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Multivariate relationships between cognition and brain anatomy across the psychosis spectrum Short title: Cognition and brain anatomy in psychosis

Amanda L. Rodrigue, Ph.D.[a], **Jennifer E. McDowell, Ph.D.**[a], **Neeraj Tandon, Ph.D.**[b], **Matcheri S. Keshavan, M.D.**[b], **Carol A. Tamminga, M.D.**[c], **Godfrey D. Pearlson, M.D.**[d], **John A. Sweeney, Ph.D.**[c,e], **Robert D. Gibbons**[f], and **Brett A. Clementz, Ph.D.**[*,a]

[a]Departments of Psychology and Neuroscience, Bio-Imaging Research Center, University of Georgia, Athens, GA

[b]Department of Psychiatry, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

[c]Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas. TX

[d]Departments of Psychiatry and Neuroscience, Yale University School of Medicine, New Haven, CT and the Olin Neuropsychiatry Research Center, Institute of Living, Hartford Hospital, Hartford, CT

[e]Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH

[f]Department of Medicine and Public Health Sciences, University of Chicago, Chicago, IL

Abstract

Background—Cognitive and structural brain abnormalities range from mild to severe in psychosis. The relation of specific cognitive functions to specific brain structures across the psychosis spectrum is less certain.

Methods—Participants (n=678) with bipolar, schizoaffective, or schizophrenia psychoses, and healthy controls, were recruited via the Bipolar-Schizophrenia Network for Intermediate Phenotypes. The Schizo-Bipolar Scale was used to create a psychosis continuum (from purely affective to purely nonaffective). Canonical correlation between 14 cognitive measures and structural brain measures (volume, thickness, surface area, and local gyrification indices) for 68 neocortical regions yielded constructs that defined shared cognition-brain structure relationships.

[*]Corresponding Author: Brett A. Clementz, Psychology Department, 125 Baldwin St., Athens, GA 30602; Telephone: 706-542-4376; Fax: 706-542-3275; clementz@uga.edu.

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Canonical discriminant analysis was used to integrate these constructs and efficiently summarize cognition-brain structure relationships across the psychosis continuum.

Results—General cognition was associated with larger volumes and thicker cortices, but smaller surface area, in frontal/parietal regions. Working memory was associated with larger volume and surface area in frontal/temporal regions. Faster response speed was associated with thicker frontal cortices. Constructs that captured general cognitive ability and working memory and their relationship to cortical volumes primarily defined an ordered psychosis spectrum (purely affective, least abnormal through purely nonaffective, most abnormal). A construct that captured general cognitive ability and its relationship to cortical surface area differentiated purely affective cases from other groups.

Discussion—General cognition and working memory with cortical volume deviations characterized more nonaffective psychoses. Alternatively, affective psychosis cases with general cognitive deficits had deviations in cortical surface area, perhaps accounting for heterogeneous findings across previous studies.

Keywords

sMRI; Cognition; Psychosis; Canonical Correlation Analysis; Schizo-Bipolar Scale; Multivariate Statistics; Canonical Discriminant Analysis

Introduction

There is significant overlap of clinical and biological features across bipolar disorder with psychosis, schizoaffective disorder, and schizophrenia (1). One feature is cognitive impairment (2–6), which is present before disease onset (7), reasonably stable throughout the course of illness (8–10), and predicts functional outcome (11, 12). The range of cognitive impairment observed in patients with psychotic disorders includes disruptions in behavioral inhibition, working memory, context processing, problem solving and reasoning, processing speed, and verbal memory (13–18). Another feature is structural brain abnormalities. In general, people with psychosis show reductions in regional volumes and cortical thickness compared to healthy controls, although findings in bipolar cases tend to be less clear (19–21).

Understanding the structural correlates of neurocognition could give insight into the etiology and treatment for psychotic disorders. In healthy controls, better cognition is generally associated with, larger brain volumes (22, 23), thicker cortices (24), larger surface area (25), and greater gyrification (26, 27). The direction of cognition/structure relationships in schizophrenia tend to mirror that in healthy controls; poor cognition is often associated with reduced frontal and temporal volumes (28), thinner cortex (24, 29–31) and lower gyrification indices (27, 32). Studies in bipolar disorder are less common and consistent than those in schizophrenia, with some studies reporting altered relationships between cognition and brain structure in the frontal lobes (related to volume) (33, 34) and cingulate and temporal regions (related to cortical thickness and gyrification measures) (35, 36). Findings in bipolar disorder, however, remain unclear given that psychosis status is inconsistently reported and studies are more likely to focus on deep structures like the hippocampus, amygdala,

thalamus, and basal ganglia (36–39). Studies in schizoaffective disorder are sparse with problems arising from the inclusion of schizoaffective samples with schizophrenia samples (40). Combination of these two groups is at least consistent with a recent meta-analysis concluding that volumetric and cognitive deficits in schizoaffective disorder may be closer to those seen in schizophrenia (41, 42) than those seen in bipolar disorder (43).

