Multivariate Relationships Between Cognition and Brain Anatomy Across the Psychosis Spectrum

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Participants

Inclusion criteria for all participants were as follows: age between 18 and 60 years old, English proficiency, score of 70 or greater on the WRAT word reading test, no known history of head trauma or neurological disorders, and no substance abuse within the last month and/or substance dependence within the last 6 months as reported in the Structured Clinical Interview for DSM IV (1, 2). Participants were also required to pass a urine screening for illicit substances upon recruitment into the study. Healthy controls reported no personal or immediate family history of psychotic disorders and/or recurrent depression. Individuals with psychosis were stable and a majority were receiving consistent drug therapies from 4 weeks prior to study participation. There were 19 psychosis individuals who were unmedicated (i.e. reported no use of any psychotropic medications). Further details of recruitment procedures and clinical characterization of patient samples have been outlined elsewhere (3, 4). Thirty-three participants were missing gyrification measures, therefore gyrification analyses were based on 645 individuals rather than 678.

MRI Scanning Protocols

All B-SNIP sites followed the Alzheimer's Disease Neuroimaging Initiative (ADNI1) protocol (see http://adni.loni.usc.edu/methods/documents/mri-protocols/ for full list of parameters). The MPRAGE or IR-SPGR parameters (depending on the scanner type) were as follows:

Site 1: GE Signa (University of Chicago, Chicago IL): 3D acquisitions, sagittal slab, shot interval 2300ms, inversion time 700ms, TR 6.99ms, TE 2.85ms, flip angle 8º, FOV 260 (foot-to-head) x 260 (anterior-to-posterior) mm^2, matrix 256x256, in-plane resolution 1x1 mm^2, 166 slices, slice thickness 1.2 mm, voxel size 1x1x1.2 mm^3, total scan duration 10min 28sec.

Site 2: Philips Achieva (UT Southwestern Medical Center, Dallas TX): 3D acquisitions, sagittal slab, shot interval 3000ms, inversion time 846ms, TR 6.8ms, TE 3.1ms, flip angle 8º, FOV 256 (foot-to-head) x 240 (anterior-to-posterior) mm^2, matrix 256x240, in-plane resolution 1x1 mm^2, 170 slices, slice thickness 1.2 mm, voxel size 1x1x1.2 mm^3, total scan duration 9min 19sec.

Site 3: Siemens Allegra (Olin Institute of Living, Hartford Hospital, Hartford CT): 3D acquisitions, sagittal slab, shot interval 2300ms, inversion time 900ms, TR 7.2ms, TE 2.91ms, flip angle 9º, FOV 256 (foot-to-head) x 240 (anterior-to-posterior) mm^2, matrix 256x240, in-plane resolution 1x1 mm^2, 160 slices, slice thickness 1.2 mm, voxel size 1x1x1.2 mm^3, total scan duration 9min 14sec.

Site 4: Siemens Trio (Maryland Psychiatric Research Center, University of Maryland, Baltimore MD): 3D acquisitions, sagittal slab, shot interval 2300ms, inversion time 900ms, TR 6.8ms, TE 2.91ms, flip angle 9º, FOV 256 (foot-to-head) x 240 (anterior-to-posterior) mm^2, matrix 256x240, in-plane resolution 1x1 mm^2, 160 slices, slice thickness 1.2 mm, voxel size 1x1x1.2 mm^3, total scan duration 9min 14sec.

Site 5a: GE Signa HDxt (Harvard Medical School, Boston MA): 3D acquisitions, sagittal slab, inversion time 650ms, TR 7.0ms, TE 3.0ms, flip angle 8º, FOV 256 (foot-to-head) x 256 (anterior-to-posterior) mm^2, matrix 256x256, in-plane resolution 1x1 mm^2, 166 slices, slice thickness 1.2 mm, voxel size 1x1x1.2 mm^3, total scan duration 9min 58sec.

Site 5b: Siemens Trio (Wayne State University, Detroit MI): 3D acquisitions, sagittal slab, shot interval 2300ms, inversion time 900ms, TR 6.8ms, TE 2.74ms, flip angle 8º, FOV 176 (foot-to-head) x 256 (anterior-to-posterior) mm^2, matrix 176x256x176, in-plane resolution 1x1 mm^2, slice thickness 1.2 mm, voxel size 1x1x1.2 mm^3, total scan duration 10min 09sec.

MRI Pre-processing

Structural measures were obtained using a standard pipeline in FreeSurfer v5.1 (5). After conversion of MRI data to NIfTI format, all images underwent rigorous data quality control as in Nanda et al. (6) and Padmanabhan et al. (7). Images were visually screened for scanner artifacts by trained raters. After this pre-check, they were run through a first-level auto-reconstruction (auto-recon1) in FreeSurfer. After auto-recon 1, brains were checked for remaining dura or sinus that could interfere with accurate segmentation. When non-brain tissue was found, images were edited manually by trained raters. All raters had inter-rater reliabilities (intra-class r) above 95%. An independent rater then approved the images for further processing and were run through auto-recon 2 & 3. Gray matter volume (GMV), cortical thickness (CT), cortical surface area (CSA), and local gyrification index (LGI) measures were then extracted from 68 cortical regions using a standard cortical parcellation (Desikan-Killiany Atlas) available in FreeSurfer (8, 9) (see Table S2).

Schizo-Bipolar Scale

Fifteen (5 from each diagnostic group) of the 438 individuals with psychosis included in the canonical correlation analysis had not been assigned Schizo-Bipolar Scale scores and were not included in further analyses. Assignment of SBS scores was performed by trained clinical raters across all B-SNIP sites. Intraclass Correlation Coefficients (ICCs) as well as other psychometric details of the SBS can be found in Keshavan et al. (10). Breakdown of SBS groups by DSM-IV diagnosis are in Table S3.

Supplementary Results

Symptom and Antipsychotic Medication Associations

Associations between latent variate scores, symptoms sub-scales, and anti-psychotic medication are listed in Table S4. There were a total of four significant associations after Bonferroni correction: the cognitive variate in the first pair of the CT (PANSSpos) and GMV (PANSSneg) analyses, the structural variate in the first pair of the CSA analysis (PANSSpos), and the structural variate in the second pair of the CT analysis (CPZ daily dose). All significant symptom associations were negative, with more severe symptomatology associated with lower scores on latent variates. Effect sizes for significant symptom associations, however, were small (ranging between $\eta^2 = .02$ and $\eta^2 = .03$). Larger daily CPZ doses were associated with higher latent scores on the CT structural variate (thinner cortex). The effect size, like those for symptoms, was small ($\eta^2 = .02$).

