Biological Psychiatry

Commentary

The Power of Collaboration and Data Aggregation

Deanna M. Barch

The field of psychiatric genetics moved forward by leaps and bounds when it deployed its efforts toward aggregating samples and conducting analyses on larger and larger datasets, allowing well-powered and unbiased identification of risk alleles for schizophrenia and other disorders (1). The Enhancing Neuroimaging Genetics through Meta-analysis (ENGIMA) consortium is helping to create this type of major field change for work on the structural variation associated with psychiatric disorders, including schizophrenia, bipolar disorder, and depression. The article by van Erp *et al.* (2) in this issue of *Biological Psychiatry* is a strong example of the significant utility of aggregating samples across many datasets and using meta-analysis and metaregression to address questions about the relationship between structural variation and psychopathology (2). In particular, this collaborative analytic approach allows for well-powered whole-brain analyses of neuroimaging data that engender a similar type of "unbiased" search for structural correlates of schizophrenia as has been done with genetics. Many have argued that this type of approach is critical for generating both more definitive and potentially novel insights into the structural variation associated with disorders such as schizophrenia. This is not the first time that either individual studies or even meta-analyses have examined whole-brain analyses of volume or thickness differences among individuals with schizophrenia. For example, a recent meta-analysis by Haijma *et al.* (3) included data from 18,000 participants to examine whole-brain analyses of volume data in schizophrenia (3). However, the work by van Erp *et al.* (2) extends beyond previous meta-analyses in two important ways. First, all data included in this meta-analysis were processed using the same approach, which helps reduce error variance associated with differences in preprocessing across studies. Second, this is the first such meta-analysis that reports on thickness and surface area, two different components that contribute to cortical volumes.

The findings regarding differential patterns of impaired surface area and thickness deficits in schizophrenia are one of the novel contributions of this meta-analysis. Research on surface area alterations associated with schizophrenia has received relatively little attention compared with the work on volume and thickness. van Erp *et al.* (2) show that there are widespread reductions in surface area found in schizophrenia, with little evidence for regional specificity or relationships to medication status or dose. This pattern contrasted strongly with the findings for cortical thickness, which although also broadly reduced in schizophrenia did show robust evidence for regional specificity (i.e., greater in some frontal and temporal regions) and consistent relationships to medication status (greater reductions in individuals taking antipsychotics) and individual difference factors, such as antipsychotic dose, symptom severity, illness duration, and age of onset. This dissociation is not surprising given that development and variation in cortical thickness and surface area are driven by dissociable genetic (4), evolutionary (5), and neurobiological mechanisms (6) and show different trajectories across neurodevelopment (7). Early in life, surface area expansion reflects at least in part the generation of cortical columns while thickness may reflect the creation of neurons within these columns (6). In typical development, thickness trajectories may be the primary contributor to changes in volume during adolescence (7), hypothesized to reflect at least in part synaptic pruning. If so, one speculative hypothesis is that the relationships of cortical thickness to age of onset and illness duration found by van Erp *et al.* (2) might reflect the timing and onset of putative aberrations in synaptic pruning that may contribute to the onset of psychosis, but more work is needed to determine what triggers the timing of the onset of such alternations.

Additional important implications of the van Erp *et al.* (2) meta-analysis come from what they did not find as much as what they did find. As illustrated in Figure 1, an intriguing 2015 meta-analysis by Goodkind *et al.* (8) examined the common structural differences found across psychiatric disorders, including psychotic and nonpsychotic disorders. This meta-analysis identified the dorsal anterior cingulate and the bilateral insula as regions that showed reduced volume across the spectrum of psychopathology, suggesting that such impairments reflected the structural correlates of the "p" factor of general psychopathology. These regions form part of the cingulo-opercular network thought to be important for cognitive control (9), and Goodkind *et al.* (8) hypothesized that these shared structural deficits might reflect common deficits in cognitive control systems across forms of psychopathology. The van Erp *et al.* (2) meta-analysis also clearly identified structural differences in the bilateral insula. In terms of thickness, both the right and left insula showed reductions that exceeded the magnitude predicted by the mean thickness reduction, and both the right and left insula were correlated with age of onset (positively) and illness duration (negatively). Further, insula thickness reductions were present even among unmedicated individuals, with among the large effect sizes. There were also surface area reductions in the bilateral insula, but as noted above, no regions showed a decrease in surface area that was disproportionate to the mean surface area reductions. In contrast, the dorsal anterior cingulate [best captured by the caudal anterior cingulate label by van Erp *et al.*

