HHS Public Access

Author manuscript

Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2020 June 30.

Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2018 December ; 3(12): 978–980. doi:10.1016/j.bpsc.2018.08.013.

Cognitive deficits, structural neuropathology, and psychotic illness: is it all a matter of severity?

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How does structural neuropathology give rise to cognitive deficits in different psychotic illnesses? Is there a common substrate (e.g. colloq., “bad brain”) across diseases that leads to poor cognition? Or alternatively, are there multiple pathological mechanisms leading to dysfunction that are featured more in certain diseases than others? Answering this question is of great interest to both clinicians and basic researchers as it will help elucidate the underlying neurobiology of mental illness as well as identify potential biological targets for intervention within and across disorders.

To that end, in this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Rodrigue et al. (1) analyzed a large (n = 240 controls and 438 patients with psychotic disorders (bipolar disorder (BD), schizoaffective disorder, and schizophrenia (SZ))) multisite dataset with the goal of shedding light on the relationships between brain structure (gray matter volume, cortical thickness, cortical surface area, and gyrification) and neurocognition. Using a multivariate technique called canonical correlation analysis (CCA) to extract patterns of correlated variate pairs (cognitive-structural pairs) across all subjects, Rodrigue et al. found that overall cognition (broadly across multiple domains) was positively associated with gray matter volume, thickness, and gyrification, but (somewhat surprisingly) negatively associated with cortical surface area. These correlations were primarily observed for frontal and parietal regions. Next, using discriminant analysis to compare canonical variate latent scores between groups, Rodrigue et al. found that the positive associations between brain and cognition identified in the CCA (particularly volume) were captured across the psychosis spectrum. Specifically, healthy subjects had the greatest volumes/best cognition, patients with the most schizophrenia (SZ)-like symptoms the smallest volumes/worst cognition, and patients with the most BD-like symptoms in-between. More interestingly, however, Rodrigue and colleagues also identified a second diagnosis-dependent variate pattern specific to patients with the most BD-like symptoms that captured the inverse relationship between cognition and surface area. Indeed, only patients that scored 0 or 1 on the 9-point Schizo-Bipolar scale (i.e. most BD-like) demonstrated significantly different loadings on the cortical surface area/cognition canonical variate, suggesting the combination of large surface area and poor cognition was largely exclusive to these patients. These results suggest that potentially different processes may underlie cognitive deficits in

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Disclosures

None.

psychotic disorders. Specifically, one type of process may lead to gray matter volume reductions and is featured most strongly in severe in patients with the most SZ-like symptoms. A second process may lead to increased cortical surface area and is only featured in patients with predominantly BD-like symptoms. The fact that these processes were identified by CCA further suggests that they are not related, as CCA is designed to minimize correlations between constructs. Concordantly, correlation coefficients between sets of CCA pairs for each structural measure in the Rodrigue et al. analysis were approximately zero.

The notion that distinct processes may influence gray matter volume/cortical thickness vs. cortical surface area is consistent with the neurodevelopmental radial unit hypothesis (RUH) postulated by Rakic (2). The RUH stipulates that during cortical development, precursor cells migrate along radial glia from the periventricular proliferative zone towards the pial surface. The route of migration is tangentially (horizontally) restricted by the periventricular zone's columns of radial units, helping ensure spatial specificity and consequent location-dependent cell differentiation. As new cells emerge from the proliferative zone, they migrate along the same vertical route as previous cells from the same column, thereby increasing cortical thickness/volume but not affecting surface area. Cortical thickness, therefore, is influenced by the number of cells within each column, whereas cortical surface area is influenced by the number of radial columns. Consistent with a hypothesis for separate processes, surface area and thickness are genetically uncorrelated and follow different longitudinal trajectories over the lifespan (2). Also consistent with the RUH, previous work by Schnack et al. (3) has demonstrated inversely related longitudinal trajectories for surface area and thickness as a function of intelligence. Specifically, the study found that at a young age (10 years), healthy children with high intelligence quotients (IQs) had thin cortices and large cortical surface areas which then became thicker and smaller up to age 42. Conversely, children with lower IQs had thicker cortices and smaller surface areas that then become thinner and larger with age.