There are additional factors that have significantly impacted the evaluation of cognition/structure relationships in psychosis. One factor is symptom overlap across and symptom heterogeneity within diagnoses, which can complicate distinctions between psychosis syndromes. A second factor is the use of extensive univariate strategies that adopt a one cognitive test to one brain region approach, which is not optimal given that one brain region is unlikely to underlie the various operations required for completion of complex cognition assessments. Measures of complex cognition work well for quantifying brain dysfunction because they rely on distributed brain structures for their successful performance. There are many paths to dysfunction, so many syndromes can have phenotypic similarity on measures of complex cognition; what is needed is a means for differentiating distinct brain correlates of phenotypically similar cognitive dysfunction within psychosis.

In general, studies of cognition-structure relationships have been constrained by limited sample sizes, limited cognitive assessment, and selective focus on a particular structural measure or brain region of interest in psychosis groups with overlapping symptomatology. The purpose of this study was to define the relationships between cognition and brain structure, independent of specific syndromal definitions (i.e. a DSM diagnosis), using a multivariate data-driven approach in a large sample of psychosis and healthy participants. This method allowed for simultaneous analysis of multiple cognitive domains and structural brain measures (volume, cortical thickness, surface area, and gyrification) in order to define bi-directional relationships between them. We then determined how these bi-directional relationships differ along an affective-nonaffective psychosis continuum using a quasi-dimensional scale. We hypothesized that, in general, better cognition would be associated with larger volumes, thicker cortex, larger surface area and greater gyrification (22–27), although altered relationships between cognition and brain structure may be present in bipolar disorder (33–36). In terms of inter-related deficits in cognition and brain structure, we expected nonaffective psychosis cases to be the most and affective cases to be the least deviant on cognition-cortical brain structure constructs.

Materials and Methods

Participants

Patients with bipolar disorder (BP) with psychosis, schizoaffective disorder (SAD), or schizophrenia (SZ) (as defined by the DSM IV-TR) and healthy controls (HC) were recruited as part of the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP)(44). Six hundred and seventy eight participants (438 people with psychosis and 240 healthy controls) had complete datasets (scores on all cognitive and brain structure measures) (see Table 1 and Supplementary Methods for further details). This study was approved by the Institutional Review Boards at all sites and all participants provided written informed consent.

Cognitive Assessment

Cognitive assessments included the reading sub-test of the Wide Range Achievement Test 4th edition (WRAT IV) (45), Brief Assessment of Cognition in Schizophrenia (BACS) battery (46), the spatial span of the Weschler Memory Scale (WMS-III) (47), the Dot Pattern Expectancy task (DPX) (48, 49), and antisaccades (AS) (50). Procedures and findings for each cognitive measure from the B-SNIP study are available in previous reports (16, 17, 51, 52). Cognitive tests that did not yield scores based on normative data (DPX and AS) were normed to the healthy sample that underwent extensive screening (53) and did not have elevated Cluster A personality disorder traits (within 1 symptom of disorder). See Table S1 for descriptive data for cognitive measures.

MRI Structural Imaging

Brain gray matter volume (GMV), cortical thickness (CT), cortical surface area (CSA), and local gyrification indices (LGI) were obtained from 68 regions of interest from high-resolution T1-weighted scans (see list in Table S2). MRI acquisition parameters and findings with morphometric parameters used in this study are available in prior reports (54–56). Further details of MRI protocols and pre-processing are in Supplementary Methods.

Statistical Analysis

To evaluate the bi-directional relationships between cognition and neocortical brain structure, we performed canonical correlation analyses (CCAs) across all groups using Statistic Analysis System (SAS) software (SAS Institute Inc., Cary, NC). CCA is a data-driven, multivariate approach that identifies the relationship between two sets of variables by maximizing correlations between ‘predictor’ and ‘criterion’ variable sets (57). CCA is particularly useful when there are high inter-correlations within variable sets and the relationship between variable sets is non-directional/bi-orthogonal (57). Results of a CCA are correlated pairs of latent variates. Each pair is independent and composed of weighted sums of the predictor variables that maximally correlate with the weighted sums of the criterion variables. Interpretation of what the latent variates represent and how they are related to each other can be determined by the weighted sums or loadings of individual measures on the latent structure, much like principal components analysis.

In the present study, variable sets were 14 cognitive measures (listed in Table S1) and structural measures extracted from each of 68 ROIs (listed in Table S2). There were four types of structural measures (GMV, CSA, CT, LGI); we conducted a separate CCA for each type. Cognitive measures were adjusted for age, sex, and race. Parameter estimates of age, race, and sex on cognitive measures were obtained in the healthy group and subsequently applied to adjust cognitive measures in all psychosis subgroups, an approach we have taken in previous B-SNIP publications (17, 51, 52, 56, 58). A similar adjustment procedure (with the addition of intracranial volume-ICV) was performed for structural measures (for each ROI) when relationships with these variables were significant (uncorrected threshold of $p < .05$) in the healthy group (59). Cognitive and structural measures also were standardized before insertion into the CCA to eliminate differences in scale from contributing to the outcome. The multivariate nature of CCA does not require multiple testing within a CCA analysis, although multiple testing across the four CCA analyses does and was accounted for

using Bonferroni correction with the threshold for significance set at p = .0125 (.05/4 CCA analyses).

