Exploring the influences of functional connectivity architecture on cortical thickness networks in patients with early psychosis

Kristina M. Holton*, University of Delaware
Shi Yu Chan*, McLean Hospital, Harvard Medical School
Austin J. Brockmeier, University of Delaware
Dost Öngür, McLean Hospital, Harvard Medical School
Mei-Hua Hall, McLean Hospital, Harvard Medical School

Introduction

Cortical thickness and functional connectivity are two parallel approaches that have been widely used to gain insights into psychotic disorders. Significant abnormalities in these modalities, even at the early stage of psychosis, have been shown in the literature. However, few have studied them together or explored the influences of functional connectivity on cortical thickness networks. Prior studies using gyral-based atlases reported that cortical thickness regions susceptible to thickness reductions are strongly interconnected[1] and that brain tissue volume loss in schizophrenia is conditioned by structural and functional connectivity[2]. With data-driven approaches, we assessed:

1) How are cortical thickness networks organized, functionally or structurally?
2) What features drive this organization, and do features vary by diagnosis?
3) What are the relationships between cortical thickness reductions and clinical assessments?

Methods

Participants and Scans

Data were collected from 237 participants (82 controls, 155 early-stage psychosis (ESP) patients stratified by affective psychosis (AP) and schizophrenia spectrum disorder (SSD)) of both sexes. Structural magnetic resonance imaging (MRI) data were acquired on a 3T Siemens scanner, and processed with FreeSurfer v6.0 using a parcellation corresponding to 17 functional networks[3]

Non-Negative Matrix Factorization

Orthonormal projective Non-negative Matrix Factorization (NMF)[4] determined regions that covary with thickness across individuals and formed features. The optimal number of features to describe the 237 patient by 114 region matrix was determined using cophenetic correlation, and features for each region were extracted.

Bayesian Belief Networks

Regions were organized into networks using Bayesian Belief Networks (BBN)[5] to find the dependency structure. The BBN network topology identified the most interconnected regions (based on BIC) that served a key role in the structure of the network.

Feature Discriminatory Statistics

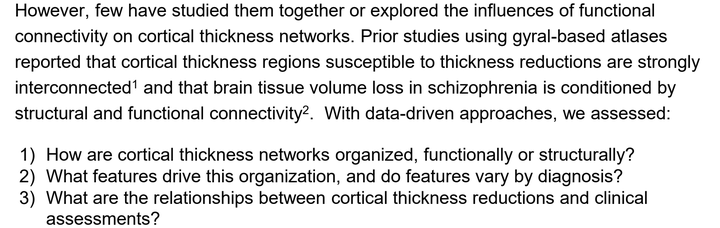
The differences in the distribution between diagnosis (controls, affective psychosis (AP), non-affective psychosis (SSD)) for each feature in the NMF embedding coefficients through a Kolmogorov-Smirnov test.

Clustering and Clinical Variables

Hierarchical clustering on the NMF coefficients matrix revealed clusters of participants who followed similar trends across the features. Diagnoses and clinical variables were stratified by cluster to further characterize attributes that define and differ between clusters.

Results

3.1 Cortical Thickness Organization



Regions comprising each NMF feature colored by Yeo17 functional network

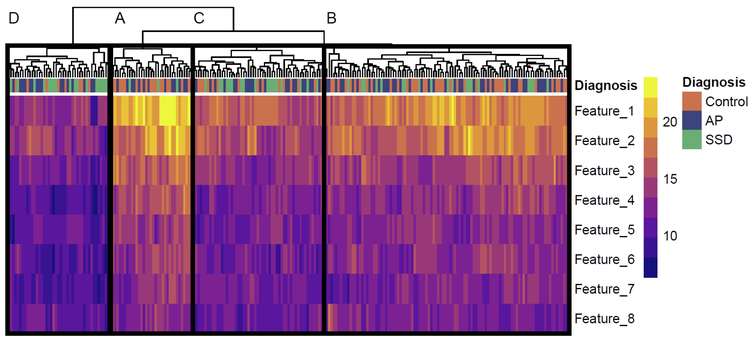
NMF decomposed the brain into an optimal 8 features, and the regions making up each feature were spatially organized, rather than by functional network.