Table S1. List of Cognitive Assessments, Domain of Cognition Assessed, and Group-Wise Comparison of Normed Means

		HC		SBS 0-1		SBS 2-4		SBS 5-7		SBS 8-9		ANOVA		
Assessment	Cognitive Domain	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F (3,659)	p	Post hoc[c]
WRAT Reading Subtest	Premorbid IQ	104.5	13.7	104.5	13.8	100.1	14.1	98.8	16.3	95.9	16.1	11.8	<.0001	HC>SBS 5-7,SBS 8-9 SBS 0-1>SBS 8-9
BACS[a]														
TOL	Executive Function	0.1	1.1	-0.1	1.0	-0.4	1.3	-0.6	1.2	-0.6	1.3	12.6	<.0001	HC>SBS 2-4, SBS 5-7, SBS 8-9 SBS 0-1>SBS 8-9
Digit Sequencing	Working Memory	-0.05	1.1	-0.5	1.2	-0.5	1.1	-0.9	1.1	-1.2	1.2	31.4	<.0001	HC>all SBS SBS 0-1, SBS 2-4>SBS 8-9
Symbol Coding	Attention/ Processing Speed	0.1	1.0	-0.9	1.0	-1.0	1.0	-1.1	1.2	-1.4	1.2	74.9	<.0001	HC>all SBS SBS 0-1, SBS 2-4>SBS 8-9
Verbal Memory	Verbal Memory	0.02	1.0	-0.5	1.3	-0.6	1.2	-1.0	1.3	-1.1	1.5	25.6	<.0001	HC>all SBS SBS 0-1>SBS 5-7, SBS 8-9 SBS 2-4> SBS 8-9
Verbal Fluency	Processing Speed	0.2	1.0	-0.1	1.2	-0.1	1.3	-0.4	1.1	-0.7	1.1	22.8	<.0001	HC>SBS 2-4, SBS 5-7, SBS 8-9 SBS 0-1, SBS 2-4>SBS 8-9
TMT	Motor Speed	0.04	1.0	-0.8	1.2	-1.1	1.2	-1.2	1.2	-1.4	1.2	62.0	<.0001	HC>all SBS SBS 0-1>SBS 5-7, SBS 8-9
WMS Spatial Span[a]														
Forward Span	Working Memory	0.03	1.0	-0.5	1.1	-0.4	1.0	-0.4	1.1	-0.3	1.0	8.9	<.0001	HC>all SBS
Backward Span	Working Memory	0.1	0.9	-0.6	1.0	-0.5	1.1	-0.6	0.9	-0.6	1.1	24.9	<.0001	HC>all SBS
DPX[b]														
Correct RT	Reaction Time	-0.1	1.0	0.5	1.0	0.2	1.1	0.5	1.2	0.7	1.4	18.6	<.0001	HC< SBS 0-1, SBS 5-7, SBS 8-9 SBS 2-4<SBS 8-9
D-Prime	Signal Detection	0.1	0.8	-0.5	1.1	-0.5	1.2	-0.5	1.2	-0.7	1.4	19.6	<.0001	HC>all SBS
BX-AY	Goal Maintenance/ Inhibition	-0.01	0.9	0.0	1.0	0.1	1.0	-0.1	1.2	0.0	1.1	.06	.62	
Antisaccades[b]														
Error Rate	Inhibition/ Working Memory	-0.1	1.0	0.7	1.5	0.8	1.7	1.1	1.6	1.7	1.8	44.6	<.0001	HC<all SBS SBS 0-1, SBS 2-4, SBS 5-7 < SBS 8-9

Assessment	Cognitive Domain	HC Mean	HC SD	SBS 0-1 Mean	SBS 0-1 SD	SBS 2-4 Mean	SBS 2-4 SD	SBS 5-7 Mean	SBS 5-7 SD	SBS 8-9 Mean	SBS 8-9 SD	ANOVA F (3,659)	ANOVA p	ANOVA Post hoc[c]
Correct RT	Reaction Time	-0.01	1.0	0.4	1.1	0.3	1.4	0.4	1.3	0.6	1.4	8.9	<.0001	HC<SBS 8-9

WRAT = Wide Range Achievement Test; BACS = Brief Assessment of Cognition in Schizophrenia; TOL = Tower of London; TMT = Token Motor Task; WMS= Wechsler Memory Scale; DPX = Dot Pattern Expectancy Task; RT = Reaction Time; HC= Healthy Control

[a]Means were calculated on z-scores and based on respective test norms.

[b]Means were calculated on z-scores and based on the study-wide healthy comparison sample without any elevated Cluster A traits.

[c]Post hoc tests were performed using Tukey's HSD. Comparisons listed were significant at $p < .05$.

Table S2. CCA Regions of Interest

Lobe	Component Sub-regions (Right and Left)
Frontal	Caudal middle frontal, rostral middle frontal, medial orbitofrontal, lateral orbitofrontal, frontal pole, pars opercularis, pars orbitalis, pars triangularis, superior frontal, precentral, and paracentral regions
Parietal	Inferior parietal, superior parietal, supramarginal, precuneus, and postcentral regions
Temporal	Bank of superior temporal sulcus, inferior temporal, middle temporal, superior temporal, fusiform, entorhinal, parahippocampal, transverse temporal, temporal pole, and insula regions
Occipital	Cuneus, lingual, pericalcarine, and lateral occipital regions
Cingulate	Caudal anterior cingulate, isthmus cingulate, rostral anterior cingulate, and posterior cingulate regions

Regions of the Desikan-Killiany Atlas used for each CCA analysis.

Table S3. Schizo-Bipolar Scale Groups by DSM IV Diagnosis

		DSM Diagnosis		
		BP	SAD	SZ
Schizo-Bipolar Scale (SBS) Score	0-1	92	0	0
	2-4	56	41	2
	5-7	0	60	38
	8-9	0	10	124