To evaluate the consistency of the models produced by the CCA solutions and latent variate pairs, we used a resampling method implementing a delete-n jackknife procedure (Lee 2007). We conducted delete-2, 4, 8, and 16 jackknife analyses with 10,000 replicates constructed using random sampling without replacement. The CCA was then conducted on each replicate. Variates were deemed to be consistent and valid for interpretation 1) if they reached significance in the original analysis and 2) if the individual measures that loaded the highest in the original analysis did not include "0" in the 99% confidence interval across all jackknife outcomes.

The subsequent set of analyses evaluated the unique contribution of the significant CCA pairs (cognition-structure constructs) across an affective-nonaffective psychosis symptom continuum. The psychosis continuum was defined using the Schizo-Bipolar Scale (SBS) as in prior studies (60, 61). The SBS ordinal scale ranges from 0–9 and reflects the proportion of non-affective psychosis symptoms and affective symptoms in relation to total illness duration as well as which mood symptoms (manic vs. depressive) are predominant when present. SBS scores closer to 0 indicate more BP-like and affective psychosis presentations whereas scores closer to 9 indicate more SZ-like and nonaffective psychosis presentations (62) (see Supplementary Methods for details). To gain the advantage of an ordered psychosis continuum, we parceled the continuum into 4 groups defined by SBS score (0–1, 2–4, 5–7, 8–9). Four groups sufficiently retained the nature of the continuum but also provided enough observations per group for further analysis.

Canonical discriminant analysis (CDA) (63, 64) with group membership as the criterion (healthy, SBS 0–1, SBS 2–4, SBS 5–7, SBS 8–9) and significant CCA variates as predictors was used to quantify cognition-brain structure features across the psychosis continuum. CDA creates a linear combination of the predictors that have the highest possible within-group correlations and returns canonical variables (a linear combination of the predictors). The nature of significant canonical variables (i.e. which of the predictors contribute most) can be determined by inspecting standardized coefficients and group differences can be evaluated by plotting the group means of the scores generated by CDA. A general linear model with factors for group membership, sex, and sex by group membership was performed on significant canonical variables from the CDA. If there were significant effects in the omnibus general linear model, group means were compared using Tukey's HSD.

Results

Canonical Correlation Variate Pairs

CCA latent variate pairs were retained for further analysis if their correlation was significant ($p \leq .0125$) and if the loadings of individual variables was stable, as determined by the jackknife outcomes. These criteria were met for 1) the first canonical correlation pairs for all four structural analyses and 2) the second pairs for the GMV, CT, and CSA analyses (See Table 2 and Figure S1). All significant canonical correlations were positive (ranging from r

= .42 to r = .55), meaning higher scores on latent cognitive variates were associated with higher scores on latent structural variates (See Figure S2 for an example).

Variate Loadings

For each CCA pair, loading strength of individual measures on the latent variate were used to define their nature (see Figure 1). Signs of loadings (positive or negative) were used to interpret how scores on individual measures with moderate-strong loadings (beyond −.3 or .3) related to the latent variates: positive values indicate higher scores on individual measures; negative values indicate lower scores on individual measures. Loadings, therefore, indicate what aspect of cognition is captured in each analysis, the cortical structural characteristics with which they are associated, and the nature of the relationship between them. The pattern of loadings across the GMV, CT, CSA, and LGI analyses in Figure 1 also indicates the extent to which structural parameters capture similar or different aspects of associations with cognition (See also Table 3). A visual summary of the cognitive variates and the spatial distribution of cortical regions associated with them (regions with an absolute loading beyond .3) can be seen in Figure S3 and Table S5.

Pair 1 variates assessed highly related constructs (See Table 3). The latent cognitive variate from the first CCA pair of each analysis (GMV, CT, CSA, and LGI) was composed of higher scores on measures that represented general cognitive ability (65, 66) (Figure 1A). Better general cognitive ability was associated with larger volumes, thicker cortex, and smaller surface area in mostly frontal/parietal regions (Figure 1D). The negative loadings for CSA in pair one may indicate that bigger surface area is not always better for cognitive performance. Although the LGI pair was significant, structural loadings were weak, with no regions loading beyond −.3 or .3.

Pair 2 variates of the GMV and CSA analysis also captured similar constructs (See Table 3) but were related to more specific cognitive domains. The latent cognitive variate was composed of higher scores on measures that represent working memory (Figure 1B). Better working memory ability was associated with larger volume and surface area in frontal and temporal regions (Figure 1E). The second cognitive variate in the CT analysis was composed of higher scores on measures that represent reaction time (Figure 1C). Slower reaction times were associated with thinner cortex in lateral frontal and temporal regions (Figure 1F).

Psychosis Continuum Analyses

The seven significant CCA constructs were used as predictors in the CDA. Associations between the CCA latent scores, symptom measures, and medication were negligible and were not considered further (see Supplementary Results and Table S4). Because each canonical variate from the CCA indexes a single cognition-brain structure construct (all positive correlations-refer to Figure S2), cognition and brain structure variate scores within each significant CCA pair and within each subject were averaged before entering them into the CDA as predictors.

