**Multivariate Association between Functional Connectivity Gradients and Cognition in Schizophrenia Spectrum Disorders**

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**Running title**: Gradient-cognition associations in schizophrenias

**Keywords**: principal gradient analysis, schizophrenia spectrum disorders, social cognition, functional connectivity, partial least squares correlation, fMRI

Number of Words in abstract: 235

Number of Words: 3960

Number of Figures: 4

Number of Tables: 3

**Abstract**

**Background:** Schizophrenia Spectrum Disorders (SSDs), which are characterized by social cognitive deficits, have been associated with dysconnectivity in “unimodal” (e.g., visual, auditory) and “multimodal” (e.g., default-mode and frontoparietal) cortical networks. However, little is known regarding how such dysconnectivity relates to social and non-social cognition, and how such brain-behavioral relationships associate with clinical outcomes of SSD.

**Methods:** We analyzed cognitive (non-social and social) measures and resting-state functional magnetic resonance imaging data from the ‘Social Processes Initiative in Neurobiology of the Schizophrenia(s) (SPINS)’ study (301 stable SSD and 185 healthy controls, ages 18-55). We extracted gradients from parcellated connectomes and examined the association between the first 3 gradients and the cognitive measures using partial least squares correlation (PLSC). We then correlated the PLSC dimensions with functioning and symptoms in the SSD group.

**Results:** The SSD group showed significantly decreased differentiation on all three gradients. The first PLSC dimension explained 67.39% (*p<*.001) of the covariance and showed a significant difference between SSD and controls (bootstrap *p*<.05). PLSC showed that all cognitive measures were associated with gradient scores of unimodal and multimodal networks (Gradient 1), auditory, sensorimotor, and visual networks (Gradient 2), and perceptual networks and striatum (Gradient 3), which were less differentiated in SSD. Furthermore, the first dimension was positively correlated with negative symptoms and functioning in SSD.

**Conclusions:** These results suggest a potential role of decreased differentiation of brain networks in cognitive and functional impairments in SSDs.

**Introduction**

Schizophrenia spectrum disorders (SSDs) are characterized by positive, negative, and general psychopathology symptoms, as well as deficits in social and non-social cognition that affect daily life. Two prior studies found consistent network segregation patterns in SSDs characterized by dysconnectivity in “unimodal” (e.g., visual, auditory) and “multimodal” (e.g., default mode, frontoparietal) cortical networks (1,2). Such changes in cortical network configuration can be explored using an emerging technique known as principal gradient analysis, which is a data reduction method used to characterize participants’ brain connectivity profiles (3). This approach provides a topographical representation of functional connectivity and network organization by extracting principal gradients (i.e., a type of latent dimension) from a participant’s brain connectivity pattern and identifying the dominant network segregation patterns from each gradient.

Human behaviors and cognitions are often generated from the coordinated functioning of different brain regions (4), which is closely linked to the geometry of brain (5). By integrating geodesic features, gradient analysis generates hierarchical levels in brain network organizations that map onto different levels of cognition, and has been used to examine how functional connectivity relates to cognition; e.g., creativity performance (6) and semantic cognition (7,8), where the neurocognitive system of semantic cognition was found to also regulate social cognition (9). By using such gradient technique to examine functional connectivity of SSDs, recent studies found that, compared to controls, people with SSDs feature less distinct unimodal-multimodal (1,10,11) and visual-sensorimotor (1,12) network segregations; because the decreased segregation is represented by networks moving toward the center from both ends of the gradient axes, it is termed ‘gradient compression.’ In these studies, the gradient compression on the unimodal-multimodal axis was found to correlate with clinical symptoms (1,11) and lower processing speed (11). As people with SSDs vary extensively in symptoms (13), treatment response (14,15), cognition (16,17), and brain activity (18–20), gradient analysis provides a general principle of quantifying functional brain organization to investigate individual differences in brain configurations of SSD while accounting for heterogeneous brain features, which relate to treatment responses (21) and psychotic symptoms (1,11,21) of people with SSDs.

Social and non-social cognition are critically important to functioning in people with SSDs (22). Recent work by our group suggests that non-social cognitive performance, and particularly social cognitive performance may relate to network segregation in people with SSDs (2,20). With a large sample of participants measured on social and non-social cognition, application of gradient analysis may help further our understanding of how network segregation relates to these two aspects of cognitive deficits in SSDs. As social and non-social cognition are strongly related to functional outcomes (2,21,23,24), further examination on brain gradient-cognitive relationships can reveal how such relationships influence individual differences in the functional outcomes in SSDs.

To examine brain gradient-cognitive relationships, we used data from the National Institute of Mental Health (NIMH)-funded “Social Processes Initiative in the Neurobiology of Schizophrenia(s) (SPINS)” multicenter study (24). These harmonized data included functional brain imaging and comprehensive assessments of both social and non-social cognition. To account for inter-assessment associations and maximize statistical power, we examined brain-behavior relationships with a multivariate approach, which extracts latent dimensions that identify the dominant association between large sets of variables. The individual differences within associations were then used to examine how brain-behavior relationships manifest individual differences in functioning. In addition to replicating prior findings of gradient compression in SSDs, we specifically aimed to 1) identify the gradients that are associated with social and non-social cognition, and 2) examine how such associations contribute to clinical outcomes, including functioning, quality of life, and clinical symptoms in people with SSDs.