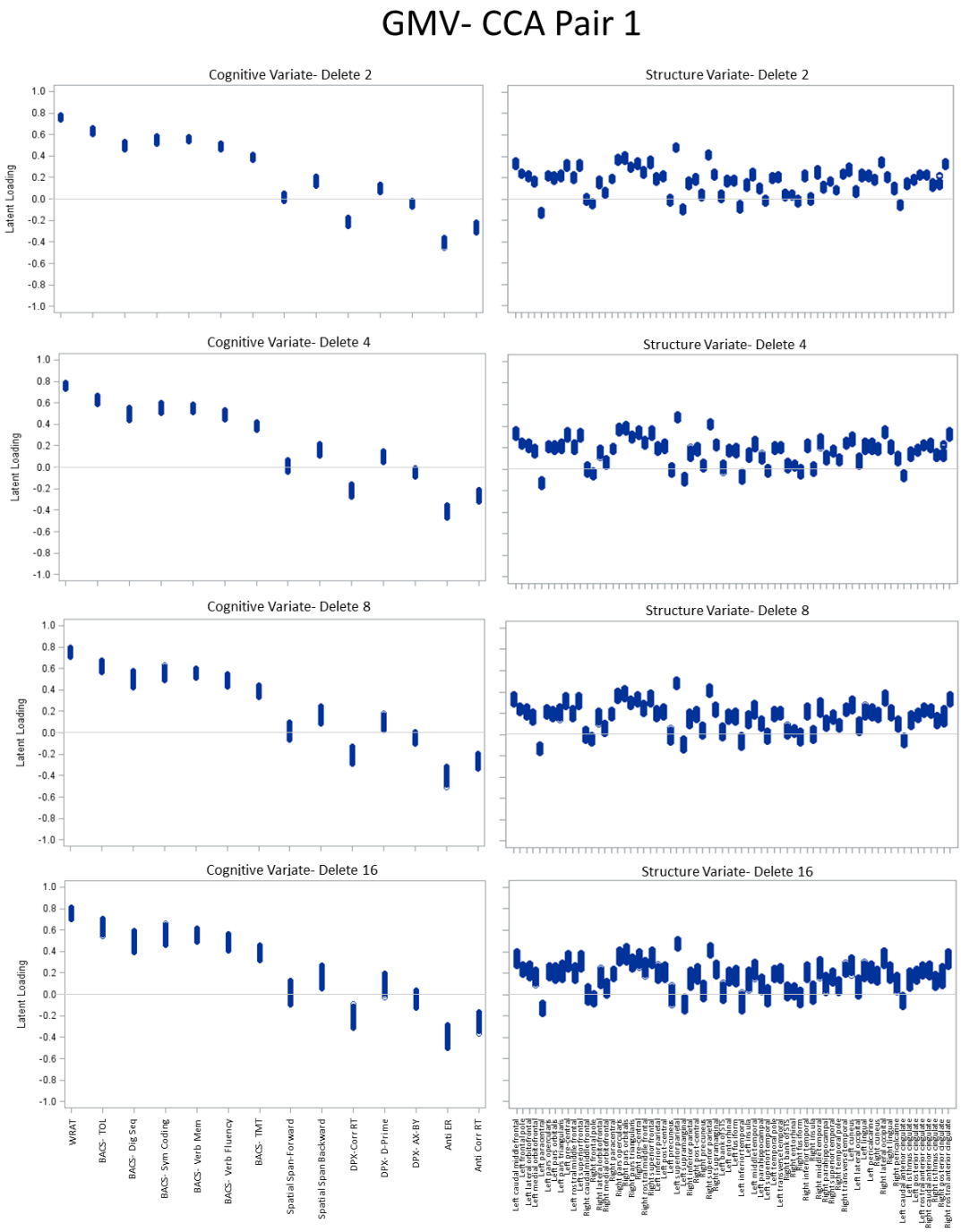
Cells show number of DSM diagnoses in each of the groups determined by the SBS. DSM = Diagnostic and Statistical Manual; BP= Bipolar with psychosis; SAD= Schizoaffective; SZ= Schizophrenia

Table S4. Symptom and Anti-psychotic Medication Effects on CCA Latent Variates

	PANSS Total			PANSS pos			PANSS neg			YMRS			MADRS			CPZ		
Cognitive Variates	β	p	η^2	β	p	η^2	β	p	η^2	β	p	η^2	β	p	η^2	β	p	η^2
Pair 1 GMV	-0.009	.005	0.02	-0.026	.005	0.02	-0.035	<.001[a]	0.03	< 0.001	.95	< 0.01	0.005	.38	< 0.01	< 0.001	.01	0.02
Pair 1 CT	-0.007	.02	0.01	-0.031	.001[a]	0.03	-0.019	.04	0.01	-0.007	.40	< 0.01	0.008	.17	< 0.01	< 0.001	.02	0.02
Pair 1 CSA	-0.006	.05	0.01	-0.021	.02	0.01	-0.020	.04	0.01	< 0.001	.95	< 0.01	0.006	.29	< 0.01	< 0.001	.05	0.01
Pair 1 LGI	-0.007	.04	0.01	-0.018	.06	0.01	-0.024	.01	0.02	< 0.001	1.00	< 0.01	0.006	.25	< 0.01	< 0.001	.04	0.02
Pair 2 GMV	0.001	.78	< 0.01	0.004	.62	< 0.01	-0.008	.39	< 0.01	0.004	.65	< 0.01	0.005	.37	< 0.01	< 0.001	.65	< 0.01
Pair 2 CT	0.004	.27	< 0.01	< 0.001	1.00	< 0.01	0.025	.01	0.02	-0.020	.02	0.01	< 0.001	.93	< 0.01	< 0.001	.03	0.02
Pair 2 CSA	-0.003	.35	< 0.01	-0.009	.30	< 0.01	-0.012	.17	< 0.01	-0.008	.29	< 0.01	0.003	.50	< 0.01	< 0.001	.87	< 0.01
Structural Variates																		
Pair 1 GMV	-0.007	.02	0.01	-0.030	.00	0.02	-0.026	.01	0.02	-0.002	.78	< 0.01	-0.002	.68	< 0.01	< 0.001	.17	0.01
Pair 1 CT	-0.008	.02	0.01	-0.028	.00	0.04	-0.018	.07	< 0.01	0.003	.72	< 0.01	-0.003	.53	< 0.01	< 0.001	.13	< 0.01
Pair 1 CSA	-0.007	.02	0.01	-0.036	<.001	0.02	-0.009	.35	0.01	0.006	.49	< 0.01	-0.001	.87	< 0.01	< 0.001	.94	0.01
Pair 1 LGI	-0.008	.01	0.02	-0.022	.014	0.02	-0.018	.05	0.01	-0.006	.44	< 0.01	0.001	.90	< 0.01	< 0.001	.83	< 0.01
Pair 2 GMV	-0.003	.28	< 0.01	-0.009	.32	< 0.01	-0.020	.02	0.01	-0.002	.84	< 0.01	-0.002	.68	< 0.01	< 0.001	.18	0.01
Pair 2 CT	-0.006	.07	0.01	-0.013	.15	0.01	-0.002	.82	< 0.01	-0.015	.08	0.01	-0.014	.01	0.02	0.001	.002[a]	0.03
Pair 2 CSA	-0.004	.16	< 0.01	-0.017	.06	0.01	-0.012	.17	< 0.01	-0.007	.35	< 0.01	-0.010	.06	0.01	< 0.001	.16	0.01

Table shows parameter estimates, p-values, and eta^2 for the effects of symptoms and antipsychotic medication on CCA latent variates. GMV = Volume Analysis; CT= Cortical Thickness Analysis; CSA= Surface Area Analysis; LGI= Gyrification Analysis; PANSS= Positive and Negative Syndrome Scale, YMRS=Young Mania Rating Scale, MADRS=Montgomery Asberg Depression Rating Scale; CPZ= Chlorpromazine Equivalent

