Mapping Heterogeneous Patterns of Brain Atrophy in Schizophrenia to A Common Brain Network

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Background

- Schizophrenia presents significant heterogeneity in its neuroanatomical correlations across various neuroimaging studies, particularly regarding brain atrophy patterns[1]. This variability impedes the development of reliable biomarkers or targeted interventions.
- Amidst this heterogeneity, we hypothesized that atrophy coordinates reported in published studies of patients with schizophrenia would converge to a common brain network unique to the disorder.

Methods

- We utilized the human connectome[2] as a wiring diagram and employed coordinate network mapping (CNM)—a method that identifies network-level connections between heterogeneous brain coordinates (Fig 1). While traditional neuroimaging meta-analytic approaches such as activation likelihood estimation (ALE) identify common brain regions across studies, CNM enables the mapping of brain disorders to connected brain networks.
- Our analysis incorporated data from 113 published studies, totaling more than 11,000 individuals. Our sample included patients with schizophrenia (n= 3,756), individuals at high risk for psychosis (n= 1,507), and healthy controls (n= 6,007).

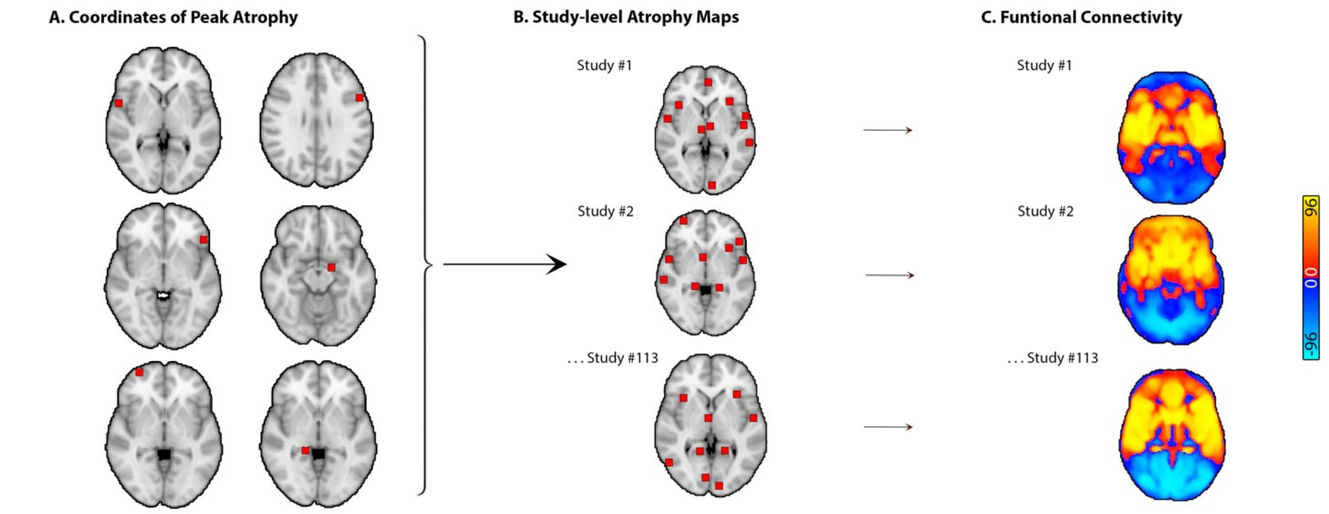

Fig. 1. Coordinate network mapping. A. Atrophy coordinates from 11,270 individuals (5,263 in four clinical groups and 6,007 healthy controls) from 113 voxel-based morphometry studies were extracted. **B.** Individual coordinates of peak atrophy were combined to 113 study-level maps. **C.** Functional connectivity between peak atrophy coordinates in each study-level map and the rest of the brain was computed using a normative connectome (n= 1,000). Positive functional connectivity is represented by warm colors, while negative functional connectivity, or anticorrelation, is depicted in cool colors.

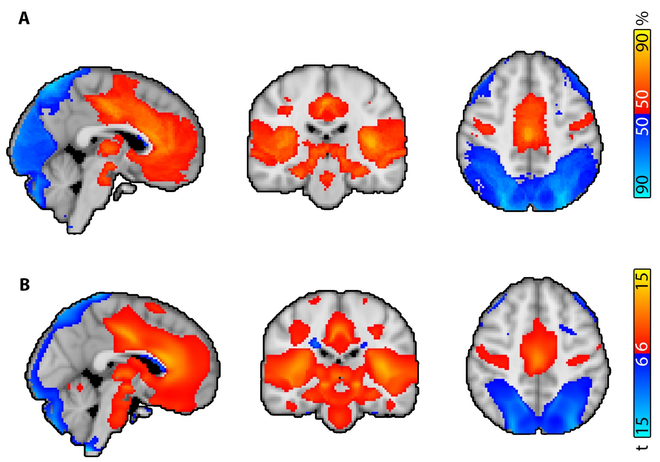

Fig 2. Sensitivity and consistency analyses. A. Sensitivity analysis: Overlap (90%) of positive (warm) and negative (cool) functional connectivity networks of atrophy coordinates in schizophrenia. **B.** Consistency analysis: Voxels shown represent the significant results of a one-sample t-test after correction for multiple comparisons in TFCE(pFWE< 0.05). Peak brain regions for both maps are the dorsal cingulate and mid-insula bilaterally.

