Subcortical and cortical variations in schizophrenia: the ENIGMA SZ Working Group

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Introduction:

Within schizophrenia studies of brain structure, the changes in subcortical structures are noteworthy and reliable[1] . The work of the ENIGMA and ENIGMA2 consortia have highlighted the value of large-scale collaborations for meta-analysis, in which each collaborator provides the same analytical results, so that the aggregated meta-analysis is highly sensitive. This has already led to identified genetic effects on hippocampal volume[2]. The goal of the ENIGMA-SZ working group to identify the most robust disease effect across the subcortical measures, using the same analysis techniques and statistical models across all participating samples. The sharing of statistics requires no additional Institutional Review Board approval and standard analysis pipelines used in the projects minimize efforts by the contributors while maximizing the gain of data sharing.

Methods:

The ENIGMA Schizophrenia Study Consortium currently comprises samples from fifteen studies around the world. No individual imaging or clinical data were shared across institutions for this analysis.

The final meta-analysis included 4698 participants (43% were patients) who were predominantly male (60%), and approximately 33 years old on average. A few samples specifically targeted early phase SZ; as a result, the average duration of illness (where reported) ranged from less than a year to almost 30 years. Medication information was reported for some but not all studies.

At each site, a version of Freesurfer was used to extract total intracranial and subcortical volumes (for bilateral pallidum, hippocampus, putamen, lateral ventricle, amygdala, caudate, thalamus, and nucleus accumbens) from high-resolution T1-weighted brain MRI scans. Cohen's d effect size estimates were obtained separately at each site using shared R ; the analyses of each sample included age, sex, and estimated total intracranial volume as covariates, and dummy variables for site effects in multi-site datasets.

The results were pooled using an inverse variance-weighted random-effects meta-analysis. Separate analyses determined whether various moderating variables of the imaging values or of the sample population had an effect across samples.

Results:

The maximal effect size was the decreased mean hippocampal volume in patients (-0.46, $p = 4.85*10\text{-}14$), followed by left and right hippocampal; the increases in mean ventricle sizes were the next largest (0.37, $1.38*10\text{-}9$). All effect sizes for all subcortical volumes were significantly different from zero ($p < .05$ uncorrected) with the exception of the left, right, and mean caudate, and the right and mean putamen values. See Figure 1.

