Subtyping Schizophrenia Subjects Using Working Memory and Approach Motivation Neuroimaging Markers

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Introduction

- Negative symptomology is central to psychotic disorders, particularly common in individuals with schizophrenia.
- Working memory (WM) and approach motivation (AM) behaviors, constructs in the Research Domain Criteria (RDoC) project, have shown relationships with various components of negative symptoms (1).
- Brain systems involved with AM (2) and WM (3) constructs may be involved with these disorders.
- Function of multiple brain regions have been linked to AM, including the nucleus accumbens (NAc) and caudate (Cd) (4). Thalamus (Th) is central to WM functions (5). NAc and Th have been observed to show altered morphology in individuals with negative symptoms (6, 7).
- In this study, we compiled measures across two levels of analysis (imaging and behavior) for two constructs (AM and WM) from two dimensions (positive valence and cognitive systems).

Methods

Participants

- MPRAGE scans from 220 subjects (100 schizophrenia, 120 controls)
- Surfaces of Th, Cd, NAc computed using high-dimensional brain mapping methods (9) and Principal Components Analysis (PCA) to generate PC scores for each individual representing shape (8)
- Standardized cognitive performance and psychopathology (positive symptom, negative symptom, and disorganized thoughts) measures

Cluster Analysis

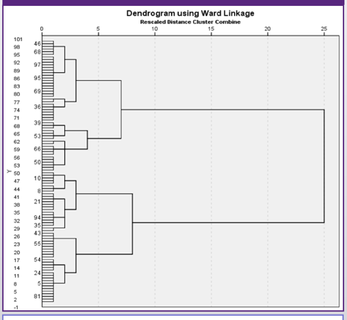
- Hierarchical clustering, followed by K-means clustering were performed on the first ten PC scores from Th, Cd, NAc of all subjects.
- A similar process was run on just the schizophrenia subjects.

Statistical Analysis

- Cognitive performance and psychopathology measures of the schizophrenia clusters were compared to each other as well as with controls using ANOVA.
- Surface measures of Th, Cd, NAc of the schizophrenia clusters were compared to each other as well as with controls using MANOVA.

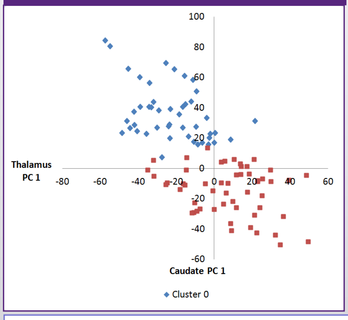
Results

A. Schizophrenic Clusters 0 and 1

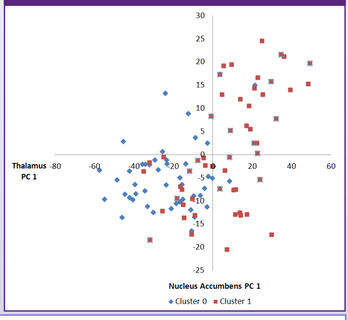


- Dendrogram above shows the results of an initial hierarchical clustering of schizophrenia subjects. The dendrogram suggests a 2-cluster solution.
- A k-means clustering solution specifying 2 clusters was then run to determine the final cluster membership of the subjects.

B. PC 1 of Th & Cd

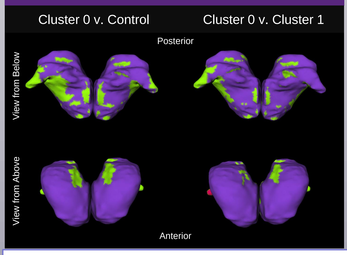


C. PC 1 of Th & NAc

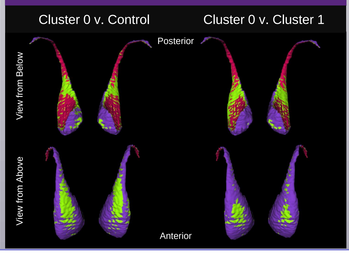


- Scatter plots show scores from the 1st principal component (PC) of Th and Cd (left panel), and Th and NAc (right panel). The 1st PCs were used as examples of visualizing the distribution of clusters. They were also the most important in determining cluster membership.
- Plot of the Th and Cd shows a clear separation of cluster 0 and cluster 1.
- Plot of the Th and NAc does not show separation of cluster 0 and cluster 1.
- This suggests that the NAc shape scores were not significant determinants of cluster membership. This corroborates the finding that shape scores were not significantly different between cluster 0, cluster 1 and controls.