[a]Significant at Bonferroni corrected p = .003.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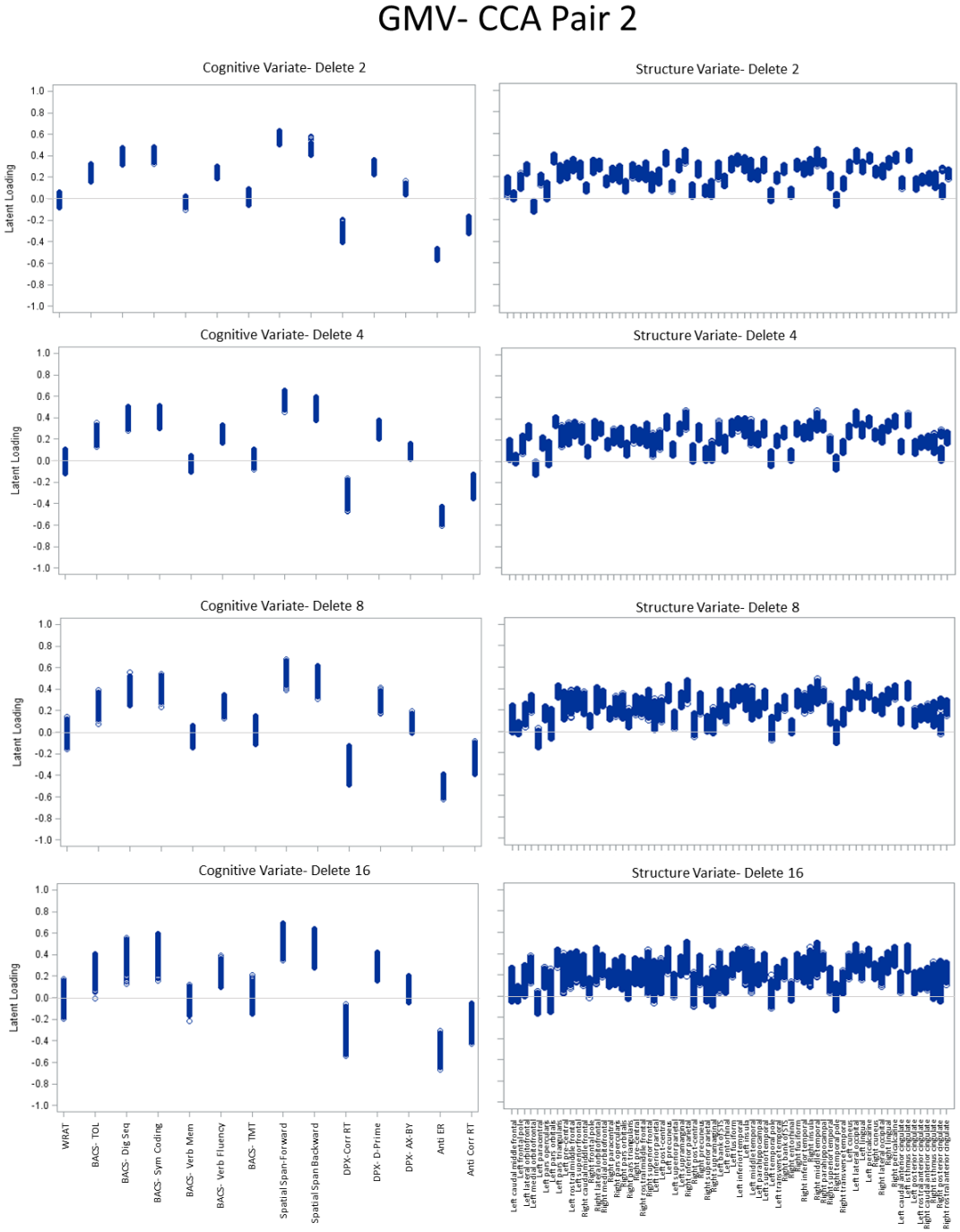
Structure Variate- Delete 2
Cognitive Variate- Delete 4
Structure Variate- Delete 4
Cognitive Variate- Delete 8
Structure Variate- Delete 8
Cognitive Variate- Delete 16
Structure Variate- Delete 16
Latent Loading
WRAT
BACS- TOL
BACS- Dig Seq
BACS- Sym Coding
BACS- Verb Mem
BACS- Verb Fluency
BACS- TMT
Spatial Span-Forward
Spatial Span Backward
DPX- Corr RT
DPX- D-Prime
DPX- AX-BY
Anti ER
Anti Corr RT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Cognitive Variate- Delete 8
Structure Variate- Delete 8
Cognitive Variate- Delete 16
Structure Variate- Delete 16
Latent Loading
WRAT
BACS- TOL
BACS- Dig Seq
BACS- Sym Coding
BACS- Verb Mem
BACS- Verb Fluency
