

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:

We read with interest the meta-analysis on cortical brain abnormalities in schizophrenia completed by the ENIGMA Schizophrenia Working Group (1).

van Erp *et al.* (1) pooled and quantitatively analyzed cross-sectional magnetic resonance imaging (MRI) data from an impressively large sample of patients with schizophrenia ($n = 4474$) and healthy control subjects ($n = 5098$) assessed at 39 centers worldwide. Compared with healthy volunteers, individuals with schizophrenia showed widespread thinner cerebral cortex. The study also demonstrated regional differences between subjects with schizophrenia and healthy control subjects in cortical thickness, with more involvement of frontal and temporolimbic structures in patients. As for the potential moderators of the observed effect sizes, the study showed that cortical thickness reduction was two to three times higher in antipsychotic treated relative to unmedicated individuals, and significant negative correlations were demonstrated between cortical volume and normalized doses of antipsychotics.

These findings are only in part consistent with those reported in previous meta-analyses of longitudinal MRI studies comparing patients with schizophrenia and healthy control subjects (2–4). Both longitudinal reviews and this cross-sectional quantitative review show that brain abnormalities in schizophrenia do not involve cortical gray matter (GM) uniformly. However, longitudinal studies have shown that progressive changes of cortical GM in schizophrenia affect the left (dominant) hemisphere and the superior temporal structures more than other parts of the cortex and appear to be especially active in the first stages of the disease (3). The findings from van Erp *et al.* (1) fail to show lateralization of cortical brain abnormalities and do not allow researchers to make crucial inferences about the time course of cortical GM volume over time in schizophrenia given the cross-sectional design of the study and the lack of subgroup analyses of patients at different stages of illness. Moreover, the findings obtained in the present meta-analysis do not add relevant information about the effects of antipsychotic medication on brain morphology in the context of an ongoing sensitive debate, active even outside the scientific community, about the pros and cons of antipsychotic treatment—although they seem compatible with the finding from longitudinal MRI studies of a somewhat different impact of first- versus second-generation antipsychotic intake on cortical GM changes (4).

Although the results of the study by van Erp *et al.* (1) add another strong piece of evidence to the notion that schizophrenia is associated with structural brain abnormalities, they raise a number of both theoretical and methodological key questions that may be applicable to other mega-analyses.

First, 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 and by pooled analyses conducted with a non-hypothesis-driven approach that does not take into account a number of known or supposed significant moderators, with the paradoxical risk of clouding or dissipating well-grounded notions about the nature of the pathological process under consideration. The general assumption that meta-analyses provide better evidence than large, well-designed, hypothesis-driven, high-quality individual trials may be sometimes misleading and even more awkward in the case of mega-analyses.

Second, current evidence about the complex pathophysiological trajectory of brain abnormalities in schizophrenia through the lifespan should give the scientific community the sense of what may be the probing value of meta- or mega-analyses of cross-sectional MRI data and of their chance to add meaningful information about the pathological process of the disease: in fact, the heuristic value of longitudinal MRI studies and of their quantitative reviews overcomes the value of cross-sectional investigations.

The impressive amount of brain imaging studies already produced and published to date suggests 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.

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Article Information

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