The CDA returned 2 significant canonical variables (CV1: $\Lambda = .47$, $F(16, n = 663) = 7.1$, $p < .001$; CV2: $\Lambda = .20$, $F(16, n = 663) = 1.9$, $p = .010$). The first canonical variable was highly associated with the first and second CCA constructs in the GMV analysis (larger volume

associated with better scores on general cognitive ability and working memory). The second canonical variable was largely accounted for by the first CCA construct in the CSA analysis (smaller surface area associated with better general cognitive ability). Loading coefficients for each CCA construct on CDA canonical variables are reported in Table 4. There was a main effect of sex for both canonical variables (M<F; CV1: $F(1,620)= 4.2$, $p= .04$; CV2: $F(1,620)=13.9$, $p= .002$), but no significant sex by diagnosis interactions.

The first canonical variable described a psychosis continuum (See Figure 2). The healthy group had the highest scores (best cognition and largest brain volumes) with canonical scores decreasing incrementally as scores on the SBS increased. The most purely nonaffective psychosis cases had the worst cognition and smallest cortical volumes. Low scores on the second canonical variable (worse general cognition associated with larger surface area) were peculiar to the most purely affective psychosis cases (SBS 0–1). The SBS 0–1 cases significantly differed from all groups, but the other groups did not significantly differ from each other (see Figure 2).

Discussion

Behavior-brain relations in psychosis are of considerable interest, but associations between cognitive deviations and indices of brain structure had yet to be examined using multivariate methods in a sufficiently large sample. Previous strategies had limited coverage of cognitive functions and their association to a small number of brain regions, yielding an interesting but incomplete picture of cognition-brain structure relationships. In addition, considering relationships at one level of analysis (e.g. within cognition alone or within brain structure alone) independent of a different but related level of analysis (e.g. cognitive functioning is associated with distributed brain structure) may have provided incomplete, perhaps incorrect, answers to pressing questions in psychosis research. In the present project, we used a means for differentiating distinct structural brain correlates of phenotypically similar cognitive dysfunction. The outcome may advance our understanding of differences between the mechanisms associated with cognitive deviations observed between more purely affective and more purely nonaffective psychosis manifestations.

The initial canonical correlation analyses, which constructed bi-orthogonal constructs relating general and specific cognitive domains to cortical structure, generally supported hypotheses about projected cognition/structure relationships except for surface area. Cognitive variates in the first pair of each CCA captured general cognitive ability given the high loadings of the WRAT and BACS. This is consistent with a previous study that reported a unitary factor of generalized cognitive ability underlying the BACS (66). General cognitive ability was associated with brain structure in particularly frontal/parietal cortices (see Figure S3), regions consistently linked to diverse cognitive functions (67–69). Correlations between general cognitive ability and GMV and CT were positive and consistent with studies of healthy individuals (25, 27, 36), whereas correlations between general cognitive ability and CSA were negative. Studies correlating CSA and cognition yield inconsistent results, with some showing positive correlations (25, 36, 70) and others showing negative (71) or no correlations between the two measures in healthy samples (72). The use of ICV as an adjustment variable may contribute to the negative relationship between general cognitive

ability and CSA. Without ICV adjustment, CSA loadings were positive for the first pair (data not shown). Negative relationships between CSA and other structural measures like CT have been reported elsewhere (73), so it is not unexpected that larger volumes and thicker cortices associated with smaller surface areas. It could be that more neuronal bodies (as measured by larger volume and thicker cortices) in a smaller space result in a more efficient brain. Such a brain configuration may enhance local neural processing because local neural signals travel a shorter distance to support the required operations.

The second variates captured relationships between brain structure and more specific cognitive domains. For the GMV and CSA analyses, the CCA variates in the second pair indexed working memory constructs, given the high loading of spatial span, digit sequencing scores, and antisaccade error rate. While spatial span and digit sequencing are not equivalent (74), they both capture aspects of working memory (46, 75). Those with higher working memory capacity also typically display lower antisaccade error rate (76, 77), which is consistent with its negative loading on these constructs. Working memory abilities were associated with structural measures in lateral and medial frontal and in parietal-temporal cortices, all of which support working memory abilities (78–82). For the CT analysis, the second cognitive variate indexed reaction time given the singular high loading of DPX reaction time; this was paired with volumetric measures predominantly in frontal cortex, which passes information to motor outputs to guide behavior initiation (83–85).

An important consideration when interpreting cortical regions with high variate associations, particularly those that share the same cognitive constructs, is that structural measures are not necessarily, or even likely fully independent. Volume measures correlate with both cortical thickness and surface area measures (20) in that larger volumes can result from thicker cortices, larger surface area or both. The magnitude of the inter-correlations between the cognition-brain structure constructs can be seen in Table 3 (see also Figure S4). For illustration, in CCA analyses capturing general cognitive ability (left panel in Figure S3), most of the regions that loaded the highest in the volume analysis also loaded the highest in other analyses (purple, orange, and pink regions). Regions in pink are of interest because they show overlap among GMV, CT, and CSA measures. Given that structural loadings were positive for GMV and CT and negative for CSA, it could mean that pink regions loaded highly in the volume analysis due to thicker cortices and not surface area. The subsequent canonical discriminant analysis that used the seven significant cognition-brain structure constructs to differentiate groups across the affective-nonaffective psychosis continuum allowed for the determination of which of the cortical quantification approaches best captures psychosis associated deviations. Using multiple cortical quantification schemes was important because each reflects at least some distinct neurobiological processes (86), so the outcome of such comprehensive investigations can inform future cognition-brain structure projects while also informing particular neurobiological theories.