**Methods and Materials**

**Participants**

In total, 301 participants with SSDs and 185 Controls were recruited for the SPINS study (24). The diagnoses of SSDs (i.e., schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, and psychotic disorder) were based on the DSM-5 as assessed by the Structured Clinical Interview for DSM (SCID-IV-TR). All participants with SSDs had no changes in antipsychotic medication or functioning/support level for 30 days before enrollment. Participants were excluded if they had a history of head trauma, substance use disorder, intellectual disability, unstable medical illness, or other neurological diseases. Controls were excluded if they had any lifetime Axis I psychiatric disorder (except adjustment disorder, phobic disorder, and past major depression with 2+ years remission and currently unmedicated) or a first-degree relative with a psychotic disorder. Chlorpromazine (CPZ) equivalents were calculated for the 222 participants with SSDs based on available medication information (25). All participants provided informed consent; the research followed the Declaration of Helsinki and was approved by relevant ethics and institutional review boards.

**Demographics, Cognitive, and Clinical Assessment**

Premorbid IQ was estimated by the Wechsler Test of Adult Reading (WTAR) (26). Psychiatric symptoms in SSDs were evaluated using the Brief Psychiatric Rating Scale (BPRS) (27) and Scale for the Assessment of Negative Symptoms (SANS) (28,29). Functional outcomes were assessed using the Birchwood Social Functioning Scale (BSFS) (30) and Quality of Life Scale (QLS) (31).

The study collected a comprehensive battery of non-social and social cognitive measures that have previously been described in detail (24,32). Non-social cognition was assessed using the 6 domain scores of the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) (33): processing speed, reasoning/problem solving, attention/vigilance, working memory, verbal learning, and visual learning. The social cognitive battery included the Penn Emotion Recognition Test (ER40) (34), Reading the Mind in the Eyes Test (RMET) (35), and The Awareness of Social Inference Test – Revised (TASIT) (36), which included three sub-tests: TASIT 1, identifying emotions; TASIT 2 minimal social inferences including sincere, simple sarcasm, and paradoxical sarcasm; and TASIT 3 measuring social inferences (lies and sarcasm) with enriched contextual cues. These 14 cognitive variables (including ER40 total, RMET total, TASIT 1 total, 3 subscores from TASIT 2, 2 subscores from TASIT 3, and the 6 domain scores from MCCB) were used as cognitive data to examine associations with the principal gradients.

**MRI Data Acquisition and Quality Control**

Multimodal MRI scans were obtained using 3T scanners with multichannel head coils (see **Supplementary Material**). Anatomical T1-weighted scans were collected using a fast-gradient sequence (0.9mm isotropic voxels, see supplemental for site specific parameters). Resting-state scan was a 7-minute EPI sequence (TR=2000 ms, TE=30 ms, flip angle=77°, field of view=20°, in-plane resolution=3.125 mm2, and slice thickness=4 mm). Participants were instructed to let their mind wander with their eyes closed.

All scans were quality checked before and after being preprocessed by fMRIPrep 1.5.8 (37) and ciftify 2.3.1 (38) workflows. From the preprocessing, all scans were performed nuisance regression to correct for head motion, white matter signal, cerebral spinal fluid signal, and the global signal (see details for imaging preprocessing in **Supplementary Material**). Participants with excessive motion (mean framewise displacement>0.5 mm) were excluded from further analysis (see **Figure S1**).

**Connectivity Matrix Construction**

To construct connectivity matrices, we parcellated the brain using the cortical Multimodal Parcellation (39) atlas (360 regions) and the Melbourne Subcortex Atlas (40) with all cortical regions categorized into twelve networks according to the Cole-Anticevic Brain Network Parcellation (41) (see **Figure 1A**), with the subcortical regions grouped separately. For each participant, a 392 × 392 functional connectivity matrix was created via the Fisher *Z*-transformation of the Pearson’s correlation of the time-series from each parcel. Finally, we used the neuroCombat R package to perform ComBat, a batch-effect correction, on the *Z*-transformed connectivity to harmonize the connectivity data across 6 MRI scanners (42,43).

**Network Hierarchy Measures: Gradient Analysis**

To quantify network hierarchy, gradient analysis uses a dimension reduction approach to extract principal gradients from a brain connectivity matrix. In the procedure, the data were transformed back to Pearson correlation coefficients after ComBat, and the data for each participants underwent diffusion map embedding (44) using the *BrainSpace* package (45) to extract principal gradients (3). These gradients capture specific network segregations that contribute to the overall functional connectivity pattern. Gradients are ordered such that they contribute to the total variance in a descending order. Principal gradients also account for geodesic features between brain regions – i.e., given the assumption that two closer brain regions are more likely to be functionally connected, the geodesic features are accounted for such that two regions that are physically closer are also more likely to be closer in values on these gradients. To allow comparisons between gradients across participants, we aligned them via Procrustean rotation with a template gradient map (3). This gradient map reveals the three gradients shown in **Figure 1B-C**. The ROIs are represented by scores on each gradient, and these gradient scores are averaged across brain networks to illustrate the representations of these networks on these gradients. As expected, the first gradient differentiates connectivity between the unimodal networks (e.g., primary and secondary visual (VIS1 and VIS2), auditory (AUD), and somatomotor (SMN) networks) from the multimodal networks (e.g., default mode (DMN), frontoparietal (FPN), and language (LAN) networks). The second gradient further differentiates connectivity within the unimodal networks (i.e., VIS1 and VIS2 vs. AUD and SMN), and the third gradient differentiates within the multimodal networks (i.e., DMN and LAN vs. FPN and cingular opercular network (CON)). This gradient analysis was performed with Python 3.8.6-GCCcore-10.2.0. Distributions of eigenvalues of all extracted gradients are shown in **Figure S2** to illustrate the variance explained by each gradient.