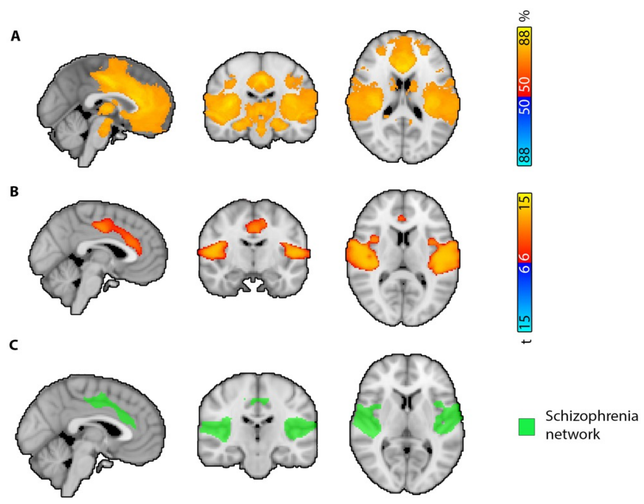

Fig 3. Mapping atrophy patterns in schizophrenia to a common brain network. A. Combined sensitivity and consistency analyses. A map representing brain areas that are both sensitive and consistent (overlap map at 50% threshold masked by significant one sample t-test results). **B. Specificity analysis:** CNM results were specific to schizophrenia compared to 9 other brain conditions. Voxels displayed show significant results of a two-sample t-test after multiple comparisons correction in TFCE (pFWE< 0.05). **C. Schizophrenia network:** A convergence map showing brain areas that were sensitive, consistent, and specific to schizophrenia. Peak areas are the dorsal cingulate and mid insula, bilaterally.

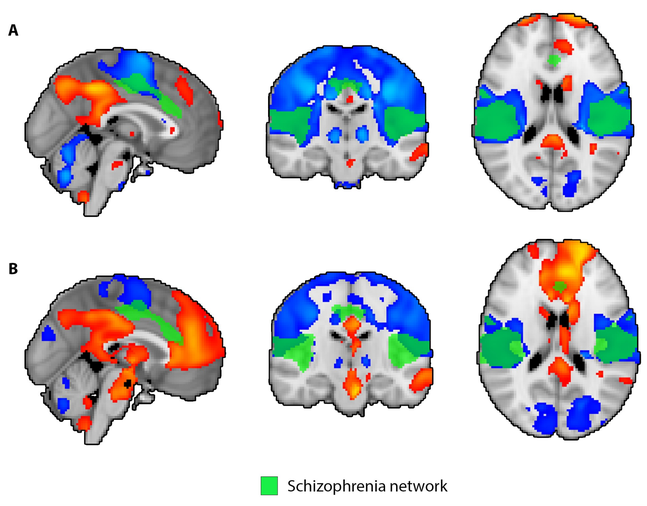

Fig 4. Overlap of schizophrenia network with lesion network mapping results. Schizophrenia network (bright green) overlaid on functional connectivity networks of lesions associated with suspiciousness (top row) and unusual thought content (bottom row). The figures highlight overlap between the schizophrenia network and brain regions with negative functional connectivity(cool colors) to lesions.

Results

- We identified a common brain network preferentially connected to atrophy coordinates in schizophrenia, which we refer to as the 'schizophrenia network' (Figs. 2,3). After correcting for multiple comparisons using TFCE (pFWE< 0.05), the dorsal anterior cingulate cortex and the mid-insula, bilaterally, emerged as peak brain regions in the network.
- The schizophrenia network is distinct from atrophy patterns observed in high risk individuals (clinical and genetic high risk), normal aging (n= 4,195), neurodegenerative disorders (n= 3,707), and other psychiatric conditions (n= 3,432). The network also remains stable with disease progression and across various clusters of psychotic symptoms.
- Interestingly, we found that patterns of brain atrophy in schizophrenia were negatively correlated with lesions associated with psychosis-related thought processes in an independent cohort (n= 181) of patients with penetrating head trauma (p< 0.05) (Fig. 4)

Conclusions

A unique, stable, and unified schizophrenia network addresses a significant portion of the heterogeneity observed in prior atrophy studies. The stability of this network across disease progression underscores its potential as a trait-like characteristic, and its uniqueness suggests it could be useful for development of biomarkers and brain stimulation targets in patients with schizophrenia. Our findings also challenge traditional understanding, revealing that brain atrophy in schizophrenia could represent a compensatory process. Future studies may investigate this network further, potentially leading to improved diagnostic and therapeutic strategies for schizophrenia.

References

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