SEE CORRESPONDING ARTICLE ON PAGE 644

https://doi.org/10.1016/j.biopsych.2018.06.005
Biological Psychiatry November 1, 2018; 84:626–628 www.sobp.org/journal
ISSN: 0006-3223

Biological Psychiatry

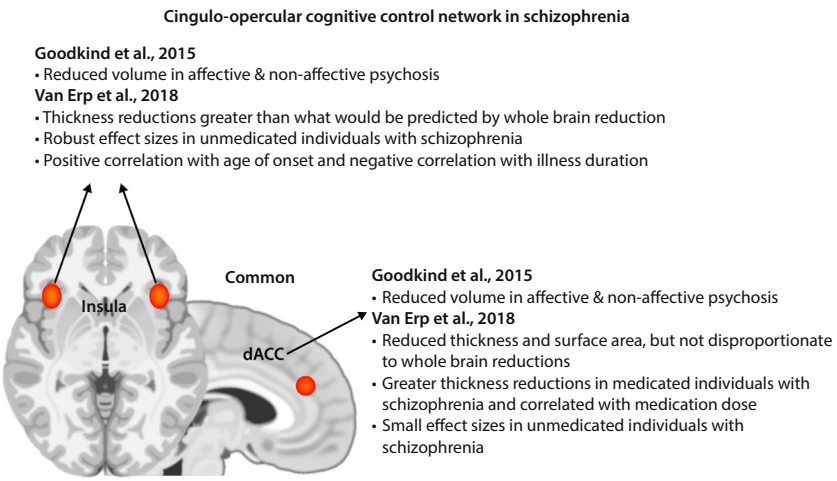

Figure 1. Relationship between results in van Erp *et al.* (2) and Goodkind *et al.* (8).

(2)] did not show disproportionate reductions in either thickness or surface area, showed little evidence of reduction in unmedicated individuals with schizophrenia, and was not associated with age of onset or illness duration. The caudal anterior cingulate parcellation is large and includes several potentially dissociable regions (e.g., Brodmann area 32 and parts of Brodmann area 24), and it is possible that a region more centrally focused on the dorsal anterior cingulate (e.g., Brodmann area 32) would have revealed clearer evidence for disproportionate thickness reductions. Nonetheless, the current results suggest possible important dissociations between the nature of structural deficits in the insula versus the dorsal anterior cingulate and their potential role in risk factors associated with transdiagnostic psychopathology.

Another domain of interesting null results was the absence of any interactions between diagnostic group and sex, suggesting similar structural deficits among males and females with schizophrenia. This result contrasts with some reviews of the literature (10), which suggest evidence for greater structural deficits in males than females with schizophrenia, particularly in frontal and temporal regions. As such, the absence of any significant interactions with sex might be seen as surprising. However, the literature on sex differences in brain structure and function in schizophrenia, as well as many other disorders, has been mixed. This is in part because few studies were directly designed to test for sex or gender differences, and most analyses are post hoc and subject to the many spurious positive finding biases associated with post hoc and often underpowered analyses. However, on the other hand, some of the putative sex differences in brain structure or function in schizophrenia have been argued to reflect altered patterns of lateralization that might relate to normative sexual dimorphisms. van Erp *et al.* (2) did not specifically examine interactions with hemisphere, and thus it is possible that a different approach to data analysis might reveal greater evidence for sex differences.