**Statistical Analyses**

We examined group differences between participants with SSDs and controls in demographics and cognition with two-sample *t*-tests (or equivalent tests to account for non-normally distributed or heterogeneous data; see **Supplementary Material**). Group differences (SSD-control) in gradient scores were also examined with two-sample *t*-tests using the linear model approach (i.e., the *lm* function in R) and were corrected for multiple comparisons with a false discovery rate (FDR) approach (*q*<.05). From the linear model, we report the number (*n*) of significant ROIs of each network with their range of *F*-statistics.

Multivariate associations between the cognitive and network hierarchy measures across SSD and control groups were then analyzed by partial least squares correlation (PLSC) (46), relating 14 cognitive variables (8 social cognitive scores and 6 MCCB domain scores) to 1176 brain variables (gradient scores of the first 3 dimensions of 392 brain regions). Age, sex, and mean framewise displacement (FD) were regressed out from all behavior and brain measures prior to PLSC. In PLSC, each variable is centered (i.e., having a mean of 0) and normalized (such that the sum of squared values equals 1). PLSC then extracts, from their cross product, latent dimensions, which are analogous to components in principal component analysis (PCA), explaining associations between the brain and cognitive measures. On each dimension, PLSC generates pairs of latent variables, analogous to factor scores in PCA; consisting of one computed from the cognitive variables (i.e., *cognitive scores*) and one from the brain variables (i.e., *brain scores*), which together have maximum covariance. Significance of PLSC dimensions was assessed via permutation tests (47), while bootstrap tests (48) were used to examine the stability of the loadings for each variable. From both tests, we derived *p* values to indicate significant differences. Additionally, the bootstrap test gives a *Z-*analogous statistic called bootstrap ratio (BR), of which a value of 2.88 is associated with a *p* of .005. This allows identification of variables which significantly contribute to each dimension. The effect sizes of variables were quantified by their contributions, computed as squared loadings, to determine the importance of each variable to each dimension. See **Supplementary Material** for further details.

To examine the clinical representation of PLSC results, we performed Pearson correlation tests within the SSD sample between the brain and the cognitive scores from PLSC and all subscores of the symptom and functioning measures. Participants with missing values were removed from related analyses. Results were FDR-corrected for 8 comparisons with *q*<.05. All data analyses were performed using R 4.1.1 (49) with PLSC being performed using the *TExPosition* and the *data4PCCAR* packages (<https://github.com/HerveAbdi/data4PCCAR>).

**Results**

**Demographics and Behavioral Characteristics**

After quality control (detailed in **Figure S1**), the data analysis included 248 participants with SSDs (*M*age=31.42, *SD*age=9.77, 79 females) and 172 Controls (*M*age=31.95, *SD*age=10.40, 80 females). Participant characteristics and cognitive test scores are shown in **Table 1**. Two-sample *t*-tests showed no significant age difference between the SSD and the Control groups. SSD had lower mean scores than Controls for all cognitive measures except TASIT 2 sincere videos, consistent with prior findings (2,32) (See **Table 1**).

**Decreased Differentiation Across all Three Gradients in SSDs vs. Controls**

The significant group differences in gradients across brain regions are shown in **Figure 2A** and illustrated by arrows representing each region of interest (ROI) in **Figure 2B-2D** pointing from the mean gradient scores of Controls to those of the SSD group. Overall, participants with SSDs showed decreased differentiations at FDR-corrected *α=*0.05 along all three gradients. Specifically, on Gradient 1 (unimodal vs. multimodal), somatomotor (SMN), primary and secondary visual (VIS1 and VIS2), and default mode networks (DMN) are found to be less differentiated from auditory (AUD), cingulo-opercular (CON), frontoparietal (FPN), and subcortical (SUB) networks in participants with SSDs than in Controls, *q*<.05. Although participants with SSDs have reliably higher gradient scores compared to Controls for ROIs from the default mode network (DMN), these ROIs have different patterns from those of the other networks. Descriptively, the ROIs from other networks showed decreased differentiation between networks for participants with SSDs, whereas the ROIs from DMN showed decreased differentiation within the network for participants with SSDs, as indicated by red arrows moving towards each other or the mean scores in **Figures 2B**-**2D**, **S3** and **S4**. On Gradient 2 (visual vs. auditory), the SSD group has less differentiation of CON, SUB, SMN, AUD, and FPN from dorsal attention (DAN), VIS1, and VIS2, *q*<.05. Similar to Gradient 1, we also see decreased within-network differentiation in DMN (see **Figures S3** and **S4**). On Gradient 3 (default vs. frontoparietal), the SSD group showed decreased differentiation of CON and SUB from DAN, VIS1, VIS2, and language (LAN) networks, *q*<.05. Detailed statistics are reported in **Table 2** with ranges of significant *F* statistics and numbers of significant ROIs of each network.