Might genetic differences between BD and SZ explain why gray matter volume/thickness and cortical surface area make distinct contributions to cognitive deficits depending on the disease? A recent genome-wide association study (GWAS) of 20,129 BD and 33,426 SZ cases successfully identified four genes (DARS2, ARFGEF2, DCAKD, and GATAD2A) that distinguish between the two diseases (4). Interestingly, all four genes are highly expressed in the brain and associated with neuronal development (DARS2 mutations cause delayed psychomotor development and white matter disease, ARFGEF2 mutations are associated with abnormal neuronal proliferation and migration, and DCAKD and GATAD2A are preferentially expressed during the juvenile mouse and fetal human developmental stages, respectively (4)). Although roles for these genes in predicting neuroanatomical trajectories are highly speculative, based on the significant differences identified by GWAS their associations with structural features and neurocognition may be of interest in future research.

As noted by the authors, a limitation of the findings of Rodrigue et al. is that subcortical regions were not included in the analyses. These areas were excluded by necessity to ensure that canonical variates from all four of the same structural imaging metrics could be used for discriminant analysis, as subcortical regions are typically only characterized by volume and

not thickness and surface area. How subcortical regions contribute the observed cognitive phenotypes could therefore not be determined, which is unfortunate given that loss of gray matter has been observed in in the amygdala, hippocampus, and thalamus in large-scale studies in both SZ (5) and BD (6). A 2016 study also found that genetic influences on cortical and subcortical volumes may be distinct (7), suggesting that the processes that influence loss of cortical volume are separate from those that influence loss of subcortical volume. Future analyses may examine relationships between volume and cognition including both cortical and subcortical regions to determine if these areas make separate contributions to explaining variance in cognitive performance dependent on cognitive domain.

As with any study involving medicated BD and/or SZ patients, the potential role(s) of antipsychotic and/or mood-stabilizers in explaining the results presented by Rodrigue et al. must be considered. Interestingly, discriminant analysis using chlorpromazine equivalent dose as the dependent variable yielded no significant differences in canonical variate latent scores, suggesting no effect of antipsychotic medications on the observed brain-behavior relationships. Mood stabilizers, however, were not analyzed, and unmedicated and medicated patients were not directly compared. Given that previous work suggests that the mood stabilizer lithium protects from (6) and antipsychotics exacerbate (8) gray matter decline, further investigation into medication effects seems warranted.

Given the lack of effective treatments for cognitive deficits in BD and SZ, it is critical to increase our understanding of the neuronal mechanisms that are associated with such deficits in these disorders. Indeed, the field has long recognized that neuronal mechanisms do not line up well with DSM-based nosology, necessitating the creation of alternative, biologically-based frameworks (such as Research Domain Criteria (9)) for classifying and characterizing these disorders. To that end, as demonstrated by Rodrigue and colleagues' analysis of consortium data, researchers are increasingly using sophisticated multivariate analysis techniques on large datasets across multiple disorders to determine the extent to which certain processes are shared (or vary in severity) and others entirely specific to certain diseases. Some of these analyses have found dimensional patterns of neurocognitive performance across disorders (e.g. in cognitive control (10)) whereas others such as the Rodrigue et al. study have identified both dimensional and categorical features. These results suggest that improving cognitive function in these patients may require a multifaceted approach designed to target multiple processes.

As a final note, it should be emphasized that results from many of these cross-diagnostic analyses have been data-driven, using methods specifically tailored to achieve a desired statistical outcome (e.g. maximize within-group correlation and/or between-group independence). One must be careful, therefore, to not overstate the implications of findings from the Rodrigue et al. study or similar purely data-driven studies. Although their results suggest distinct processes that underlie cognitive deficits in BD vs. SZ, these findings at present should still be considered hypotheses that will require more systematic testing and evaluation for complete validation. Related to this study, important next steps may include 1) replication of their findings in independent samples, 2) examination of relationships between cognition, cortical surface area, and volume/thickness longitudinally and/or cross-sectionally

across a wide range of ages in BD and SZ (as well as high-risk individuals) to determine if these relationships are state or trait-like, 3) additional investigation into causal links between genes that increase risk for BD and/or SZ and how these genes may differentially influence cortical surface area and gray matter volume or thickness. Overall, however, the study by Rodrigue and colleagues is rigorous, well-powered and thorough, and is an essential first step in understanding how structural processes may differentially influence cognition depending on the symptomatic presentation of the illness.

Acknowledgement

JS is supported by grant F32 MH114325 from the National Institutes of Mental Health.

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