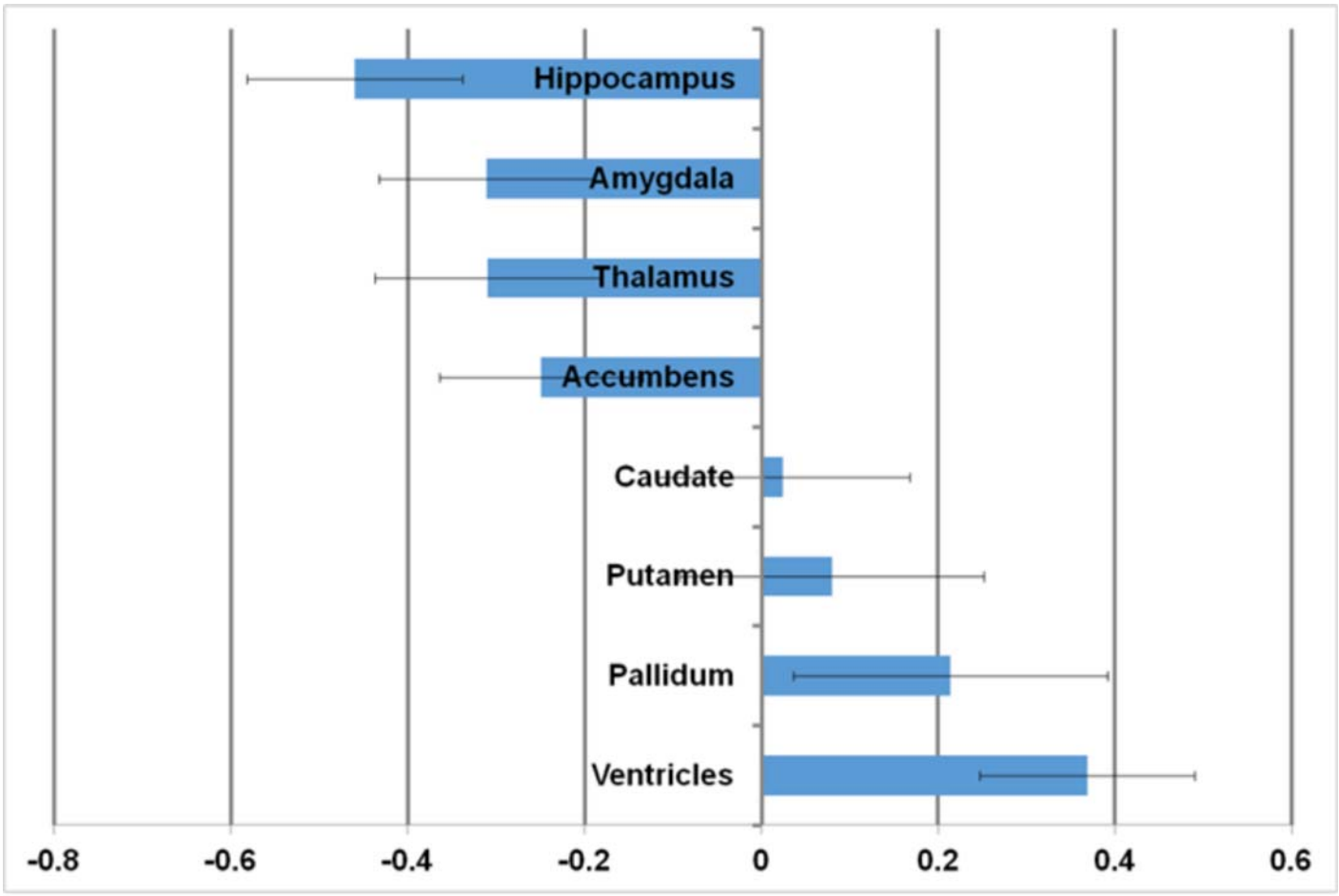

Figure 1. The meta-analytic Cohen's d for the effect of cases > controls for the mean volume of each of the subcortical regions, from the site-wise analyses including age, gender, and ICV as covariates. Error bars include 2* standard error.

Conclusions:

The most robust differences between cases and controls in subcortical volumes are found in the hippocampus and the ventricles. The caudate and putamen, however, are much more variable in their effects across samples, and may be more sensitive to disease aspects such as duration of illness or medication history.

The infrastructure which allowed >4,000 subjects' datasets to be included in this meta-analysis has spawned ongoing other projects with more nuanced goals. Secondary projects include:
1) Reliability of cortical measures in healthy subjects across these samples (led by Derrek Hibar, USC).
2) Differences in subcortical shape in cases and controls (led by Lei Wang, Northwestern University)
3) The relationship between cortical measures and symptom scores (led by Stefan Ehrlich, Technische Universität Dresden).
4) Sibling variation in subcortical structures (led by Neeltje van Haren, University Medical Centre Utrecht).
5) Normal variation across the age range (led by Danai Dima, King's College London).

These projects are currently seeking collaborative sites and samples. ENIGMA is open to the wider research community as a platform to share data through meta-analyses, to advance our understanding of neuropsychatric and neurological brain disorders.

Disorders of the Nervous System:

Schizophrenia and Psychotic Disorders

Reference

1. Haijma, S.V., et al., Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr Bull, 2013. 39(5): p. 1129-38.
2. Stein, J.L., et al., Identification of common variants associated with human hippocampal and intracranial volumes. Nat Genet, 2012. 44(5): p. 552-61.