**Multivariate analysis of cognitive-network hierarchy PLSC reveals a significant dimension, whereby networks with decreased differentiation relate to cognitive performance**

PLSC analysis identified one significant dimension, as determined by permutation test (*p*<.001), explaining 67.4% of the cognition-gradient covariance. This dimension features the general correlations between all cognitive measures (both social and non-social; **Figure 3A**) and network hierarchy (**Figure 3B**). The loadings in **Figure 3A** show that all cognitive measures contribute similarly (i.e., in the same direction). In this dimension, participants with SSDs and Controls are significantly different according to a bootstrap test both in brain and in cognitive scores as indicated by non-overlapping 95% bootstrap confidence intervals of their means (**Figure 3C**).

As Dimension 1 differentiates participants with SSDs from Controls, to better illustrate the PLSC results of network hierarchy, we plotted the group differences of each ROI in Figures **3D**-**3F** (similar to **Figures 2B-2D**) and highlighted those that contributed reliably (BR>2.88, *p*<.005).

Overall, this network hierarchy–cognition association, identified by the first dimension of PLSC, is driven by contributing ROIs, which also happened to show decreased differentiation along all three gradients. For instance, PLSC identified ROIs from SMN, VIS2, DMN and Thalamus, which in SSD showed decreased differentiations on Gradient 1 (unimodal vs. multimodal networks). For Gradient 2 (visual vs. auditory networks), PLSC identified ROIs from CON, AUD, SMN, FPN, VIS2, and DAN, where the decreased differentiations of SSD were found mainly between different perceptual networks; more specifically, between AUD, SMN, FPN, CON and VIS2 with DAN. For Gradient 3 (default vs. frontoparietal networks), PLSC identified ROIs from the perceptual, language, and subcortical networks, where decreased differentiations of SSD were found between the unimodal networks (i.e., VIS and SMN) and LAN versus SUB.

Given the heterogeneity of ROIs in the DMN, it is worth noting that these identified DMN ROIs identified for Gradient 1 are those that are located closer to the visual networks. On Gradient 2, the identified ROIs within DMN were those medial regions closer to FPN and temporal regions closer to VIS. Interestingly, the identified ROIs of Gradient 3 from SMN, CON, and AUD networks were also those that were close to LAN.

**The first PLSC dimension is significantly related to functioning via both brain scores and cognitive scores**

From the SSD group, the correlation between the first latent variables (i.e., the behavior and the brain scores) and the clinical assessments of functioning or symptoms are illustrated in **Figure 4**. **Figure 4A** shows that, for Dimension 1, the cognitive scores are negatively correlated with the total score of BSFS (*r*=-.19, *df*=246, CI=[-.31, -.07], *q*=.0029) and total scores of QLS (*r*=-.33, *df=*244, CI=[-.44, -.22], *q*<.0001), positively correlated with the SANS total score (*r*=.23, *df*=244, CI=[.11, .35], *q*=.0003), but have no significant correlation with symptoms on the BPRS total score (*r*=.12, *df*=246, CI=[.0003, .25], *q*=.0564). These correlations remained significant after controlling for CPZ dosage equivalent (**Table S1**).

Similarly, the brain scores of this dimension are negatively correlated with functioning, including the BSFS (*r*=-.25, *df*=246, CI=[-.36, -.13], *q*=.0002) and QLS (*r*=-.28, *df=*244, CI=[-.39, -.16], *q*<.0001, two missing values) total scores. However, these brain scores are positively correlated only with the SANS total score (*r*=.24, *df*=244, CI=[.12, .36], *q*=.0002), but not general psychopathology as measured by the BPRS total score (*r*=.11, *df*=246, CI=[-.01, .23], *q*=.0753). Correlation results with individual subscales are detailed in **Table 3** and **Figure 4B**.

**Discussion**

This study examined gradients from the resting-state functional connectivity of SSDs and Controls, using PLSC to explore multivariate associations with social and non-social cognition. Gradients offer an advantage of prior work focused on functional connectivity strength, as the gradient analysis considers topographical properties of how the brain networks are organized (e.g., in terms of well or poor segregation between unimodal and multimodal networks). With a well-powered sample, we successfully replicated prior findings of unimodal-multimodal (Gradient 1) (1,10,11) and visual-sensorimotor (Gradient 2) (12) gradient compressions in SSDs and extended those findings via a compression of Gradient 3 between different multimodal networks. The PLSC results revealed the association between compressions along three gradients and the group differences between SSDs and Controls in both social and non-social cognitive abilities. Finally, in the SSD group, the identified brain-cognition dimension was found correlated with clinical symptoms and functional outcomes with higher latent cognitive and brain scores correlated with higher negative symptoms and lower functioning and quality of life. Overall, by combining this rich brain, behavioral, and functioning data with advanced multivariate methods, we identified how changes in the underlying properties of brain network organization, specifically decreased differentiation of canonical networks, relates to cognitive impairments in SSDs, and ultimately psychopathology and functioning.