After deriving cognition-brain structure constructs, we used canonical discriminant analysis to determine which of the constructs most efficiently captured deviations across an affective-nonaffective psychosis continuum. There were two important outcomes, and their differences highlight the possible importance of multi-level approaches to understanding the neurobiology of the psychoses. The first canonical variable from the CDA captured an

affective to nonaffective psychosis continuum. This canonical variable was associated with primarily cortical volumes and their relation to general cognition and working memory. Healthy persons had the highest scores on this variable. The most purely affective psychosis cases were the least and the most purely nonaffective psychosis cases were the most deviant on this variable, with an ordered continuum describing the intermediate psychosis groups. Such a pattern is consistent with previous studies of global cognitive and structural deficits in psychosis (5, 28, 87–89) and the Kraepelinian-type distinction between schizophrenia-type disorders and bipolar disorders (90). Such a pattern also suggests that cognition-cortical volumetric deviations are scalable and have illness severity consequences across the psychosis spectrum.

The second canonical variable, which was primarily associated with a poor general cognition-larger cortical surface area construct, differentiated the mostly affective psychosis cases (SBS 0–1) from all other groups. This could suggest that general deficits in cognition in individuals with BP-like features are more a consequence of deviations in surface area rather than deviations in volume, as in those with SZ-like features. Such differentiations between psychosis individuals could provide information about the etiology of cognitive impairment and suggest different physiological and biochemical mechanisms underlying them. Differential patterns in BP-like individuals are also consistent with altered associations between cognition and structure in studies of bipolar disorder, although previous studies have focused on volume, thickness, and gyrification (33–36).

Limitations of the study include the possible effects of medication on both cognition and brain structure. Effect sizes between daily CPZ dose and all variates were small and consistent with existing literature (5, 10, 56, 58, 91, 92), making drug effects an unlikely confound. Association between variates and symptoms were similarly small and previous studies of relationships between symptoms and brain structure have produced inconsistent results (58, 93, 94). This project also mostly included chronic and clinically stable cases, so the similarities to cases in other stages of illness are uncertain. Multivariate procedures are further dependent on the included variables. B-SNIP included a reasonably comprehensive battery covering multiple cognitive domains of known relevance to psychosis. Although the cognitive measures were normed on different samples (published norms for BACS and WMS and sample based norms for the remaining measures), it seemed prudent to use published norms when possible. Correspondence between our healthy sample norms and published norms have been calculated for the BACS in a previous publication with correlations >.98 (16). Although the correlations between our healthy sample and published norms is high, this does not rule out that there may be a systematic bias in using norms from different groups, so the specificity of test-based results may not hold up in other samples. Another factor could be shared methods variance in some tests, such as the Spatial Span forward and backward. We conducted the CCA with the Spatial Span measures collapsed and the same regions and cognitive measures loaded above .3, so this does not appear to have influenced our results. We also acknowledge that some brain regions (e.g. amygdala and basal ganglia) known to be involved in cognition in psychotic disorders were not included in our analysis. This stemmed from our desire to consider regions that could be measured on all four structural measures. Future studies could usefully extend similar investigations to more subcortical brain structures.