The type of large-scale diagnostic group comparisons enabled by data aggregation collaborations such as ENIGMA are making critical contributions to our understanding of the most robust and consistent alterations in brain structure found in schizophrenia and other forms of psychopathology. This may be just the first step in the types of analyses empowered by this type of data aggregation. For example, to date, the ENIGMA analyses in schizophrenia have focused on brain structure, including both T1-weighted imaging and diffusion tensor imaging. This focus makes sense, because these types of imaging modalities have reasonable evidence for the ability to harmonize across sites and platforms. However, future work may focus on the aggregation of brain function measures in psychopathology, such as resting-state functional magnetic resonance imaging or electroencephalography. In addition, there has been much debate in the literature about the challenges of traditional categorical classification systems. The ENIGMA consortium has moved beyond solely examining categorical comparisons by examining variation in brain structure associated with variation in symptom severity within schizophrenia, such as negative and positive symptoms. A next important step will be to examine these types of associations transdiagnostically, as well as many potential others for which there might be consistent data across samples (e.g., substance use, physical health, birth trauma, life stress, socioeconomic status). The power of the large sample sizes afforded by data aggregation would allow critical tests of whether such dimensional relationships hold across putative diagnostic boundaries, a key question that few individual studies have sufficient power to answer in a definitive fashion but that is fundamental to moving toward a modern empirical approach to nosology.

Acknowledgments and Disclosures

DMB has received grants from the Brain and Behavior Research Foundation, the National Institutes of Health, and the National Science Foundation.

DMB is a consultant for Pfizer on studies related to the treatment of negative symptoms in schizophrenia.

Article Information

From the Departments of Psychological and Brain Sciences, Psychiatry, and Radiology, Washington University in St. Louis, St. Louis, Missouri.

Address correspondence to Deanna M. Barch, Ph.D., Departments of Psychological and Brain Sciences, Psychiatry, and Radiology,

Washington University, Box 1125, One Brookings Dr., St. Louis, MO 63130; E-mail: dbarch@artsci.wustl.edu.

Received May 31, 2018; accepted Jun 9, 2018.

References

1. Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014): Biological insights from 108 schizophrenia-associated genetic loci. Nature 511:421–427.
2. van Erp TGM, Walton E, Hibar DP, Schmaal L, Jiang W, Glahn DC, *et al.* (2018): Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) consortium. Biol Psychiatry 84:644–654.
3. Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS (2013): Brain volumes in schizophrenia: A meta-analysis in over 18,000 subjects. Schizophr Bull 39:1129–1138.
4. Eyler LT, Chen CH, Panizzon MS, Fennema-Notestine C, Neale MC, Jak A, *et al.* (2012): A comparison of heritability maps of cortical surface area and thickness and the influence of adjustment for whole brain measures: A magnetic resonance imaging twin study. Twin Res Hum Genet 15:304–314.
5. Geschwind DH, Rakic P (2013): Cortical evolution: Judge the brain by its cover. Neuron 80:633–647.
6. Bhardwaj RD, Curtis MA, Spalding KL, Buchholz BA, Fink D, Bjork-Eriksson T, *et al.* (2006): Neocortical neurogenesis in humans is restricted to development. Proc Natl Acad Sci U S A 103:12564–12568.
7. Tamnes CK, Herting MM, Goddings AL, Meuwese R, Blakemore SJ, Dahl RE, *et al.* (2017): Development of the cerebral cortex across adolescence: A multisample study of inter-related longitudinal changes in cortical volume, surface area, and thickness. J Neurosci 37:3402–3412.
8. Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata LB, *et al.* (2015): Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry 72:305–315.
9. Dosenbach NU, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RA, *et al.* (2007): Distinct brain networks for adaptive and stable task control in humans. Proc Natl Acad Sci U S A 104:11073–11078.
10. Mendrek A, Mancini-Marie A (2016): Sex/gender differences in the brain and cognition in schizophrenia. Neurosci Biobehav Rev 67:57–78.