In contrast to previous gradient studies in SSD (1,11,12), we included a broad assessment of social cognitive measures and examined multivariate associations with network organization. Although PLSC does not differentiate social from non-social cognition in brain-behavioral associations, the results were not a surprise as non-social and social cognitive performance are correlated and depend on overlapping networks (2,22). Our study showed that the differences in general cognitive ability between participants with SSDs and Controls are most related to the compression between the networks of vision (VIS1 and VIS2) and CON, along with other sensory modalities (AUD and SMN). These results are similar to Dong et al. (1) and Holmes et al. (12) and could be related to atypical connectivity especially in the visual and auditory networks (50), which give rise to positive symptoms or changes in cognition (51). Furthermore, from Dimension 1 of our PLSC, we identified associations between cognition and decreased distinctions of two other areas: 1) between striatum and LAN on Gradient 3 and 2) between thalamus and unimodal networks on Gradient 1. These findings are consistent with increased thalamic-sensorimotor connectivity in previous literature (52–54) and support the hypothesis proposed by Andreasen et al. (55) that the dysfunction of the cortical-subcortical-cerebellar circuit (with thalamus being one of the main nodes) contributes to symptoms and cognitive deficits in SSDs. In addition, the contributing subcortical ROIs identified on Gradient 3 include caudate and nucleus accumbens, of which the connectivity to cortical regions were also found associated with improving psychosis after treatments for participants with first-episode SSDs (21).

Similar gradient compression has been shown in other populations and disorders, such as aging (56), sleep deprivation (57), usage of lysergic acid diethylamide (49), and to other psychiatric disorders, such as major depressive disorder (18) and autism spectrum disorder (ASD; 60). With similar cognitive challenges, SSDs and autism feature similar gradient compression, but different regions affected were found, which may relate to the difference between their symptom manifestation and onset time. Specifically for autism, another heterogenous disorder, Choi et al. (60) showed that only the most severe of three delineated subgroups featured gradient compression. Similar compression to SSDs was found in autism for sensorimotor regions, anterior cingulate cortex (ACC), visual cortex, and right inferior temporal cortex (ITC), where ACC and ITC were associated with semantic control and social cognition (9). Their study found compression in autism in the posterior cingulate cortex but not in the auditory network, which was found in our study, suggesting that disorder-specific functional brain organizations could exist.

Previous studies have shown the alignment between principal gradients and human microstructural gradients of brain regions and the T1/T2 myelination map (61–63). A significant proportion of gene sets that show differential expression across the myelination map are also shown associated with SSDs (64). As a result, the identified gradient compression of SSDs could be related to myelin abnormalities. As SSDs tend to present clinically while myelination is in progress, a “demyelination hypothesis” of SSDs has been proposed (65). Recently, decreased cortical myelination has been found in people with SSDs (65,66) encompassing inferior longitudinal fasciculus (ILF) and superior longitudinal fasciculus (SLF) (66). Between them, ILF connects temporal and occipital cortices, which align with the two ends of the visual-sensorimotor gradient, and SLF connects frontal and occipital cortices, which align with the two ends of the unimodal-multimodal gradient. Therefore, the observed visual-sensorimotor and unimodal-multimodal gradient compressions could be related to the disruption of myelination in these white matter tracts, ILF and SLF respectively, which connect those networks.

These results provide insights into the network mechanisms of SSDs but also have some sample characteristics that may influence the nature of our results. Participants with SSDs in the SPINS data set were on stable antipsychotic treatment. Although our correlation analysis replicated previous literature on the absence of an association between network compression and positive symptoms, this result could be influenced by examination of a clinically stable sample. Antipsychotic medication has also been shown to impact brain structure (67), though the effects on gradients are unknown - we regressed out CPZ equivalents to help address this issue. Furthermore, though site and motion effects were present in our data, they were mitigated using harmonization by statistical regression, and preprocessing workflows and quality checks, respectively. In addition, although our study only includes SSDs, the observed results could relate to general risk of mental health and future studies expanding into transdiagnostic samples is worthwhile.

The majority of prior work examining connectivity in SSDs and relation to cognition largely focused on the strength of specific connections (24,53,68). Gradients analysis allows exploration of broader changes in the organizational structure of these networks across individuals (3,56). Specifically, we found that reduced segregation across networks is associated with psychopathology and weaker performance in social and non-social cognition, which in turn predicts functional outcomes. We therefore propose that cognitive deficits in SSDs are not driven only by ‘reduced’ connectivity, but deficits in the organizational structure of canonical brain networks and consequent reductions in network segregation. The correlations within SSDs to clinical symptoms and functional outcomes demonstrates that these associations between gradients and cognition were clinically meaningful. These results provide insights into the mechanisms of brain organization underlying cognitive impairment and behavioral outcomes across individuals with SSDs, and may serve as prognostic markers and potential treatment targets moving forward.

**Acknowledgement**

The authors would like to thank all participants for their contribution to this work, and the research staff who performed data collection and management. This work was supported by National Institute of Mental Health grants 1/3R01MH102324–01 (to Dr. Voineskos), 2/3R01MH102313–01 (to Dr. Malhotra), and 3/3R01MH102318–01 (to Dr. Buchanan) as well as support from the Discovery Fund of the Centre for Addiction and Mental Health (CAMH) and the Canadian Institutes of Health Research (CIHR).