This study used multivariate analyses to quantify relationships between cognition and brain structure across an affective to nonaffective psychosis symptom spectrum to address a major unanswered question about deviations in behavior-brain systems in psychosis. Multivariate cortical volumes and their relationships to general cognitive ability and working memory best described a psychosis continuum of increasing deviation from affective to nonaffective cases. Additionally, poor general cognitive ability and its association with larger cortical surface area uniquely characterized more pure affective psychosis cases. The former pattern is consistent with the thesis that lower cortical density, probably secondary to reduced synaptic connectivity, is particularly import for describing a neurocognitive severity continuum in psychosis (5, 95). Alternatively, the latter pattern indicates that deviations in neocortical communication, rather than reductions in cortical tissue may account for cognitive deviations observed in more pure affective psychosis cases. Analyses integrating data across level of analysis was critical to identifying these different cognition-brain structure relationships. Different structural deviations across the psychosis spectrum may yield phenotypically similar cognitive deviations; such information may be critical for developing more effective and targeted treatments for psychosis subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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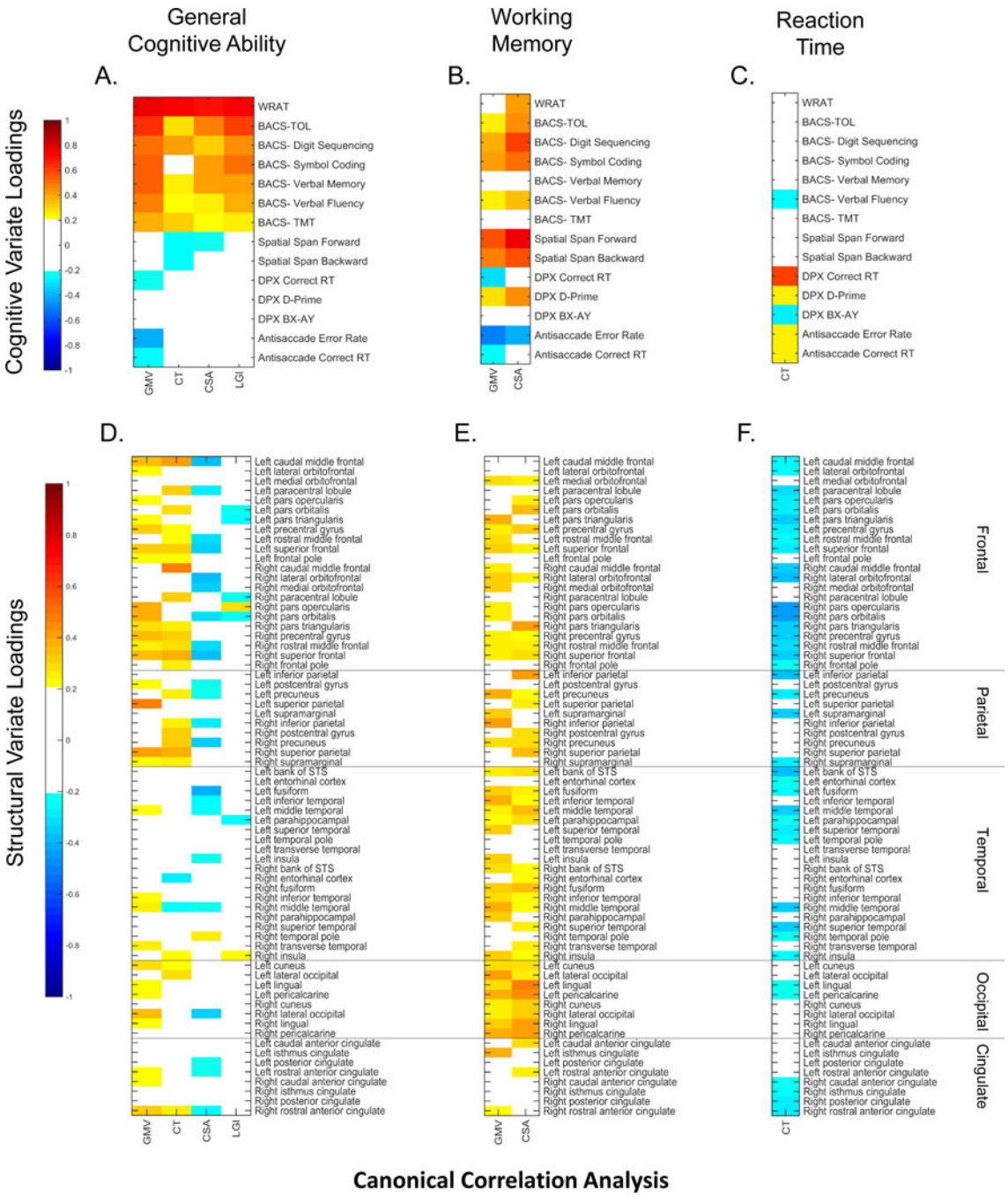

Figure 1. Loadings

Heat map colors show the loading strength of individual cognitive (A, B, C) and structural measures (D, E, F) on their respective latent variates for each CCA analysis (volume (GMV), thickness (CT), surface area (CSA), and gyrification (LGI). Heat maps are grouped based on the cognitive domain they represent (General Cognitive Ability, Working Memory, and Reaction Time). Warmer colors indicate stronger positive loadings (higher scores on an individual measure), cooler colors indicate stronger negative loadings (lower scores on an individual measure). Cognitive measures are ordered by assessment protocol; structural

measures are ordered by lobe. For clarity loadings between −.2 and .2 are shown in white. Loadings above −.3 and .3 are used for interpretation of latent variates. WRAT= Wide Range Achievement Test; BACS= Brief Assessment of Cognition in Schizophrenia; TOL= Tower of London; TMT= Token Motor Task; DPX= Dot Pattern Expectancy task; RT= Reaction Time; GMV= Volume Analysis; CT= Cortical Thickness Analysis; CSA= Surface Area Analysis; LGI= Gyrification Analysis.

