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Neural Mechanisms of Change in Schizophrenia following Cognitive Training

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Neural Mechanisms of Change in Schizophrenia following Cognitive Training

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Psychology

by

Caroline Kemper Diehl

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ABSTRACT OF THE DISSERTATION

Neural Mechanisms of Change in Schizophrenia

following Cognitive Training

by

Caroline Kemper Diehl

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2023

Professor Cindy M. Yee-Bradbury, Co-Chair

Professor Gregory Allen Miller, Co-Chair

The period following a first episode of schizophrenia (SZ) is considered a critical window for treating cognitive impairment, and cognitive training (CT) interventions have shown promising efficacy. Cognitive impairment in SZ is associated with widespread alterations in functional neural network connectivity. However, research has not identified consistent associations between specific connectivity measures and individual domains of cognitive impairment. Furthermore, few studies have examined whether CT works by promoting normalization of neural networks (i.e., reduction of pre-existing disturbances) and/or by fostering compensatory network processes. In the present studies, we used graph-theory connectivity analysis to evaluate properties of intrinsic functional network organization and their relationship to cognitive function in first-episode SZ before and after CT. Using resting-state fMRI data from

45 young adults with SZ and 32 healthy comparison participants (HC), we tested for group differences in graph properties of the 'task-positive' cingulo-opercular (CON) and frontoparietal (FPN) networks and the whole-brain network, as well as their relationship with global and domain-specific measures of cognitive function prior to CT. SZ and HC did not differ substantially on measures of network organization, and across groups, generalized cognitive performance was positively associated with centrality of a node in right dorsal anterior cingulate cortex (dACC). Cognitive function in SZ was more positively associated with whole-brain functional segregation than in HC. In SZ, cognitive performance appeared to be decoupled from bilateral dACC node centrality, though effects were non-significant after correcting for multiple comparisons. Next, using longitudinal data from 17 SZ who completed a six-month course of CT and 20 HC who received no intervention, we tested for network normalization and compensation following CT. Although effects were non-significant after correcting for multiple comparisons, we found preliminary evidence of compensation in SZ following CT. Centrality of a node in right dACC decreased after CT, and this decrease corresponded with gains in processing speed. Reduced centrality of two other nodes in right dACC following CT was associated with gains in working memory and generalized cognitive performance. Results illuminate a potential role for compensation in cognitive recovery from SZ and may contribute to increased precision of future CT interventions.

The dissertation of Caroline Kemper Diehl is approved.

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2023

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BOOK CHAPTERS

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Introduction

The Role of Cognitive Training in Schizophrenia Recovery

Recovery from schizophrenia (SZ) is multidimensional and has been defined in terms of psychotic symptom remission, patient self-assessment, and community functioning (Lahera et al., 2018; Lysaker, Roe, & Buck, 2010; Van Eck, Burger, Vellinga, Schirmbeck, & De Haan, 2018; Vita & Barlati, 2018). Although positive symptoms of psychosis can be managed effectively with medication for the majority of treatment-seekers, other aspects of recovery remain elusive for many (Green, 2016; Miyamoto, Miyake, Jarskog, Fleischhacker, & Lieberman, 2012). A major barrier to robust and meaningful recovery from SZ is cognitive impairment in domains such as attention, memory, and executive function, which typically emerges prior to the onset of other SZ symptoms (McCleery & Nuechterlein, 2019). Cognitive impairment negatively predicts social and occupational functioning in both early-course and chronic SZ (Green, 1996, 2016; Green, Kern, Braff, & Mintz, 2000; Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006; Fu, Czajkowski, Rund, & Torgalsbøen, 2017), is not substantially alleviated by pharmacological interventions (Kahn & Keefe, 2013; Miyamoto et al., 2012), and may be exacerbated by anticholinergic medication use (Joshi et al., 2021, 2023). Thus, augmenting available treatments for SZ with intervention components that promote cognitive function may be an essential step toward more widespread and lasting recovery.

A growing literature has established computerized cognitive training (CT) as a promising intervention for promoting cognitive recovery in SZ. Meta-analyses of CT for SZ suggest that it has modest beneficial effects on both cognitive performance and functional outcomes (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007; Vita et al., 2021; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). In some trials, CT has been linked to sustained benefits six months after

completion (Fisher, Holland, Subramaniam, & Vinogradov, 2010; Subramaniam et al., 2012, 2014). Although CT may be beneficial at any stage of illness, its effects appear to be markedly larger in early-course than in chronic SZ (Bowie, Grossman, Gupta, Oyewumi, & Harvey, 2014). In general, individuals with a shorter duration of untreated psychosis experience greater gains from comprehensive treatment (Browne et al., 2017; Kane et al., 2016) and have more favorable long-term functional outcomes (Santesteban-Echarri et al., 2017), indicating that the period following a first episode of SZ is a critical one for intervention and may offer the greatest potential for change along cognitive and other dimensions of recovery.

