Invited Commentary

Consistency, Replication, and Meta-analyses of Altered Brain Activity in Unipolar Depression

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Müller et al[1] provide a technically sophisticated and informative set of meta-analyses examining altered brain activity in adults with symptomatic unipolar depression. The striking overall finding of their analyses is the lack of consistent group differences across studies. The absence of replicable effects across studies remained even when they addressed a number of potentially key confounds, such as examining only patients not receiving medication, patients without comorbidities, and patients without late-life or geriatric depression. Furthermore, Müller et al[1] make a number of important suggestions for conducting high-quality meta-analyses in the future that can be replicated and that can provide guidance for future research in the field. These excellent suggestions include the use of a reasonably large number of experiments with homogenous methods, avoiding region-of-interest or restricted analysis studies that may bias results, only including studies with a sufficiently stringent false-positive correction, and providing sufficient details about the methods to allow replication.

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The inconsistency of prior results examining altered brain activity in unipolar depression revealed by Müller et al[1] should definitely give the field pause and highlights the need to address underlying causes of this lack of replication. However, some of these findings need to be interpreted with caution because Müller et al[1] do not fully follow their own recommendations, particularly regarding combining across homogenous methods. Specifically, the meta-analysis of cognitive tasks combined across paradigms that varied considerably in processing demands, and it is not clear that one would predict common regions to show altered activity in unipolar depression across quite different cognitive domains. This concern extends even to the meta-analysis of memory processing because this particular meta-analysis combined studies examining either working memory or episodic memory. Although some brain regions contribute to both working memory and episodic memory, there is also strong evidence for dissociations in the neural systems underlying working vs episodic memory and even for dissociations among subcomponents of episodic memory. Thus, to the extent that unipolar depression is associated with greater impairments in some components of memory than others,[2] one would not expect there to be consistent alterations in brain activation across all these different types of studies. Furthermore, even if unipolar depression was associated with alterations across multiple aspects of memory, different brain regions may mediate the different forms of memory impairment (eg, the prefrontal cortex for working memory[3] vs the hippocampus for episodic memory[4]).

Müller et al[1] also raise important points about sample heterogeneity and how this may influence the results of meta-analyses in depression, as well as in any other form of psychopathology. Müller et al[1] focus on medication status and psychiatric comorbidity, which are both important dimensions of variance. However, it is also important to account for variance in symptom presentation among individuals with unipolar depression, even among individuals without comorbid conditions. For example, individuals with depression vary in the degree to which their clinical presentation is associated with alterations in mood or hedonic function, or both. Interestingly, some research is now starting to suggest that negative mood and impaired hedonic capacity may relate to different types of emotion processing impairments and, thus, potentially different neural alterations.[5] As such, meta-analyses that focus on altered brain activation in relationship to specific dimensions of pathology present in depression may reveal more consistent evidence of altered brain activation, as in recent work on anhedonia.[6] Importantly, this will also entail a more consistent examination in the field of continuous measures of various symptom domains in relation to brain activity.

Müller et al[1] also make a critical point about the need to prioritize replication in future studies of unipolar depression, a concern that again applies to research on any form of psychopathology. As noted by Müller et al,[1] this is challenging because the use of common paradigms across studies is not incentivized and can be viewed as stifling the creativity and novelty of researchers designing new studies. However, these are not mutually exclusive approaches; the inclusion of common paradigms across studies that also include novel paradigms would provide hugely helpful benchmarking information that would allow for an enhanced evaluation of the robustness of impairment across studies, populations, and symptom dimensions. This meta-analysis points to several additional ways to improve replicability and transparency. For example, numerous studies were excluded from this analysis for only presenting region-of-interest results, which could skew meta-analytic findings. To improve future meta-analyses, studies could present whole-brain results in addition to any a priori region of interest.

In addition, as more and more journals allow for the inclusion of 3-dimensional neuroimaging files as figures, full voxelwise statistical maps could be easily accessed and used for meta-analyses rather than inferring activity from peak coordinates. It is also important that future studies present thorough details of sample characteristics and heterogeneity, as well as their analytic software and methods, to accurately determine their viability for inclusion in meta-analyses. Finally, Müller et al[1] also note that 38.4% of the experiments exam-

ined in their meta-analysis set a voxel-level threshold but did not correct for multiple comparisons (eg, by familywise error or false discovery rate correction). It will be critical for future research to appropriately correct for multiple comparisons to help improve replicability, particularly given recent suggestions that typical methods for corrections for multiple comparisons may still be leading to highly inflated false-positive rates.[7] As a field, we need to heed the cautionary tale offered by Müller et al[1] and work to generate robust and replicable data that will provide increasingly sophisticated and definitive answers regarding the types of brain alterations that are present in specific forms of psychopathology.

ARTICLE INFORMATION

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