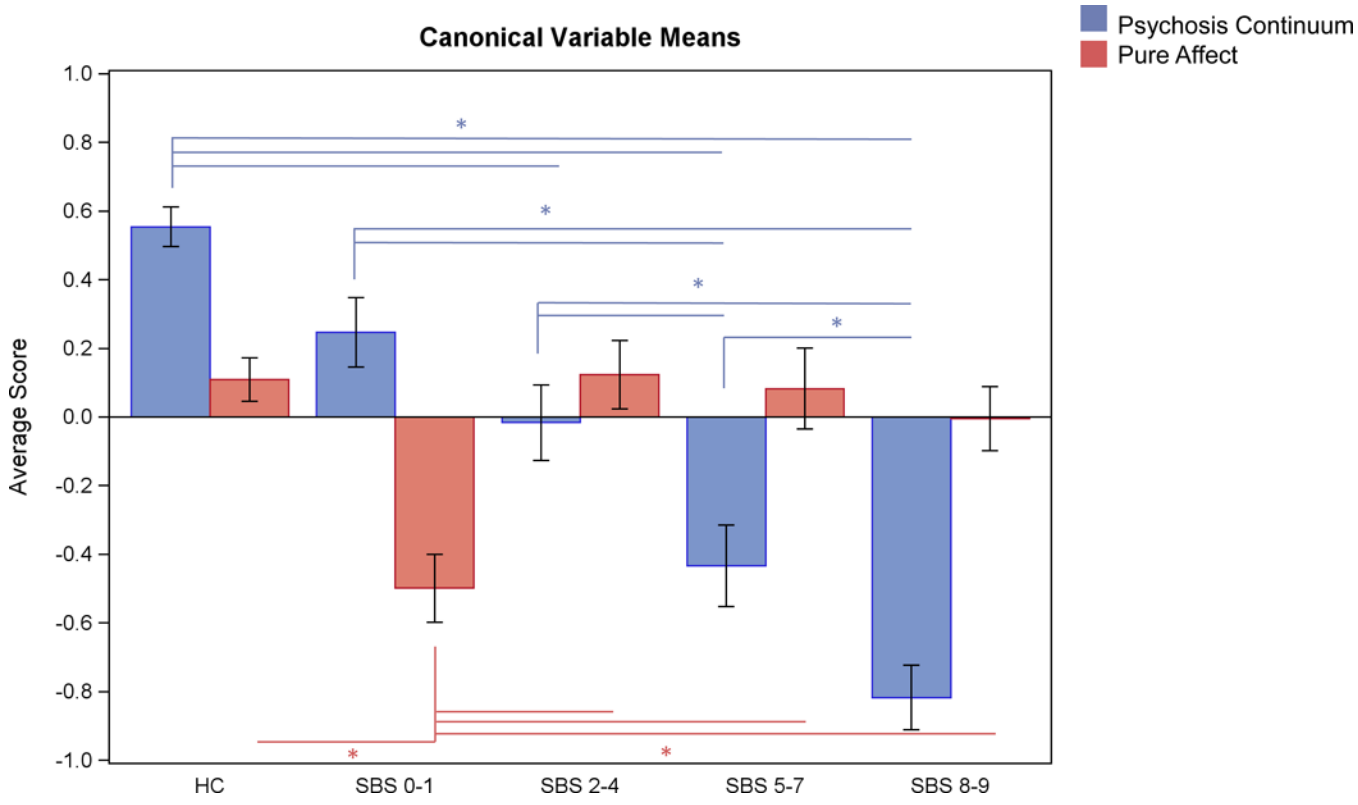

Figure 2. Group Differences in CDA Variables

Bars show SBS group means (SE) on the significant canonical variables from the CDA. The first canonical variable (blue bars) best distinguishes groups along a psychosis continuum (nonaffective cases lowest scores, affective cases higher scores), whereas the second canonical variable (red bars) distinguishes more affective cases from all other groups. Lines and asterisks represent significant pair-wise comparisons using Tukey's HSD.

Table 1

Demographic Information

	HC (N=240)		SBS 0–1 (N=92)		SBS 2–4 (N=99)		SBS 5–7 (N=98)		SBS 8–9 (N=134)			
Demographics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Statistics**	**Findings**
Age (yrs)	37.5	12.4	35.8	13.7	34.7	11.5	35.8	12.6	36.0	12.0	F(4, 658) = 1.04	
Education (yrs)	15.1	2.4	14.6	2.3	13.4	2.1	13.0	2.1	13.0	2.4	F(4, 655) = 26.3[a]	HC, SBS 0–1 > SBS 2–4, SBS 5–7, SBS 8–9
	N	%	N	%	N	%	N	%				
Male	115	47	31	33	31	31	46	46	92	68	$\chi^2(4)= 41.5^a$	SBS 8–9 >all(/br)HC>SBS 2–4
Race												
Caucasian	160	66	74	80	57	57	45	45	62	46	$\chi^2(4)= 39.3$	HC, SBS 0–1 > SBS 5–7, SBS 8–9(/br)SBS 0–1 >SBS2–4
African American	62	25	12	13	39	39	48	48	67	50	$\chi^2(4)= 51.1^a$	SBS 0–1 <all(/br)HC<SBS 5–7, SBS 8–9
Other	18	7	6	6	3	3	5	5	5	3	$\chi^2(4)= 3.9$	
Clinical Variables			Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Illness duration (yrs)	–	–	17.1	12.4	15.8	11.7	16.6	12.6	14.1	11.2	F (2, 401) = 1.38	
Total	–	–	53.7	14.4	60.6	16.1	64.5	14.9	66.8	16.6	F (2, 411) = 13.7[a]	SBS 0–1 < SBS 2–4, SBS 5–7, SBS 8–9(/br)SBS 2–4 < SBS 8–9
Positive	–	–	12.6	4.3	15.3	5.4	17.1	5.0	17.2	5.5	F (2, 413) = 17.5[a]	SBS 0–1 < SBS 2–4, SBS 5–7, SBS 8–9(/br)SBS 2–4 < SBS 8–9
Negative	–	–	12.3	4.3	13.6	4.6	14.9	4.23	17.1	6.1	F (2, 413) = 18.5[a]	SBS 0–1, SBS 2–4, SBS 5–7 < SBS 8–9(/br)SBS 0–1 < SBS 5–7
YMRS	–	–	6.2	6.9	6.9	6.6	6.8	6.0	5.3	4.9	F (2, 408) = 1.7	
MADRS	–	–	10.0	9.4	13.4	10.3	12.5	9.2	8.6	7.7	F (2, 411) = 6.5[a]	SBS 2–4>SBS 0–1, SBS 8–9(/br)SBS 5–7>SBS 8–9
Medications			N	%	N	%	N	%	N	%		
Antipsychotic	–	–	62	67	75	75	90	91	126	94	$\chi^2(6)= 38.8^a$	SBS 0–1, SBS 2–4< SBS 5–7, SBS 8–9
Lithium	–	–	28	30	20	20	10	10	8	5	$\chi^2(6)= 31.2^a$	SBS 0–1, SBS 2–4> SBS 8–9(/br)SBS 0–1 >SBS 5–7

