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***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.[1] examined 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* of 0.17). The study is the result of a huge collaborative effort, and we commend the authors on their insightful manuscript. However, as the findings present the best empirical evidence currently available, an accurate interpretation of the results is paramount, especially considering the report's goal to "robustly discriminate MDD patients from healthy controls" (p.1). We therefore add two observations and future research directions.

First, the authors did not estimate any form of classification accuracy. We simulated hippocampal volume data based on the sample and effect sizes reported by Schmaal et al.[1], yielding a prediction accuracy of 52.6% (Figure 1), only slightly above chance. Code, data and relevant citations to reproduce our analysis can be found on http://figshare.com/articles/Fried_amp_Kievit/1549680.

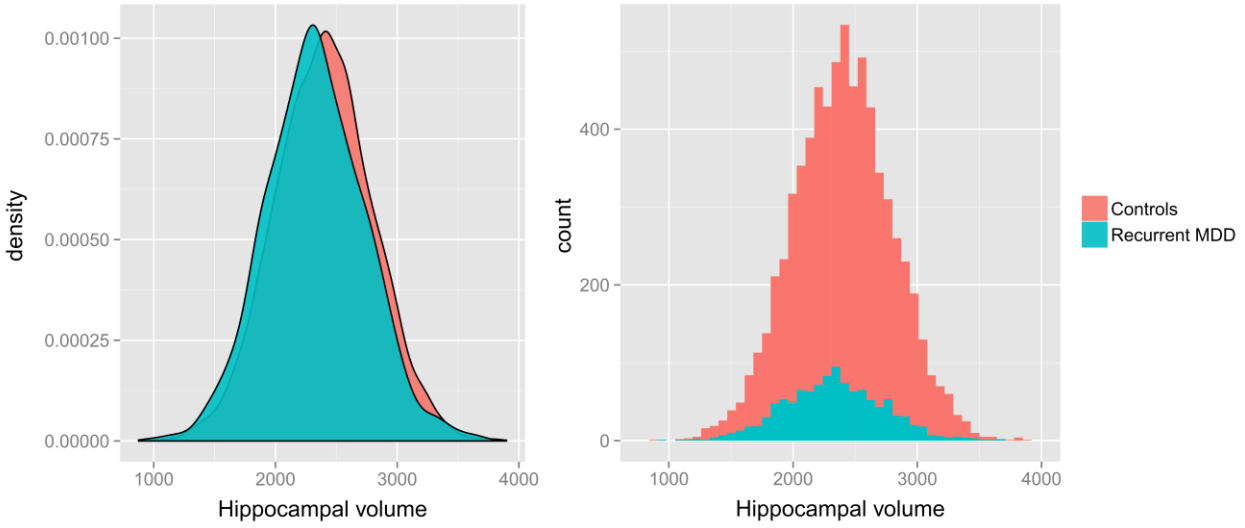


**Figure 1.** Density plot and histogram of simulated data based on the largest effect identified by Schmaal et al.[1] (1119 recurrent MDD patients, 7040 controls, Cohen's d = 0.17).

Of note, the 52.6% likely reflect an overestimate as reduced hippocampal volume is not specific to MDD and has been documented in conditions as varied as schizophrenia, PTSD, chronic alcoholism, epilepsy, Alzheimer's disease, Huntington's disease, and others[2]. We conclude that the study by Schmaal et al.[1] provides the so far strongest piece of evidence that, at least regarding the subcortical regions studied here, brains of depressed patients are *remarkably similar* to brains of healthy individuals, suggesting that numerous prior conflicting results in much smaller samples were false positives.

Second, the authors mainly discuss reduced hippocampal volume as consequence or precursor of MDD, but we see a number of alternative possibilities: the association could also be the result of a shared underlying cause (e.g., a genetic predisposition), of bidirectional/mutual reinforcement, or spurious due to confounders/mediators (lack of exercise/activity[3] and accelerated aging[4] impact on hippocampal volume and are more prevalent among depressed patients). It is noteworthy that the lack of specificity of reduced hippocampal for depression[2], the lack of discriminatory power, and also most of the above explanations are inconsistent with reduced hippocampal volume as biological marker of depression as a clinical state. This also holds for the authors' primary hypothesis that depression causes structural changes, since—unless volume increases post-MDD—all individuals with previous instances of depression would be indistinguishable (no matter if, at present, healthy or not). In the absence of convincing longitudinal support for a causal role of hippocampal volume for depression, we believe the findings may warrant a more nuanced interpretation than "this resolves for good the issue that persistent experiences of depression hurts the brain"[5].

While the authoritative report by Schmaal et al.[1] 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 (e.g., 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[6] than the 52.6% we identified here, and we are looking forward to follow-up

studies 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)—i.e. 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, RdoC dimensions, or endophenotypes[8].

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