BACS- TMT
Spatial Span-Forward
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DPX-Corr RT
DPX- D-Prime
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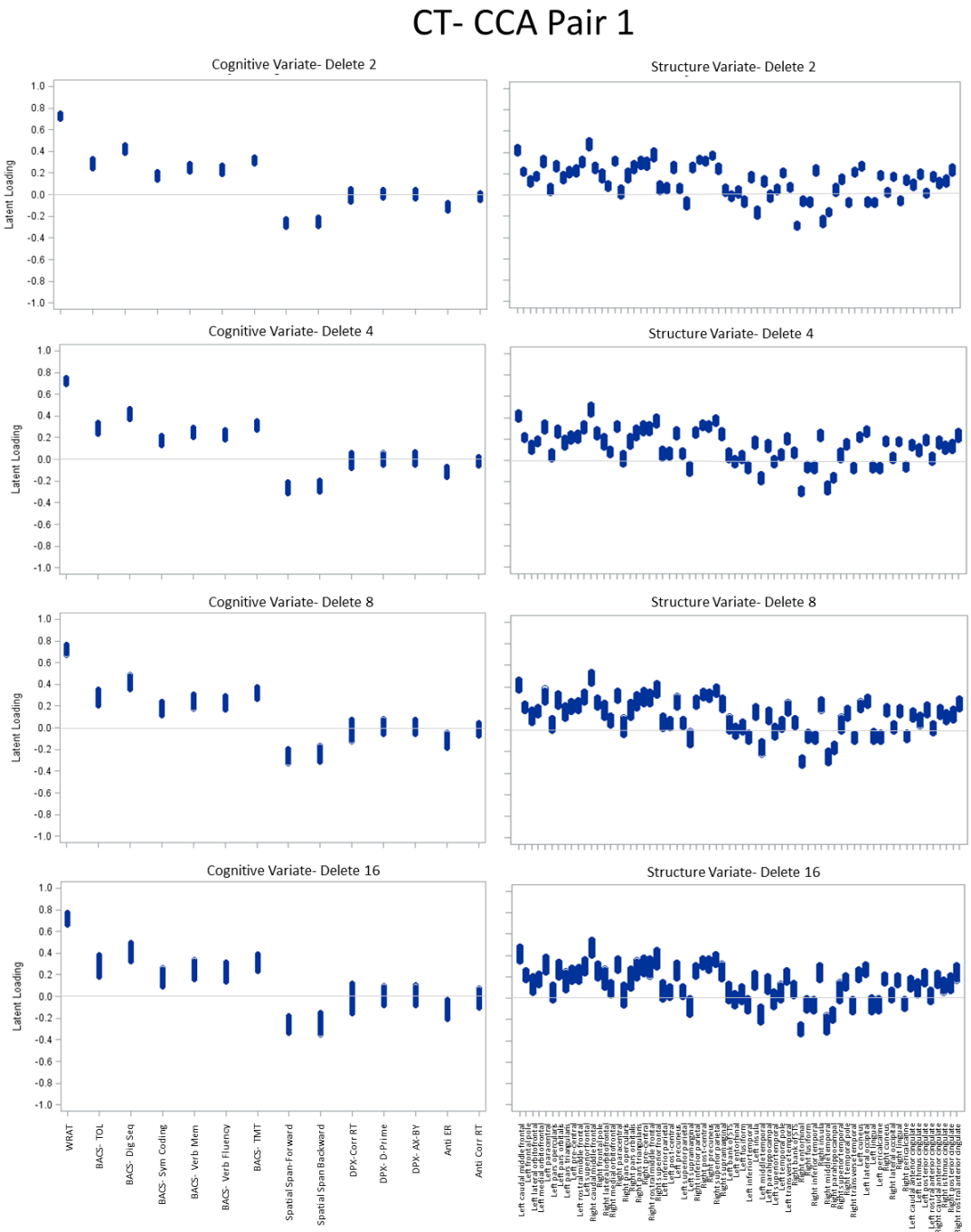
Anti ER
Anti Corr RT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Structure Variate- Delete 8
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Structure Variate- Delete 16
Latent Loading
WRAT
BACS- TOL
BACS- Dig Seq
BACS- Sym Coding
BACS- Verb Mem
BACS- Verb Fluency
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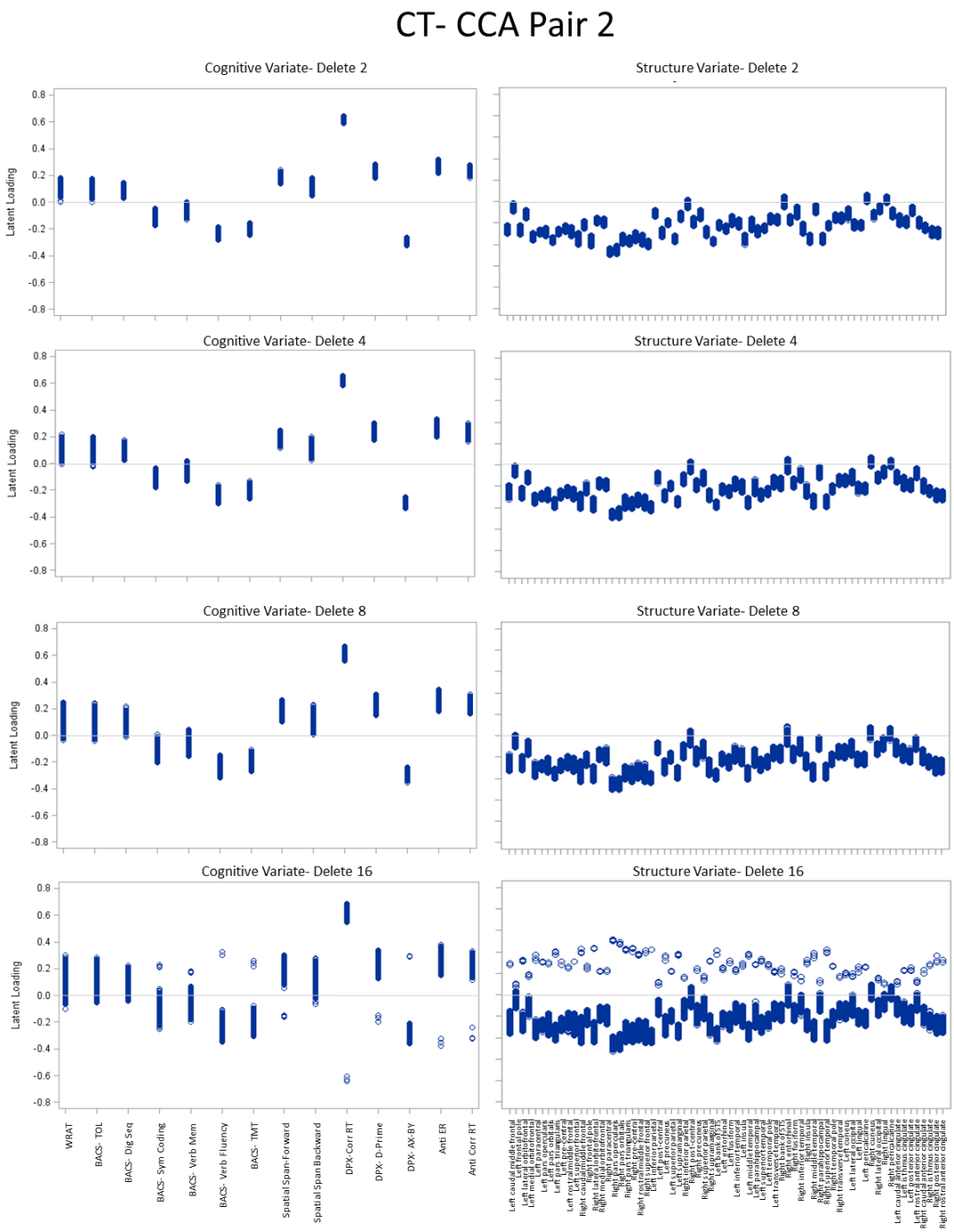
DPX- D-Prime
DPX- AX-BY
Anti ER
Anti Corr RT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Structure Variate- Delete 8
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Structure Variate- Delete 16
Latent Loading
WRAT
