthy participants based on univariate analyses of regional volumes, we see important opportunities for future research. First, the focus on brain regions in isolation leaves open the question whether regional structural differences between MDD and controls reflect a single overall pattern (for example, decreased subcortical volume) expressed slightly differently in different regions, or whether there are multiple independent patterns of structural differences. Multivariate models have shown much higher classification accuracies than the 52.6% we identified here, and we are looking forward to follow-up studies

Figure 1. Density plot and histogram of simulated data based on the largest effect identified by Schmaal et al. (1119 recurrent MDD patients, 7040 controls, Cohen’s d = 0.17).
in much larger samples to see if these effects generalize. Second, MDD is a highly heterogeneous disease, and a recent report identified 1030 unique symptom profiles in 3703 depressed patients,7 posing problems for both dimensional and categorical analyses. Associating regional volumes to depression severity (dimensional)—that is the sum-score of disparate depression symptoms, many of which are opposites (insomnia/hypersomnia, agitation/retardation, weight loss/gain)—will considerably decrease the signal-to-noise ratio;8 it may well be that hippocampal volume is more closely related to the severity of, say, psychomotor retardation than to a sum of various different symptoms. Categorical analyses of MDD as one group, on the other hand, unrealistically assume a homogeneous population and may obfuscate crucial insights. We thus encourage the investigation of smaller and more reliable units such as individual symptoms, research domain criteria dimensions or endophenotypes.8

CONFLICT OF INTEREST
The authors declare no conflict of interest.

REFERENCES