**Conflict of Interest Disclosures**

J-CY receives grant support from the Discovery Fund of the Centre for Addiction and Mental Health (CAMH). CH receives grant support from the National Institute of Mental Health (NIMH), Canadian Institutes of Health Research (CIHR), and the Centre for Addiction and Mental Health (CAMH) Foundation. LB reported no biomedical financial interests or potential conflicts of interest. LDO receives grant support from the Brain & Behavior Research Foundation (BBRF). MA reported no biomedical financial interests or potential conflicts of interest. JMG has no conflict of interest to declare. SXT receives grant support from the NIMH (K23 MH130750, R21 AG082054), she also owns equity and serves as a consultant for North Shore Therapeutics, received research funding and serves as a consultant for Winterlight Labs, and is on the advisory board and owns equity for Psyrin. GF currently receive funding from CIHR, the CAMH Foundation, and the University of Toronto. RWB has consulted for Boehringer-Ingelheim, serves on the Data Safety and Monitoring Boards of Roche, Merck, and Newron, and has served on the Advisory Boards of Merck, Acadia, Karuna, and Neurocrine. AKM receives grant support from the NIMH (R01 MH109508, R01 MH108654, R61 MH120188). SHA currently receives funding from the NIMH (R01 MH114879), CIHR, University of Toronto, and the CAMH Foundation. ANV currently receives funding from the NIMH (1/3R01 MH102324, 1/5R01 MH114970), CIHR, Canada Foundation for Innovation, CAMH Foundation, and University of Toronto. EWD has received funding from BBRF, NIMH, CIHR, and CAMH Foundation. The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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**Figure/Table Legends**

**Figure 1. Principal gradient analysis and partial least squares correlation (PLSC). A** illustrates the Glasser atlas, with 360 regions categorized into 12 networks from the Cole-Anticevic Brain Network Parcellation, indicated by different colors. **B** and **C** illustrate the network segregations of the three gradients respectively in brain and in the gradient space. **B** shows the average gradient scores across all participants (purple for positive scores and yellow for negative scores). **C** shows the average gradient scores across all participants in two scatter plots, respectively for Gradients 1 vs. 2 and for Gradient 2 vs. 3. In these scatter plots, each small dot represents a brain region and is colored according to its network; the bigger opaque dots illustrate the mean gradient scores of all 12 networks. Overall, Gradient 1 features Somatosensory vs. Frontoparietal network segregation; Gradient 2 features Auditory/Motor vs. Visual network segregation; and Gradient 3 features Default mode vs. Frontoparietal network segregation. **D** illustrates the PLSC procedure (see more details in **Supplementary Materials**).

**Figure 2. Group differences in Gradients 1-3. A** shows the brain regions with significant group differences according to two-sample *t*-tests (as linear models). Warm colors indicate SSDs being significantly closer to, respectively for each gradient, the frontoparietal, the vision, or the frontoparietal networks than Controls; cold colors indicate SSDs being significantly closer to, respectively for each gradient, the somatosensory, the auditory/motor, or the default mode networks than Controls. **B**–**D** show the brain regions with group differences along Gradients 1–3 in a 3D space; specifically, **C** shows the regions with a significant group difference along Gradient 2 (i.e., the x-axis of the plot), and **D** shows the regions with a significant group difference along Gradient 3 (i.e., the y-axis of the plot). These three figures show how each ROI moves along the three gradients from Controls to SSD (as indicated by the arrows). Each arrow represents one ROI and is colored according to the networks defined by Cole-Anticevic (cortical) and Tian (subcortical) parcellations in **Figure 1A**. The network labels illustrate where the means of the networks are for Controls.

**Figure 3**. **The first dimension of PLSC.** The loadings for the cognitive measures (**A**) and the network hierarchy (**B**) illustrate the general associations of the cognitive measures and the network hierarchy. The latent variables of Dimension 1 are shown in **C** where SSDs and Controls are significantly different according to bootstrap tests both according to the network hierarchy and to their cognitive measures. Together, **A** and **B** show associations that contribute to the group differences shown in **C**. Because this dimension is characterized by the group difference, in **D**-**F**, we highlighted such group differences (indicated by the arrows) of the identified regions of interest (ROIs) on Gradients 1 (**D**), 2 (**E**), and 3 (**F**). The highlighted arrows in these figures illustrate the group differences in the identified ROI gradients that most relate to cognition according to PLSC. On these figures, each arrow indicates the change from Controls to SSDs. The opaqueness of the arrows illustrates the amount of scaled contributions (i.e., squared loadings × 100), and the shape of the starting point illustrates the direction of how these ROIs load on Dimension 1 of PLSC (i.e., positive as square and negative as circle). The network labels illustrate where the means of the networks are for Controls.