BACS- TOL
BACS- Dig Seq
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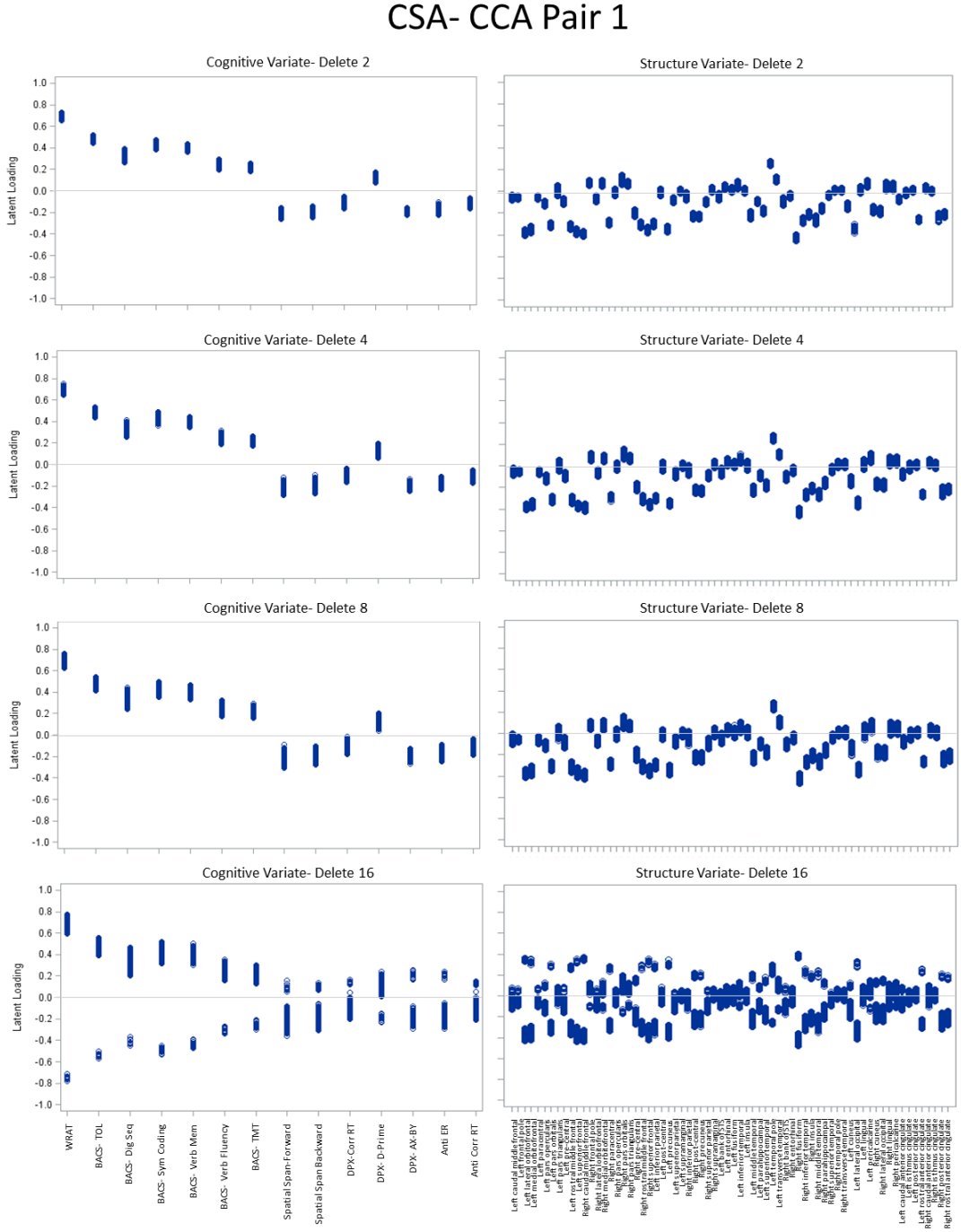
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Structure Variate- Delete 8
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Structure Variate- Delete 16
Latent Loading
WRAT
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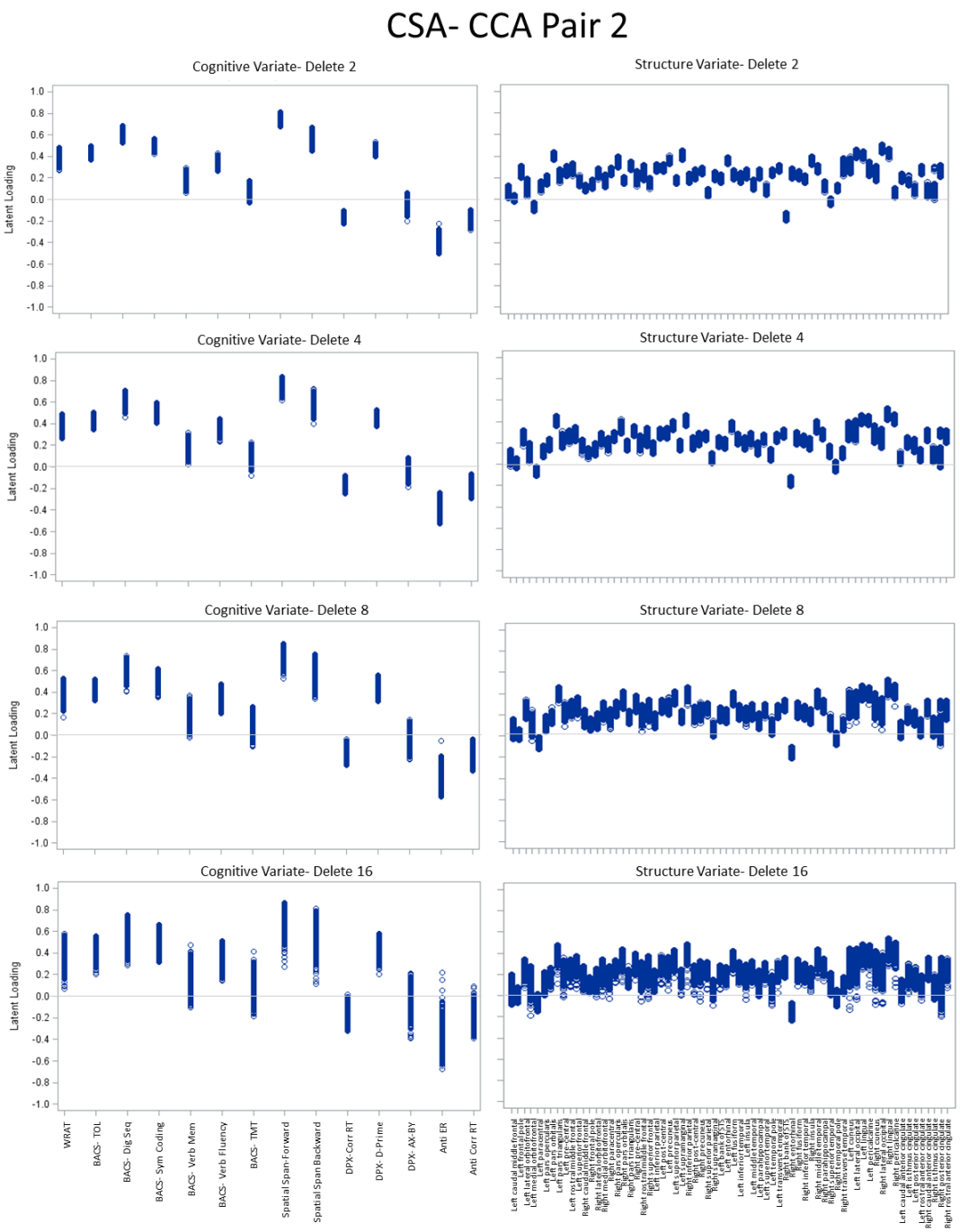
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Structure Variate- Delete 4
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Structure Variate- Delete 8
Cognitive Variate- Delete 16
Structure Variate- Delete 16
Latent Loading
WRAT
BACS- TOL
BACS- Dig Seq
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BACS- Verb Mem
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Anti ER
Anti Corr RT