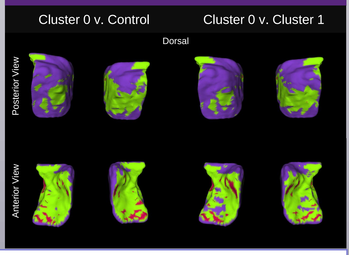
E1. Thalamus



E2. Caudate



E3. Nucleus Accumbens



Figures show vertex-wise comparison between mean surfaces of Cluster 0 subjects relative to mean surfaces of Cluster 1 subjects. Purple areas indicate significant (p=0.05) inward deformity of Cluster 0 relative to Cluster 1. Red areas indicate significant (p=0.05) outward deformity of Cluster 0 relative to Cluster 1. Green areas indicate non-significant difference. All FDR corrected.

Left:	Right	Left:	Right	Left:	Right
F=26.0, df=2,218, p < .001	F=22.6, df=2,218, p < .001	F=, df=2,218, p < .001	F= 25.2, df=2,218, p < .001	F=3.3, df=2,218, p = 0.37	F=0.81, df=2,218, p = 0.45
Cluster 0 v. Control:	p < .001	Cluster 0 v. Control:	p < .001	Cluster 0 v. Control:	ns
Cluster 0 v. Cluster 1:	p < .001	Cluster 0 v. Cluster 1:	p < .001	Cluster 0 v. Cluster 1:	ns
Cluster 1 v. Control:	ns	Cluster 1 v. Control:	ns	Cluster 1 v. Control:	ns

D1. Cognitive Performance

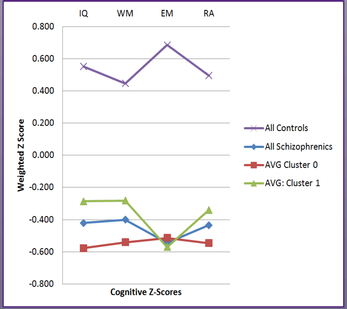


Figure shows cognitive performance of schizophrenia subjects in cluster 0 to cluster 1 and controls.
IQ = Crystalized IQ; WM = Working Memory; EM = Episodic Memory; RA = Executive Function.

Table shows cognitive and psychopathology measures for which cluster 0 and cluster 1 significantly differed.
** Indicates unequal variances were assumed.

D2. Psychopathology

	Cognition/Psychopathology Measure	Cluster	N	Mean	SD	P
Cognitive Performance	Working Memory CPT (all prime)	0 1	38 36	.59 1.08	.63 .70	.002
	WAIS Matrix Reasoning	0 1	46 53	7.9 9.5	3.24 3.13	.011
	N-back Error (0)	0 1	7 27	.89 .96	.12 .03	.007
	N-back Error (1)	0 1	7 27	.81 .88	.12 .06	.028
	N-back Error (2)	0 1	7 27	.73 .82	.13 .08	.026
Negative Symptoms	Negative Symptom Domain Score	0 1	46 54	.24 .60	.69 .71	.011
	Global Rating of Affective Flattening	0 1	46 54	7.9 9.5	3.24 3.13	.05
	Global Rating of Alogia	0 1	46 54	1.1 1.6	1.07 1.27	.05
Positive Symptoms	Delusions of Reference**	0 1	8 27	3.0 2.6	.00 .80	.013
	Persecutory Delusions	0 1	8 27	2.9 2.1	.35 .97	.038
	Other Delusions	0 1	8 27	2.2 1.4	1.03 .85	.031
	Auditory Hallucinations**	0 1	8 27	3.0 2.7	.00 .72	.043
	Visual Hallucinations	0 1	8 27	3.0 2.0	.00 .98	.006
	Other Hallucinations	0 1	8 26	2.0 1.3	1.07 .74	.045

Conclusions

- Clustering using neuroanatomic measures yielded differences along dimensions of negative symptom pathology and WM constructs. The subgroup with more severe surface deformities exhibits (1) increased deficits in cognitive functioning, (2) increased severity in negative symptoms, and (3) increased severity in positive symptoms.
- These findings are consistent with the previous work identifying neuropsychological impaired and near-normal subgroups of schizophrenics using neurospsychological measures with the impaired subgroup showing more severe cortical thinning (8).
- This study demonstrates a proof of concept of a convergent, multimodal approach to studying neurobiological dimensions.

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