Correspondence

Reply to: New Meta- and Mega-analyses of Magnetic Resonance Imaging Findings in Schizophrenia: Do They Really Increase Our Knowledge About the Nature of the Disease Process?

To the Editor:

In their letter to the editor, Vita and De Peri (1) question whether new meta- and mega-analyses of magnetic resonance imaging (MRI) findings in schizophrenia increase our knowledge about the nature of the disease process. In general, meta- and mega-analyses provide objective methods to critically summarize a body of evidence regarding a particular question. As there had been no coordinated meta-analysis of cortical thickness and surface area abnormalities in schizophrenia, it is our view that this new, collaboratively conducted meta-analysis (2) contributes to our knowledge on this question and offers information on the cross-site consistency of observed disease effects. Regional effects on cortical thickness and surface area can be difficult to summarize based on the traditional, literature-based, meta-analysis method, given the heterogeneity of analysis methods used in individual studies.

The Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) approach of collaboratively conducting meta-analyses offers additional benefits. First, ENIGMA's publicly available methods lend themselves well to independent replication of imaging findings (3,4), which is crucial given the "crisis of replication" in neuroscience (5–7). Second, the use of the same quality assurance, image processing, and statistical analysis methods across samples within and across ENIGMA working groups minimizes method-related heterogeneity and offers the potential for straightforward cross-disorder comparisons (8–12). Third, the use of similar meta-analytic methods across worldwide samples has generated imaging and genetics findings with sample sizes beyond the scope of any individual laboratory or consortium studying a single disorder (13–16).

Vita and De Peri (1) repeat one of the study weaknesses already listed in the discussion: that possible group differences in lateralization were not examined. This question is under investigation by the ENIGMA Laterality Working Group, which is currently examining healthy and disordered brain laterality (17,18). ENIGMA coordinates publication efforts across working groups to avoid overlap. Moreover, numerous ENIGMA studies make important contributions showing between-disorder brain differences without addressing laterality.

Vita and De Peri (1) also mention that the meta-analysis does not address possible differential longitudinal trajectories between individuals with schizophrenia and healthy volunteers, which is also correct as this cross-sectional meta-analysis did not aim to examine longitudinal trajectories. There are ongoing efforts by the ENIGMA Plasticity Working Group to study genetic influences on individual differences in longitudinal brain changes (19). We agree that further investigation of questions regarding longitudinal trajectories of brain changes across the lifespan, especially prior to illness onset, e.g., in adolescents at clinical high risk for psychosis, as well as after a first psychotic episode, will provide valuable information regarding schizophrenia pathogenesis, and several such analyses are planned or are ongoing.

Vita and De Peri (1) further state that the meta-analysis does not add relevant information about the effects of antipsychotic medication on brain morphology but qualify that the reported findings seem compatible with findings from longitudinal MRI studies that suggest different effects of first- versus second-generation antipsychotic treatments on cortical gray matter changes. We point out that prior meta-analyses did not dissociate effects of antipsychotic treatments on cortical surface area versus cortical thickness, whose product constitutes gray matter volume, and that the consistency of findings is important in the light of reports on nonreplication in neuroscience.

The comment that "the supposed huge statistical power of mega-analyses of MRI findings in schizophrenia may be undermined by the large variation of data obtained by different centers in disparate conditions" is incorrect. First, van Erp *et al.* (2) is a meta-analysis and not a mega-analysis, which, like any other meta-analysis, summarizes within-sample effects. In fact, joint meta-analyses tend to reduce method-related variation when compared with literature-based meta-analyses because similar analysis methods are applied across samples. Second, multiple imaging genetics meta-analyses replicate common genetic variants associated with measures of brain structure and find a greater number of common variants associated with these measures when additional independent samples are added (20–22). These findings suggest increased power as brain imaging data from independent samples are added. Finally, the suggestion that mega-analyses of MRI data are undermined by between-site variation is not borne out by the facts. Research from a decade ago showed the feasibility and the additional power gained by pooling legacy structural imaging data (23). More recent studies show that meta- and mega-analyses of structural imaging data, whether from prospective multiscanner or independent samples, yield significant and similar findings (24–26). Each analysis method has strengths, weaknesses, and pitfalls. Hence researchers must consider whether to conduct a meta-analysis, a mega-analysis, or both, to answer a particular question.

The suggestion that meta- and mega-analyses are not hypothesis-driven approaches is also incorrect. All published ENIGMA Schizophrenia Working Group meta-analyses list their hypotheses at the end of their introductions (2,3,27–29). Of note, nowhere in the article do we state that "meta-analyses provide better evidence than large, well-designed, hypothesis-driven, high-quality individual trials." On the contrary, all findings from meta-analyses depend on the quality of the studies on which they are based. Even so, meta-analyses can offer additional safeguards against false positive findings

https://doi.org/10.1016/j.biopsych.2018.10.003
ISSN: 0006-3223

generated by individual studies with small or highly heterogeneous samples by considering each sample's error terms. We do agree that missing data for known or supposed significant moderators can be an issue. However, this is a criticism of all analyses of scientific data rather than of our study specifically.

Finally, we respectfully disagree with the statement by Vita and De Peri "that the time has come for applying new approaches to the study of the nature of the disease process underlying schizophrenia, rather than promoting redundant research on mega-databases that may even dilute or confuse established knowledge" (1). We believe there is value both in taking the relatively new approach of performing large-scale collaborative research on costly, already collected data, and also in applying other innovative approaches and experimentation in adequately powered samples. We believe that most scientists who contribute to ENIGMA or other consortia as well as the funding agencies who promote large-scale data sharing and analysis recognize that both approaches make valuable contributions to the field.

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Acknowledgments and Disclosures

This work was supported by National Institute of Biomedical Imaging and Bioengineering Grant No. U54EB020403 (to the ENIGMA consortium). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

TGMvE wrote the first draft of the manuscript and all authors contributed edits and approved the contents of the manuscript.

TGMvE has had a research contract with Otsuka Pharmaceutical. AP has served as a consultant for Boehringer Ingelheim. The other authors report no biomedical financial interests or potential conflicts of interest.

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See also associated correspondence: https://doi.org/10.1016/j.biopsych.2018.07.029.

Received Oct 2, 2018; accepted Oct 5, 2018.

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