**Figure 4. Correlations between cognitive and brain scores and clinical and functioning outcomes. A** shows the scatter plot between the latent variable pair and the total scores of the clinical and functioning measures with correlation lines illustrating the linear relationships. Blue lines indicate significantly negative correlations and red lines indicate significantly positive correlations. **B** shows the squared correlation between the latent variable pair, brain scores (colored in purple) and cognitive scores (colored in dark green), and the subscales in the Birchwood Social Functioning Scale (BSFS; colored in black), the Quality of Life Scale (QLS; colored in pink), the Brief Psychiatric Rating Scale (BPRS; colored in green), and the Scale of the Assessment of Negative Symptoms (SANS; colored in cyan). The blue circles indicate positive correlations, and the red circles indicate negative correlations. The shaded area marks the magnitude of squared coefficients of correlation that are not significant in the Pearson correlation test.

**Table 1. Demographics and Behavioral Characteristics.** The table shows the means and standard deviations (SD) of the demographics and the clinical and behavioral characteristics of each participant group. The statistics of examining the group effects are shown in the last three columns for each variable.

**Table 2. Significant group differences in regions of interest (ROIs) on Gradients 1-3.** The table summarizes the group effects found in all three gradients by networks and lists, for each network, the range of the significant *F* statistics and the number of significant ROIs.

**Table 3. Correlation between latent variables and clinical and functioning subscales.** The table shows how cognitive scores and brain scores correlate with the individual subscales of the Birchwood Social Functioning Scale (BSFS), the Quality of Life Scale (QLS), and two scales of symptoms, the Brief Psychiatric Rating Scale (BPRS) and the Scale of the Assessment of Negative Symptoms (SANS). The coefficients of correlation are reported along with their 95% confidence intervals (CI), and *q*(FDR) shows the FDR-corrected *p*-value for all 38 correlation tests. In these correlation tests, QLS intrapsychic foundations, QLS common objects and activities, and SANS avolition/apathy have 1 missing value. SANS asociality/anhedonia have 2 missing values.

**Tables**

**Table 1. Demographics and Behavioral Characteristics.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | SSD  (*n* = 248) | Control  (*n* = 172) | |  |  |  |
|  | | Mean (SD) | Mean (SD) | | *df\** | *t* | *q*(FDR) |
| Age (years) | | 31.42 (9.77) | 31.95 (10.40) | | 352.94 | -0.53‡ | .597 |
| Female (*n*; %) | | 79 (31.85%) | 80 (46.51%) | |  |  |  |
| Mean framewise displacement (FD; mm) | | 0.16 (0.1) | 0.14 (0.08) | | 415 | 1.51 | .139 |
| Parental education level – Father (years) | | 14.48 (3.18) | 15.40 (3.07) | | 186.55 | -2.12‡ | .035 |
| Parental education level – Mother (years) | | 14.08 (3.06) | 14.93 (2.63) | | 198.03 | -2.16‡ | .032 |
| Wechsler Test of Adult Reading (WTAR) Standard Score | | 108.11 (14.31) | 113.71 (10.81) | | 167 | -2.67 | < .001 |
| Chlorpromazine (CPZ) equivalents | 463.68 (382.37) | | | -- | -- | -- | -- |
| ***Clinical measures*** | | | | | | | |
| Brief Psychiatric Rating Scale (BPRS) | | 31.35 (7.86) | -- | | -- | -- | -- |
| Scale for the Assessment of Negative Symptoms (SANS) | | 25.12 (12.31) | -- | | -- | -- | -- |
| Birchwood Social Functioning Scale (BSFS) | | 136.34 (23.16) | 175.16 (19.21) | | -- | -- | < .001§ |
| Quality of Life Scale (QLS) | | 73.66 (20.96) | -- | | -- | -- | -- |
| ***Social cognitive measures*** | |  |  | |  |  |  |
| Penn Emotion Recognition Task (ER40) | | 31.84 (4.55) | 33.55 (3.32) | | 413 | -4.2 | < .001 |
| Reading the Mind in the Eyes Test (RMET) | | 24.57 (5.26) | 27.60 (3.82) | | 417 | -6.45 | < .001 |
| TASIT 1 | | 22.50 (3.64) | 24.64 (2.14) | | 418 | -6.92 | < .001 |
| TASIT 2 paradoxical sarcasm | | 15.73 (3.95) | 18.52 (2.09) | | 418 | -8.48 | < .001 |
| TASIT 2 simple sarcasm | | 14.89 (4.94) | 18.47 (1.92) | | 418 | -9.06 | < .001 |
| TASIT 2 sincere | | 16.92 (3.19) | 17.48 (2.69) | | 418 | -1.91 | .061 |
| TASIT 3 lies | | 24.82 (4.12) | 27.25 (3.64) | | 393.52 | -6.34‡ | < .001 |
| TASIT 3 sarcasm | | 23.53 (5.15) | 27.47 (3.62) | | 415 | -8.65 | < .001 |
| ***Non-social cognitive measures (MCCB)*** | | | | | | | |
| Processing speed | | 39.69† (13.16) | 53.06† (10.10) | | -- | -- | < .001§ |
| |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Reasoning and problem solving | 42.91 (10.97) | 48.76 (9.54) | 397.13 | -5.8‡ | < .001 | | | | | | | | |
| Attention/Vigilance | | 39.50 (11.66) | 47.65 (12.72) | | 345.66 | -6.64‡ | < .001 |
| Working memory | | 41.27† (11.19) | 49.16 (11.36) | | -- | -- | < .001§ |
| Verbal learning | | 40.67 (8.94) | 50.30 (9.44) | | 354.82 | -10.51‡ | < .001 |
| Visual learning | | 38.73 (12.46) | 48.38 (10.06) | | 418 | -8.43 | < .001 |

† denotes a sample that did not pass the normality test, ‡ denotes a Welch’s *t*, and § denotes results from a bootstrap test. \* The degrees of freedom change between measures because of the tests being used (i.e., a *t*-test, a Welch’s *t*-test, or a bootstrap *t* test) and the number of missing values before the imputation.

