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Shared versus disorder-specific brain morphometric features of major psychiatric disorders in adulthood

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Diagnosis, the process of classification of disorders, has been fundamental to clinical practice and research in psychiatry. Psychiatric neuroscience has relied on diagnostic classification systems in order to understand the biological mechanisms underlying specific disorders and better support disease prevention and treatment(1). However, as the number and sample sizes of neuroimaging studies have grown, meta-analyses of neuroimaging data have begun to reveal two points in psychiatric neuroscience: (1) there is notable overlap in the identified abnormalities between psychiatric disorders and typically developing controls, and (2) identifying shared versus disorder-specific neurobiologic features of psychiatric illness is critical for supporting preventive and therapeutic efforts in psychiatry. Specifically, understanding shared versus disorder-specific regional dysfunction may advance the understanding of pathophysiologic processes underlying specific disorders as well as processes underlying constructs common to several different conventionally-defined psychiatric disorders, facilitate discovery of neural markers for illness trajectory, and enhance development of therapeutics.

There have been challenges to determining shared versus disorder-specific neural markers of psychiatric illness(1). Specifically, studies must be designed with large sample sizes of individuals with heterogeneity in clinical diagnoses and symptoms. Such large-scale studies must also be able to account for the age ranges inherent in these designs, as well as control for features of healthy physiologic aging. Lastly, human studies have been limited by cost, access to scanners with shared acquisition features, and data sharing practices. As these barriers have been lowered in recent years, psychiatric neuroscience is at an exciting point where higher-powered analyses can be analyzed to examine shared versus disorder-specific abnormalities among psychiatric disorders. In this issue, Opel et al. used meta- and mega-analytic data from the ENIGMA consortium to examine shared and distinct brain morphometric features across six psychiatric disorders in adulthood(2). Specifically, the authors sought to answer four questions: (1) what is the extent to which brain structural alterations are similar across psychiatric disorders; (2) what is the pattern of correlating brain structural alterations across psychiatric disorders; (3) to what degree are observed patterns of structural alterations independent from physiologic aging; and (4) what is the regional distribution of cross-disorder and disorder-specific variance in brain structural alterations?

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To answer these questions, the authors included meta- and mega-analyses examining morphometric measures of cortical thickness and subcortical gray matter volumes from published ENIGMA studies that had compared groups of healthy adult individuals and those with a psychiatric disorder. Studies were included if they examined data from specified cortical and subcortical regions, resulting 11 studies on six psychiatric disorders: Major Depressive Disorder (MDD); Bipolar Disorder (BD); Schizophrenia (SCZ); Obsessive Compulsive Disorder (OCD); Attention Deficit Hyperactivity Disorder (ADHD); and Autism Spectrum Disorder (ASD). If studies included children and adolescents, only the data regarding adults was utilized. Effect sizes for cortical thickness in 34 regions (3) and gray matter volume in 7 subcortical regions(4), corrected for age, sex, and scanner site, as well as intracranial volume (ICV) for subcortical regions, were extracted from each included study. To evaluate effects of physiologic aging, comparison effect sizes for these 41 regions were computed from two independent large cohort studies of healthy adults (Human Connectome Project(5); BiDirect Study(6)). Similarities across psychiatric disorders were initially examined using correlational analyses across all cortical and subcortical regions, followed by an exploratory factor analysis across regions to confirm whether structural alterations from correlated disorders loaded onto shared factors. To assess regional cross-disorder and disorder-specific morphometric differences, the authors used linear regression analyses to predict whether the true effect size of a region was predicted by regional factor scores.

Correlational analyses demonstrated that cortical thickness and subcortical gray matter volumes were significantly correlated among MDD, BD, SCZ, and OCD, with particularly strong correlations between SCZ and both BD and OCD. Similarly, the exploratory factor analysis revealed three latent factors across disorders, with MDD, BD, SCZ, and OCD all loading onto one shared factor that explained 48% of the variance in brain structural elements across all disorders. Within this factor, the hippocampus and fusiform gyrus were strong contributors to the overall factor score. In contrast, ADHD and ASD each loaded onto separate factors, with regional contributions from the rostral anterior cingulate cortex (rACC) and amygdala strongly contributing to the factor associated with ADHD and the entorhinal cortex and fusiform gyrus strongly contribution to the the factor associated with ASD. The three-factor solution and their contributing disorders did not change after accounting for the effects of physiologic aging.

Linear regression analyses examining the regional distribution of disorder-specific abnormalities in cortical thickness and subcortical gray matter volume within the factor comprised of 4 disorders showed disorder-specific differences between MDD, BD, SCZ, and OCD. Specifically, MDD and SCZ demonstrated a medium-sized deviation effect from the common latent factor although in opposing directions. A similar opposing effect was evident between BD and OCD and between SCZ and OCD. Disorder-specific abnormalities were observed within each disorder: greater cortical thickness was observed in the rACC and medial orbitofrontal cortex (OFC) in MDD; lower cortical thickness was observed in the superior temporal gyrus and medial OFC in SCZ; greater cortical thickness in the superior temporal gyrus and gray matter volume in the pallidum was observed in OCD; and greater cortical thickness in the parahippocampal gyrus with lower gray matter volume in the pallidum in BD.