3.2 Diagnostic differences and network characterization

Feature	Organization	BIC Driver (Hemisphere: Network *Region*)	ESP-C	SSD-C	AP-C	SSD-AP
Feature_1	Fronto-Parietal	LH Dorsal Attn Network A *superior parietal lobule*	0.148	0.014	0.358	0.032
Feature_2	Prefrontal	RH Default Network A *medial prefrontal cortex*	0.007	<0.001	0.123	0.012
Feature_3	Temporal	LH Limbic Network A *temporal pole*	0.089	0.002	0.814	0.014
Feature_4	MIxed	LH Somatomotor Network B *central*	0.053	0.017	0.301	0.065
Feature_5	Parietal-Temporal	LH Salience/Ventral Attn Network A *parietal medial*	0.046	0.098	0.138	0.818
Feature_6	Insula-Prefrontal	LH Salience/Ventral Attn Network A *insula*	0.01	<0.001	0.208	0.021
Feature_7	Mixed	RH Control Network B *lateral dorsal prefrontal cortex*	0.248	0.05	0.484	0.165
Feature_8	Cingulate-Temporal	LH Control Network A *mid-cingulate*	0.102	0.004	0.632	0.017

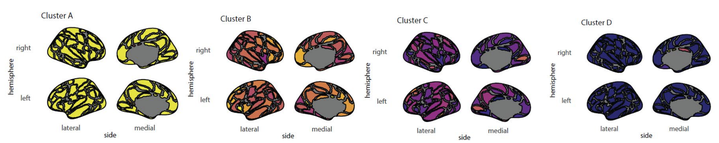
- Significant ESP-control differences were observed between Features 2, 5 and 6 (column ESP-C), corresponding to prefrontal, parietal-temporal and insula-prefrontal features.
- When patients were stratified by diagnosis, SSD patients had significant thickness reductions compared to controls in most features (column SSD.
- No significant features differed between AP and controls (column AP-C).
- Features were significantly different between patients with different diagnoses (column SSD-AP)
- BBN identified top Bayesian Information Criteria (BIC) nodes driving the network topology of each feature (BIC Driver).

3.3 Cortical thickness reductions and clinical insights

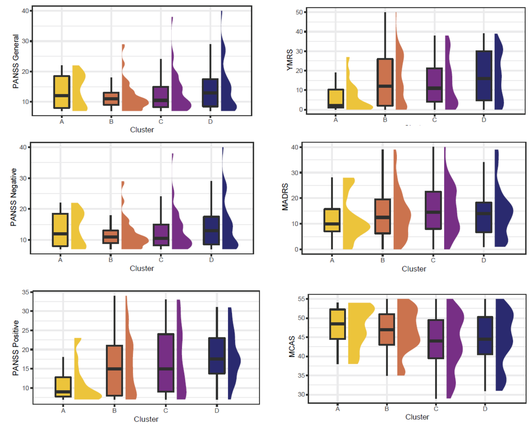


Embedding space with hierarchical clustering Euclidean distance, average linkage

Clustering the NMF basis vector of the structural features yields four distinct clusters. Cluster A has the most cortical thickness, followed by Cluster B, with C and D having higher cortical thickness reductions.



Mean cortical thickness of each feature, min-max scaled across clusters



Clinical variables stratified by cluster

Clinical variables were compared across clusters to derive clinical insights of cortical thickness reductions. Clinical variables assessed were psychotic symptom severity (PANSS General, PANSS Negative, PANSS Positive), manic symptom severity (YMRS), depressive symptom severity (MADRS), and community functioning (MCAS).
Clinical variables showed a clear graded pattern - Cluster A (highest cortical thickness) had the mildest symptoms (lowest scores) and the highest functioning (highest scores); Cluster D had the most severe symptoms, and lowest functioning; Clusters B and C had intermediate symptom severity and functioning.

Conclusion

1) Cortical thickness networks are spatially organized, rather than by functional connectivity
2) NMF embedding features preserve differences between SSD and Controls, and SSD and AP, but the differences in cortical thickness reductions between AP and Controls are less distinguished.
3) Clustering analysis stratified cortical thickness reductions which matched patterns of symptom severity and functioning.

References

1) Wannan, C.M.J., V.L. Cropley, M.M. Chakravarty, C. Bousman, E.P. Ganella, J.M. Bruggemann, et al., Evidence for Network-Based Cortical Thickness Reductions in Schizophrenia. Am J Psychiatry, 2019. 176(7): p. 552-563.
2) Shafiei, G., R.D. Markello, C. Makowski, A. Talpalaru, M. Kirschner, G.A. Devenyi, et al., Spatial Patterning of Tissue Volume Loss in Schizophrenia Reflects Brain Network Architecture. Biol Psychiatry, 2020. 87(8): p. 727-735.
3) Yeo, B.T., J. Tandi, and M.W. Chee, Functional connectivity during rested wakefulness predicts vulnerability to sleep deprivation. Neuroimage, 2015. 111: p. 147-58.
4) Sotiras, A., Resnick, S.M., Davatzikos, C. Finding imaging patterns of structural covariance via non-negative matrix factorization. NeuroImage, 2015, 108: 1-16.
5) Scutari, M., Denis, J-B. *Bayesian Networks with Examples in R, 2nd Edition*. Chapman and Hall, 2021