Demographic measures for the groups determined using the Shizo-Bipolar Scale. Fifteen subjects (5 from each psychosis group) did not have Schizo-Bipolar scores. Results of statistical tests of group differences on demographic measures are reported in the Statistics and Findings columns. PANSS= Positive and Negative Symptom Scale, YMRS=Young Mania Rating Scale, MADRS=Montgomery Asberg Depression Rating Scale

[a]Statistical test with significant effects

Table 2

Significance of CCA variate pairs

CCA	Canonical Correlation	Squared Canonical Correlation	Eigenvalue	Wilk's Lambda	F(num df, den df)	p-value	Jackknife criteria met?
GMV							
Pair 1	.54	.29	.41	.14	1.4 (952, 8243.7)	< .001	yes
Pair 2	.46	.22	.28	.19	1.2 (871,768.1)	< .001	yes
CT							
Pair 1	.56	.31	.45	.15	1.3 (952, 8243.7)	< .001	yes
Pair 2	.49	.24	.32	.22	1.1 (871,768.1)	.01	yes
CSA							
Pair 1	.54	.29	.40	.15	1.3 (952, 8243.7)	< .001	yes
Pair 2	.46	.21	.27	.21	1.2 (871,768.1)	.002	yes
LGI							yes
Pair 1	.54	.3	.42	.15	1.2 (952, 7791)	< .001	yes

Table shows significant results for latent pairs of each CCA analysis and information about the jackknife criteria. CCA = canonical correlation analysis; GMV = Volume Analysis; CT= Cortical Thickness Analysis; CSA= Surface Area Analysis; LGI= Gyrification Analysis.

Table 3

Correlations between CCA Constructs

	GMV Pair1	CT Pair 1	CSA Pair 1	LGI Pair1	GMV Pair 2	CT Pair 2	CSA Pair 2
GMV Pair1	–						
CT Pair 1	0.70718	–					
CSA Pair 1	0.79775	0.75687	–				
LGI Pair1	0.76696	0.7367	0.7917	–			
GMV Pair 2	−0.00694	−0.3081	−0.2467	−0.1462	–		
CT Pair 2	−0.16974	0.00349	0.02098	0.01553	−0.12662	–	
CSA Pair 2	0.20308	−0.0581	0.00578	0.08608	0.77634	0.21521	–

Given all CCA correlations were positive, we averaged latent scores over cognitive and structural variates for each individual within pair. Table shows pair-wise correlations between averaged latent scores for each CCA pair. GMV = Volume Analysis; CT= Cortical Thickness Analysis; CSA= Surface Area Analysis; LGI= Gyrification Analysis.

Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2019 December 01.

Table 4

CDA Standardized Coefficients

CCA Construct	Cognitive Pattern	Structural Pattern	Canonical Variable 1	Canonical Variable 2
GMV Pair 1	↑ General Cognitive Ability	↑ GMV	**0.85**	−0.60
CT Pair 1	↑ General Cognitive Ability	↑ CT	0.37	−0.49
CSA Pair 1	↑ General Cognitive Ability	↓ CSA	−0.30	**0.94**
LGI Pair 1	↑ General Cognitive Ability	–	0.14	−0.37
GMV Pair 2	↑ Working Memory	↑ GMV	**0.86**	0.38
CT Pair 2	↑ Reaction Time	↓ CT	−0.10	−0.58
CSA Pair 2	↑ Working Memory	↑ CSA	−0.38	0.33

Table shows original CCA pairs, the effect they represent, and the standardized coefficients for the averaged CCA constructs in the CDA analysis. Bolded values indicate those coefficients that were the strongest for each canonical variable. GMV = Volume Analysis; CT= Cortical Thickness Analysis; CSA= Surface Area Analysis; LGI= Gyrification Analysis.