The identification of shared versus disorder specific neural markers, as performed in the study by Opel et al. (2020), has implications for psychiatric diagnosis and treatment. Understanding commonalities between disorders may reveal shared etiologic events or behaviors that may be proximal to the development of a variety of disorders. For example, shared features may be due to a genetic disposition towards psychiatric distress(7), transdiagnostic symptoms (e.g., anhedonia), or environmental factors such as early life adversity, chronic stress, or poverty that are associated with the emergence, severity, and persistence of a variety of psychiatric disorders(8). Identifying shared factors may also result in improved diagnostic capacity based on detection of common versus distinct neural processes, as well as identifying treatments that may have a broad impact on shared neural substrates. In contrast, examining neural features that are associated with more specific disorders may reflect either different proximal processes or additional, more distal processes associated with these specific disorders. For example, as discussed by the authors, the lower cortical thickness in the superior temporal gyrus and medial OFC in SCZ may reflect core features of SCZ including hallucinations and thought disturbances(9). In MDD, the increased cortical thickness in rACC and medial OFC may reflect components of emotional blunting and heightened self-referential processing often observed in MDD(10). Understanding the specific differences between disorders, compared to other disorders and healthy controls, may help target specific features of disorder-specific distress. Specifically, such results may be able to provide neural targets for different treatments across disorders that are based on biology regardless of conventional classification of these disorders.

While this exciting report of shared versus distinct brain morphometric features of psychiatric disorders, there are limitations to this work. One prominent limitation is the number of included studies. Specifically, only 11 meta- and mega-analyses were included: 1 study for cortical thickness and 1 study for gray matter volume for MDD, BD, SCZ, OCD, and ADHD plus one mega-/meta- analysis for both cortical thickness and gray matter volume in ASD. While each of these studies, with the exception of ADHD, had over one thousand participants included, ongoing replication of these findings will be necessary to ensure validity. This is particularly relevant for studies of ADHD and ASD, where the age ranges in the included meta- and mega-analyses spanned childhood, adolescence, and adulthood yet only the adult data was included in the present study. Examining shared versus distinct brain morphometric features in childhood and adolescence may be helpful for understanding neural markers proximal to the development of symptoms, particularly in disorders that often emerge in adolescence/young adulthood. Further, as the authors note, other explanatory factors such as shared comorbidities or use of psychopharmacological treatments may have influenced the presented results.

Despite this need for ongoing research in this area, the present paper offers strong preliminary evidence for shared morphometric features across MDD, BC, SCZ, and OCD as well as unique morphometric changes within each disorder. In addition to its primary findings, this manuscript describes a strong methodological approach for the future examination of shared versus disorder-specific features of psychiatric disorders. This is an opportune area for future research, particularly in its capacity to improve understanding of the pathophysiologic mechanisms for psychiatric disorders, accelerate discovery of biomarkers for illness trajectory, and support development of novel

therapeutics. By understanding shared versus disorder-specific morphometric features, such novel therapeutics could be targeted to a variety of different psychiatric disorders based on understanding of core pathophysiological processes.

References

1. Linden DE. The challenges and promise of neuroimaging in psychiatry. Neuron. 2012;73(1):8–22. [PubMed: 22243743]
2. Opel N, Goltermann J, Hermesdorf M, Berger K, Baune BT, Dannlowski U. Cross-Disorder Analysis of Brain Structural Abnormalities in Six Major Psychiatric Disorders – A Secondary Analysis of Mega- and Meta-Analytical Findings from the ENIGMA Consortium. Biological Psychiatry. 2020.
3. Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006;31(3):968–80. [PubMed: 16530430]
4. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002;33(3):341–55. [PubMed: 11832223]
5. Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K, et al. The WU-Minn Human Connectome Project: an overview. Neuroimage. 2013;80:62–79. [PubMed: 23684880]
6. Teismann H, Wersching H, Nagel M, Arolt V, Heindel W, Baune BT, et al. Establishing the bidirectional relationship between depression and subclinical arteriosclerosis--rationale, design, and characteristics of the BiDirect Study. BMC Psychiatry. 2014;14:174. [PubMed: 24924233]
7. Grasby KL, Jahanshad N, Painter JN, Colodro-Conde L, Bralten J, Hibar DP, et al. The genetic architecture of the human cerebral cortex. Science. 2020;367(6484). [PubMed: 32327585]
8. Scott KM, McLaughlin KA, Smith DA, Ellis PM. Childhood maltreatment and DSM-IV adult mental disorders: comparison of prospective and retrospective findings. Br J Psychiatry. 2012;200(6):469–75. [PubMed: 22661679]
9. van Tol MJ, van der Meer L, Bruggeman R, Modinos G, Knegtering H, Aleman A. Voxel-based gray and white matter morphometry correlates of hallucinations in schizophrenia: The superior temporal gyrus does not stand alone. Neuroimage Clin. 2014;4:249–57. [PubMed: 25061563]
10. Yoshimura S, Okamoto Y, Onoda K, Matsunaga M, Okada G, Kunisato Y, et al. Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. Soc Cogn Affect Neurosci. 2014;9(4):487–93. [PubMed: 23327934]