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On understanding variability in brain structure volumes in schizophrenia: A reply to De Peri and Vita

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We are pleased that the topic of variability in brain structure volumes in schizophrenia is gaining renewed interest with the synthesis of MRI studies conducted over the past two decades, and we thank De Peri and Vita for the opportunity to discuss further our review of what we believe to be an important topic (Kuo and Pogue-Geile, 2019).

1. Possible effects on variability in brain structure volumes

In one of the first such reviews, our comprehensive meta-analysis of 246 MRI studies found significantly greater variability among schizophrenia patients compared to healthy controls for ventricle and intracranial volumes but not for eleven other brain volume measures. Another recent, smaller review of first-episode patients by Brugger and Howes (2017) had similar findings, using the appropriately conservative variability ratio (see Nakagawa et al., 2015). Specifically, Brugger and Howes (2017) found increased variability in schizophrenia for ventricle volumes (intracranial volume was not assessed) and no greater variability for frontal, hippocampus, and caudate volumes, though they did find significantly greater variability for temporal lobe volume in schizophrenia whereas our larger review did not.

De Peri and Vita note that they and others have reported that antipsychotic medication dosage may correlate with decreases in whole brain gray matter volume, for first-generation antipsychotics and perhaps less so for second-generation antipsychotics, and suggest that this may contribute to our findings of increased variability in schizophrenia for ventricle volumes.

If antipsychotic medication causes decreases in brain gray matter volumes in a dose-response manner and patient samples varied in their dosages within studies (as is likely), then we would expect to see increased variability in schizophrenia versus controls in some of our eleven measures of brain tissue volume but we did not. Instead, we observed only increased schizophrenia variability for ventricle and intracranial volumes. To examine just such possible medication dosage effects, we also performed meta-regressions of the

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correlation between within-sample variability in medication dosage and variability in brain volumes but none were significant.

Brugger and Howes' similar finding of increased variability for ventricle volume among first-episode patients, who presumably have little exposure to antipsychotic medications, also suggests that such results are unlikely to be largely due to medication effects. Likewise, we performed meta-regressions to examine if either average or variability of illness duration or first versus other admission samples were associated with increased schizophrenia variability. Here, we found only significant results for first versus other admission samples and intracranial volume, which is unlikely to be affected by medications.

Because we were quite interested in examining possible antipsychotic medication effects, we also performed meta-regressions correlating schizophrenia group average antipsychotic dosage and medication-naïve status with variability in schizophrenia brain structure volumes. We found significant positive regressions for average dosage (but not medication-naïve status) and schizophrenia variability for intracranial volume. Unfortunately, there were not enough studies to calculate a similar dosage regression for lateral ventricle volume, though non-medication naïve status did predict increased lateral ventricle variability. Neither medication variable predicted third ventricle volume variability nor notably variability for any brain tissue volume. Nevertheless, such a correlation between medication-naïve status and schizophrenia lateral ventricle volume variability could reflect antipsychotic medication effects.

We did not examine directly first- versus second-generation medication status, but as noted above, we did examine the correlation of variability within samples in antipsychotic medication dosage with schizophrenia variability in brain structure volumes but none were significant. If first-generation medications have larger effects on brain volume than second-generation and many study samples were composed of mixtures of patients on different medication types, then we would expect to see increased schizophrenia variability for many brain tissue volumes but we did not – instead only increased variability for ventricle and intracranial volumes.

Although the above results concerning possible antipsychotic medications effects on variability in ventricle volumes are equivocal at best, we found no evidence for associations with brain tissue volumes. Thus, as we noted in our Discussion, "antipsychotic levels may somehow be associated with greater variability in intracranial and ventricle volume in schizophrenia, although given the small number of antipsychotic-naïve studies and large number of meta-regressions, such results need to be interpreted cautiously". Of course, unless randomly assigned, medication dosage also potentially reflects a large number of factors, such as severity and chronicity. The relation between group average dosage and intracranial volume variability we observed presumably reflects such processes, given it is unlikely that antipsychotic medications directly affect skull volume during adulthood.

2. Neurodevelopmental aspects of schizophrenia

De Peri and Vita further note that our observations of increased variability in schizophrenia for both intracranial volume (which ceases development in childhood) and ventricle volume (which changes across the lifespan) may provide clues about neurodevelopmental aspects of schizophrenia. We agree completely, having noted in our Discussion, “given the young age at which the cranium usually ceases development, such results are consistent with the possibility that at least some schizophrenia causes have effects early in life” and that “renewed attention should be paid to the etiology and development of brain ventricles in schizophrenia”.

Taken together, these findings add further nuance to neurodevelopmental models of schizophrenia, suggesting that intracranial and ventricle volumes may reflect different neurodevelopmental processes in schizophrenia apart from neurodevelopmental processes affecting brain tissue volumes.

3. Summary

Overall, our findings that eleven brain structure volumes did not show increased variability in schizophrenia cannot be explained by possible medication effects and in fact represent some evidence against them. Our finding of increased variability for intracranial volumes presumably also cannot arise from medication exposures. Although it is possible that our observation of increased variability of ventricle volume in schizophrenia could be affected by medication type and dosage, our null findings from meta-regressions of illness duration and first versus other admission and Brugger and Howes’s similar findings in first-episode samples argue against any major effect. Nevertheless, we suggested in our Discussion, “the utility of examining distributional differences… to further inform the effects of medications on brain structure volumes in schizophrenia”. In closing, we support further attention to the study of brain variation and development in schizophrenia beyond merely group averages.

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