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LETTERS 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 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 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. Of note, the 52.6% likely reflects an overestimate as reduced hippocampal volume is not specific to MDD and has been documented in conditions as varied as schizophrenia, post-traumatic stress disorder, 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 a consequence or a 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] have an impact on hippocampal volume and are more prevalent among depressed patients). It is noteworthy that the lack of specificity of reduced hippocampal volume for depression,[2] the lack of discriminatory power and also most of the above explanations are inconsistent with reduced hippocampal volume as a 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 (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[6] than the 52.6%

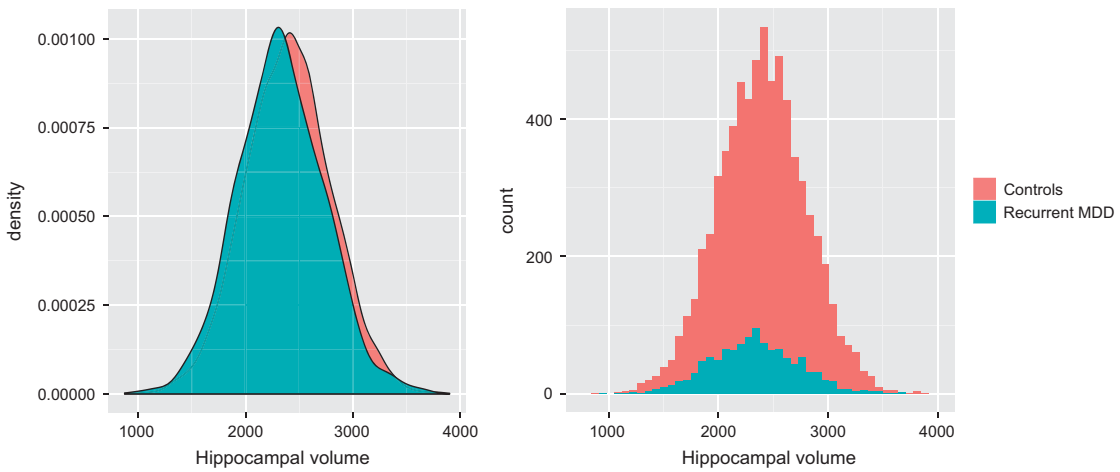


Figure 1. Density plot and histogram of simulated data based on the largest effect identified by Schmaal *et al.*[1] (1119 recurrent MDD patients, 7040 controls, Cohen's $d = 0.17$).

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)—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.

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Size matters; but so does what you do with it!

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Using meta-analysis techniques in a large neuroimaging data set derived from 1728 major depressive disorder (MDD) patients and 7199 healthy controls, across 15 centres worldwide, Schmaal *et al.*[1] attempted to identify subcortical brain alterations associated with MDD. The impetus for this, as emphasized by the authors themselves, is that current neuroimaging studies that have tackled this question suffer from three main problems: (1) limited statistical power due to small sample sizes, (2) disease heterogeneity in clinical samples and (3) complex interactions between clinical characteristics and brain morphology. Puzzlingly, the authors predominantly focus on the first of these problems despite having coalesced structural neuroimaging data from a large number of subjects, and essentially report reduced hippocampal volume in patients with MDD. But this is not a new finding and indeed it has been replicated and supported by several previous neuroimaging meta-analyses.[2,3]

The scientific merit of a research finding is governed not only by the sample size but also by how moderating factors are managed within the analyses, to reveal meaningful relationships between variables of interest. Disease heterogeneity for example is inevitable when sampling real-world clinical populations and, rather than attempting to achieve homogeneity through statistical control, a large sample size allows for distinction of clinically meaningful subtypes, such as melancholia, addressing problem (2) above. Large data sets, such as those garnered by Schmaal *et al.*,[1] often afford such an opportunity; unfortunately the authors did not take full advantage of the large data set to address these issues.

When structurally mapping hippocampal volume, extant research findings point to several moderating factors that warrant careful consideration, such as gender,[4] recurrence of mood episodes[3,5] and the effects of medication, in particular the impact of antidepressants,[6] given that each of these can produce discernible volumetric change. And while disentangling the individual effects of clinical factors upon neuroimaging parameters is a significant challenge, it is one that can be purposefully attempted in a large data set by robustly delineating subgroups defined on the basis of clinical characteristics, instead of regressing out these features or only examining these factors individually. The authors may have the ability to partition their large sample into interactive cells (for example, diagnosis x sex x recurrence x onset) and to analyse for between-subject differences across these complex interactions. In doing so, they would have the ability to show how clinical complexity plays a role in hippocampal volume in MDD, addressing problem (3) above. This type of approach is capable of revealing pertinent new findings that can potentially inform both the aetiology and treatment of MDD. In the absence of such granular analyses, reiteration of non-specific volumetric changes does little to advance our knowledge of the illness and instead risks reifying a clinically inconsequential finding.

Our concern is exemplified by the finding that there was no association between MDD severity and hippocampal volume change, and that first-episode MDD did not differentiate patients from healthy controls with respect to hippocampal size. This raises some interesting questions: does hippocampal structural change become evident early in the development of MDD? And to what extent is hippocampal volume moderated by clinical complexity? Schmaal *et al.*[1] examined early- versus late-onset MDD, but the real impact of the illness is difficult to gauge without detailed knowledge of its duration, course and clinical pattern.

The architects of ENIGMA are to be commended for achieving sufficiently large sample sizes for neuroimaging analysis through multicentre collaboration. But by not attending to the complexity of clinical manifestations, the study fails to exploit its full potential, and the reported hippocampal volume changes fail to provide a deeper understanding of MDD.

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