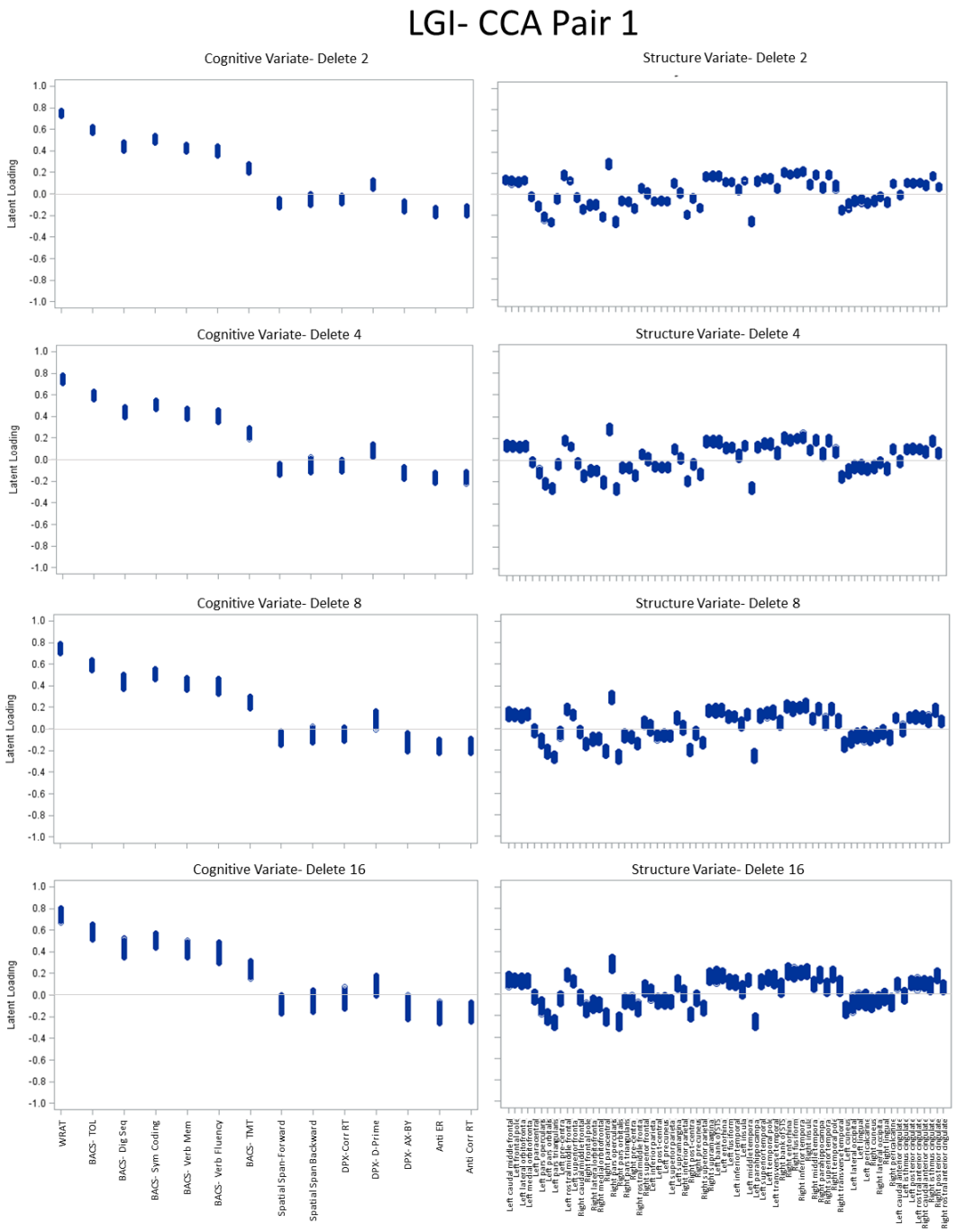

Figure S1. Jackknife Iteration Results. Plots show distribution of canonical loadings of individual measures across the 10,000 jackknife replicates for CCA pair 1 and 2 for the delete 4, 8, and 16 iterations. Reference lines are placed at zero to distinguish which individual measures included zero within the 99% confidence limits and those that did not. This aided in selection of CCA pairs for further interpretation and analysis. WRAT = Wide Range Achievement Test; BACS = Brief Assessment of Cognition in Schizophrenia; TOL = Tower of London; Dig Seq = Digit Sequencing; Sym Coding = Symbol Coding; Verb Memory = Verbal Memory; Verb Fluency = Verbal Fluency; TMT = Token Motor Task; DPX = Dot Pattern Expectancy Task; Anti = Antisaccade; ER = Error Rate; Corr RT = Correct Reaction Time

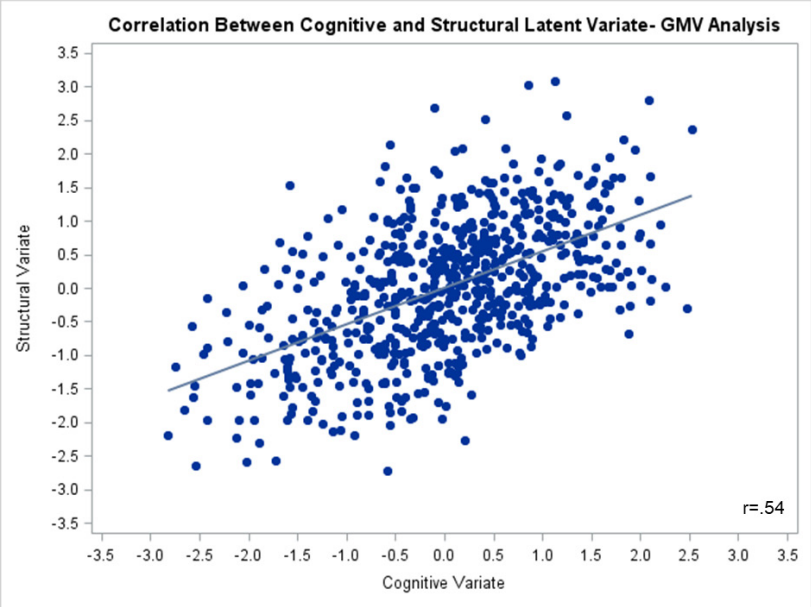

Figure S2. CCA Correlation. Plot shows the correlation between cognitive and structural latent variates from the first pair of the GMV CCA with regression line. Each dot is an individual. Given that all CCA pairs looked similar, we present only one pair here as a model.