**Table 2. Significant group differences in regions of interest (ROIs) on Gradients 1-3.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Gradient 1 | | Gradient 2 | | Gradient 3 | |
| Networks | *F* range | *n* of ROIs | *F* range | *n* of ROIs | *F* range | *n* of ROIs |
| Visual1 | [-4.79, -3.52] | 4 | [2.65, 2.93] | 2 | [-5.04, -5.02] | 2 |
| Visual2 | [-5.07, -2.96] | 9 | [2.59, 5.6] | 41 | [-3.97, 5.65] | 14 |
| Somatomotor | [-3.58, -2.62] | 13 | [-6.27, -2.69] | 21 | [-2.91, 3.12] | 2 |
| Cingulo-Opercular | [2.61, 3.42] | 12 | [-6.72, -2.59] | 32 | [2.75, 3.32] | 5 |
| Dorsal-Attention | [-3.11, -2.57] | 3 | [2.83, 4.89] | 9 | [-4.38, -2.64] | 4 |
| Language | [3.7, 3.7] | 1 | [-2.64, -2.64] | 1 | [-4, -2.79] | 7 |
| Frontoparietal | [2.76, 4.09] | 4 | [-4.03, -3.73] | 3 | -- | 0 |
| Auditory | [2.75, 3.08] | 6 | [-5.56, -2.82] | 12 | [-3, -3] | 1 |
| Default | [-5.59, -2.62] | 8 | [-4.34, 4.43] | 11 | [2.62, 3.24] | 2 |
| Posterior-Multimodal | -- | 0 | -- | 0 | [-2.91, -2.91] | 1 |
| Ventral-multimodal | -- | 0 | -- | 0 | -- | 0 |
| Orbito-Affective | -- | 0 | [-2.72, -2.72] | 1 | -- | 0 |
| Subcortical | [2.83, 4.76] | 6 | [-4.83, -2.6] | 4 | [2.64, 4.57] | 11 |

**Table 3. Correlation between latent variables and clinical and functioning subscales.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Correlation with  Cognitive Scores | | Correlation with  Brain Scores | |
|  | *r* [95% CI] | *q*(FDR) | *r* [95% CI] | *q*(FDR) |
| ***Birchwood Social Functioning Scale (BSFS)*** | | | | |
| Social engagement/withdrawn | .02 [-.11, .14] | .823 | -.02 [-.15, .1] | .785 |
| Interpersonal communication/relationship | -.05 [-.17, .07] | .490 | -.10 [-.22, .03] | .174 |
| Interpersonal prosocial activity subscale | -.08 [-.20, .05] | .284 | -.15 [-.27, -.03] | .031 |
| Recreation activity | -.21 [-.32, -.08] | .004 | -.24 [-.36, -.12] | .001 |
| Independence performance | -.14 [-.26, -.02] | .044 | -.15 [-.27, -.02] | .036 |
| Independence competence | -.23 [-.34, -.11] | .001 | -.10 [-.22, .03] | .175 |
| ***Quality of Life Scale (QLS)*** | | | | |
| Interpersonal behavior | -.25 [-.36, -.13] | .001 | -.20 [-.32, -.08] | .004 |
| Instrumental role | -.27 [-.38, -.15] | < .001 | -.24 [-.35, -.12] | .001 |
| Intrapsychic foundations | -.28 [-.39, -.16] | < .001 | -.23 [-.34, -.1] | .001 |
| Common objects and activities | -.32 [-.43, -.21] | < .001 | -.28 [-.39, -.16] | < .001 |
| ***Brief Psychiatric Rating Scale (BPRS)*** | | | | |
| Negative symptoms | .15 [.03, .27] | .032 | .09 [-.04, .21] | .235 |
| Positive symptoms | .18 [.05, .30] | .012 | .07 [-.06, .19] | .348 |
| Anxiety/depression | -.06 [-.18, .07] | .436 | .10 [-.02, .22] | .170 |
| Activation | 0 [-.13, .12] | .970 | .01 [-.12, .13] | .935 |
| Hostility | .12 [-.01, .24] | .101 | .02 [-.1, .15] | .790 |
| ***Scale for the Assessment of Negative Symptoms (SANS)*** | | | | |
| Affective flattening or blunting | .15 [.03, .27] | .031 | .14 [.02, .26] | .044 |
| Alogia | .33 [.21, .43] | < .001 | .21 [.09, .32] | .003 |
| Avolition/apathy | .16 [.03, .28] | .031 | .19 [.07, .31] | .006 |
| Asociality/anhedonia | .12 [-.01, .24] | .099 | .19 [.07, .31] | .006 |

QLS intrapsychic foundations, QLS common objects and activities, and SANS avolition/apathy have 1 missing value. SANS asociality/anhedonia have 2 missing values.