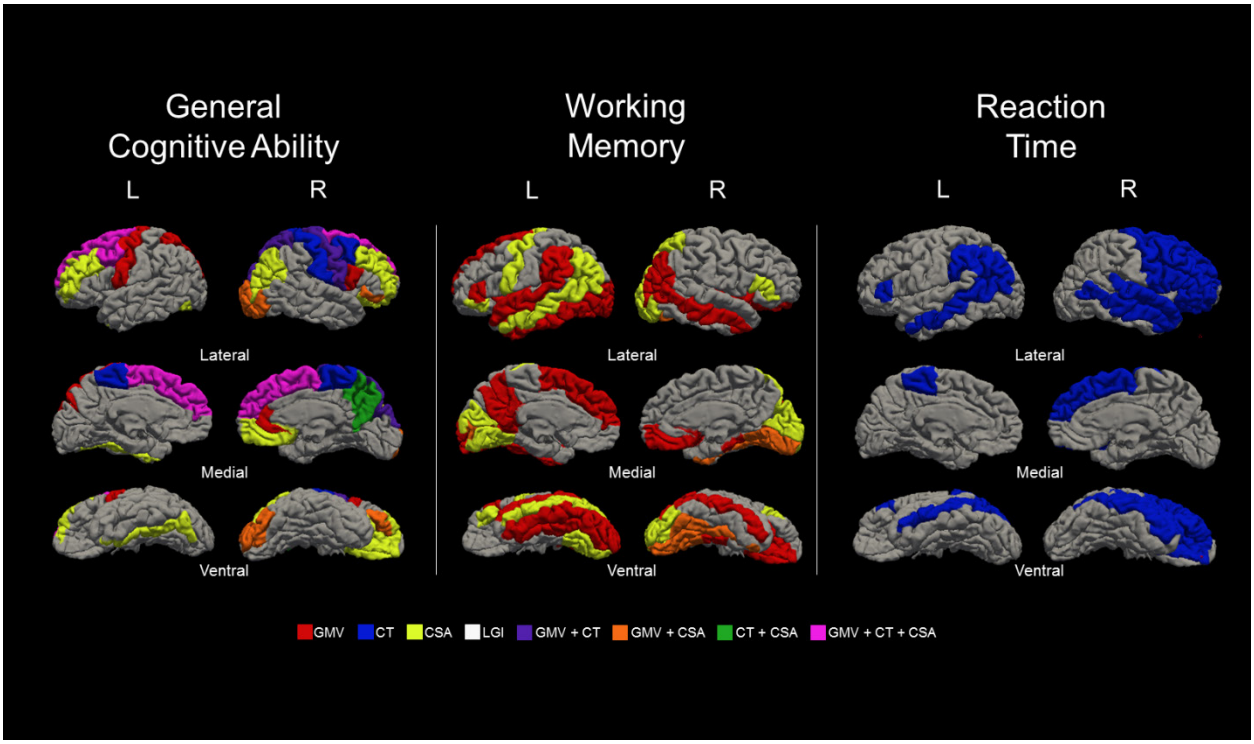

Figure S3. Spatial Pattern of Structural Loadings. Images show brain regions associated with particular cognitive abilities based on loadings obtained from the CCAs. Colors show regions with a loading beyond .3 and -.3 (moderate effect) in one or more of the CCA pairs. Regions with loadings beyond .3 in singular CCAs are in primary colors (red, blue, yellow); regions with loadings beyond .3 in multiple CCAs are a mixture of the primary colors used for the singular analyses (purple (red +blue), orange (red+yellow), green (blue+yellow)). Pink regions loaded highest in GMV, CT, and CSA analyses. General cognitive ability was associated with frontal and parietal regions. Working memory was associated with frontal-temporal regions. Reaction time was associated with regions in frontal/temporal cortex particularly in the right hemisphere and select parietal regions in the left hemisphere.

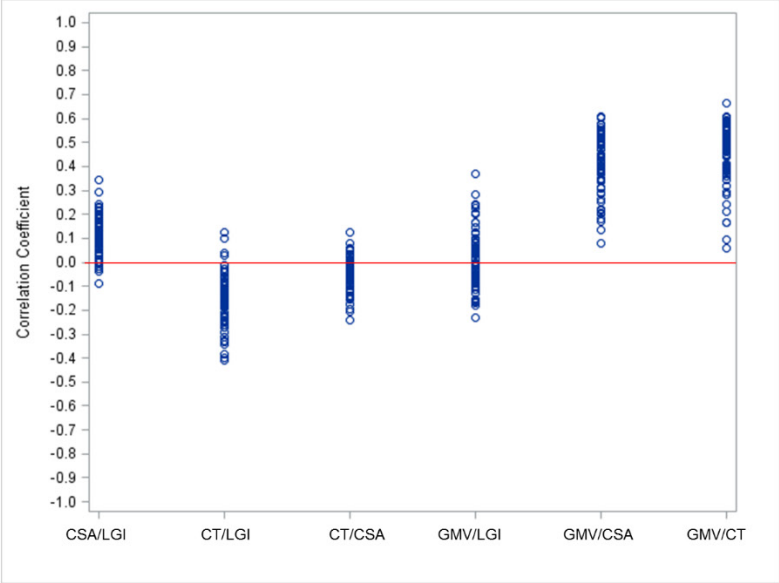

Figure S4. Correlations between Structural Measures for each ROI. Plot shows the correlations between each pair of structural measures for each ROI (blue dots). A red reference line marks a correlation coefficient of 0 (no relationship). The strongest and most consistent correlations are for those between GMV and CSA and GMV and CT, both positive. This is expected given that larger volumes can result from thicker cortices, larger surface area or both.

Table S5. Figure S3 Region Colors

ROI	General Cognitive Ability	Working Memory	Reaction Time
Left caudal middle frontal	pink		
Left lateral orbitofrontal			
Left medial orbitofrontal			
Left paracentral	blue		blue
Left pars opercularis			
Left pars orbitalis		yellow	
Left pars triangularis		red	blue
Left precentral	red	yellow	
Left rostral middle frontal	yellow		
Left superior frontal	pink	red	
Left frontal pole			
Right caudal middle frontal	blue		blue
Right lateral orbitofrontal	yellow	red	blue
Right medial orbitofrontal	yellow	red	
Right paracentral	blue		
Right pars opercularis	red		blue
Right pars orbitalis	orange		blue
Right pars triangularis		yellow	blue
Right precentral	purple		blue
Right rostral middle frontal	yellow		blue
Right superior frontal	pink		blue
Right frontal pole			
Left inferior parietal		yellow	blue
Left postcentral			
Left precuneus		red	
Left superior parietal	red		
Left supramarginal		red	blue
Right inferior parietal	yellow	red	
Right postcentral	blue		

ROI	General Cognitive Ability	Working Memory	Reaction Time
Right precuneus	green		
Right superior parietal	purple	yellow	
Right supramarginal			
Left bank of the STS			blue
Left entorhinal			
Left fusiform	yellow	red	
Left inferior temporal		red	
Left middle temporal		yellow	blue
Left parahippocampal			
Left superior temporal		red	
Left temporal pole			
Left transverse temporal			
Left insula		red	
Right bank of the STS			
Right entorhinal			
Right fusiform		orange	
Right inferior temporal			
Right middle temporal		red	blue
Right parahippocampal		red	
Right superior temporal			blue
Right temporal pole			
Right transverse temporal			
Right insula		red	
Left cuneus		yellow	
Left lateral occipital		red	
Left lingual		yellow	
Left pericalcarine		orange	
Right cuneus		yellow	
Right lateral occipital	orange	yellow	
Right lingual		orange	

ROI	General Cognitive Ability	Working Memory	Reaction Time
Right pericalcarine		orange	
Left caudal anterior cingulate			
Left isthmus cingulate		red	
Left posterior cingulate			
Left rostral anterior cingulate			
Right caudal anterior cingulate			
Right isthmus cingulate			
Right posterior cingulate			
Right rostral anterior cingulate	red		

Color key for Figure S3 for each cognitive domain represented by the CCAs. Regions with any color had moderate loadings (>.3 and > -.3) on one or more of the CCA structural variates. Regions in gray in Figure S2 are blank in the above table. Individual color values indicate in which CCA the ROI had moderate loadings. red= GMV analysis only, blue= CT analysis only, yellow=CSA analysis only, purple= GMV and CT analyses, orange=GMV and CSA analyses, green= CT and CSA analyses, pink=GMV, CT, and CSA analyses.

Supplementary References

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