CT interventions are heterogeneous in their guiding theoretical frameworks and mode of delivery (for a review, see Best & Bowie, 2017). One prevalent class of CT interventions takes a "bottom-up" approach to cognitive function by initially targeting basic cognitive processing and incrementally increasing the complexity of training tasks (Nuechterlein et al., 2014). This approach is based on findings from cognitive neuroscience suggesting that cognitive impairment and perceptual disturbances in SZ arise from disruptions in basic sensory processing (Javitt, 2009). Bottom-up approaches employ repetitive practice and dynamically tailor the difficulty of training tasks to individual recipients based on learning rate (Genevsky, Garrett, Alexander, & Vinogradov, 2010; Nuechterlein et al., 2014). In contrast, "top-down" approaches to CT (e.g., Medalia, Revheim, & Casey, 2001) directly target higher-level cognitive processes by providing training in executive skills rather than sensory 'building blocks' (Nuechterlein et al., 2014). Whereas bottom-up approaches rely on implicit learning through rehearsal of basic cognitive skills, top-down approaches typically involve explicit teaching of strategies for managing cognitive demands (Genevsky, Garrett, Alexander, & Vinogradov, 2010; Nuechterlein et al., 2014). Top-down approaches may also focus on providing opportunities for translation of

cognitive strategies to real-world contexts, typically through "bridging groups" where participants discuss their application of cognitive skills in daily life (Bowie & Medalia, 2016; Nuechterlein et al., 2014).

Although there is no firm consensus on the optimal set of intervention components that should comprise CT, treatment efficacy appears to be enhanced when CT is delivered alongside psychosocial interventions rather than in isolation (Best & Bowie, 2017; Genevsky, Garrett, Alexander, & Vinogradov, 2010). Recent studies have integrated elements of bottom-up and top-down CT approaches into a comprehensive intervention package (Nuechterlein et al., 2014) with promising results. Specifically, a recent clinical trial evaluated an integrated CT intervention that incorporated both bottom-up and top-down training strategies, a bridging skills group, case management, education and employment support, and medication management using oral or injectable risperidone. After 12 months of participation, individuals with first-episode SZ demonstrated substantial gains in both cognitive performance and occupational functioning (Nuechterlein et al., 2022). These findings highlight the potential benefits of integrating multiple theoretically driven approaches to CT and the potential for comprehensive CT interventions to significantly alter functional outcomes in first-episode SZ.

Neural Mechanisms of Cognitive Impairment and Intervention

Cognitive function is subserved by functional brain networks – systems of distinct brain regions that project to one another and exhibit coordinated activity. Cognitive impairment in SZ corresponds with disrupted connectivity within and between functional neural networks during performance of cognitive tasks and in the resting state, suggesting intrinsic, state-independent aberrations in the functional organization of the brain (Repovš & Barch, 2012). Multiple studies of functional connectivity in SZ have linked cognitive impairment to dysconnectivity within

cortico-striatal-thalamic-cerebellar networks (Ji et al., 2019a; Sheffield & Barch, 2016), as well as disturbances in the anticorrelation of task-oriented networks with the default mode network (Anticevic et al., 2012; Sheffield & Barch, 2016). However, few consistent trends have emerged regarding the contributions of specific network disruptions to discrete components of cognitive impairment (as opposed to generalized impairment), highlighting the diffuse nature of both dysconnectivity and cognitive dysfunction in SZ (Sheffield & Barch, 2016).

Previous work from our lab has indicated that during CT for first-episode SZ, psychophysiological processes act as both mechanisms of cognitive recovery and predictors of patient response to intervention. This work has focused primarily on inhibition (or 'gating') of the P50 event-related potential (captured via EEG or MEG) during exposure to extraneous auditory stimuli, which represents effective filtering of sensory information. Hamilton et al. (2015) found that following CT, first-episode SZ patients exhibited a significant increase in inhibition of P50 when presented with a redundant stimulus, which correlated with gains in cognitive function. A greater degree of P50 inhibition prior to intervention was also predictive of greater post-intervention gains. Separate studies found that a CT intervention targeting auditory discrimination and verbal memory increased sensory gating, verbal learning, and memory accuracy among participants with SZ (Popov et al., 2011) and that these effects were accompanied by changes in neural oscillations (i.e., gamma activity and alpha desynchronization) (Popov, Rockstroh, Weisz, Elbert, & Miller, 2012; Popova et al., 2018). These findings provide preliminary evidence that modulation of functional neural activity has mechanistic and clinical relevance to CT-based interventions.

Similarly, studies of functional connectivity inferred from blood-oxygen-level-dependent (BOLD) activity have suggested that modulation of functional connectivity is a key mechanism

of cognitive recovery in CT interventions. One study reported that after completing a CT intervention, SZ patients demonstrated increased activation of medial prefrontal cortex (PFC) during a reality-monitoring task, which correlated with subsequent gains in social functioning (Subramaniam et al., 2012). In the same study, CT participants showed increased activation of left middle frontal gyrus (MFG) and increased coupling of right MFG activation with performance during a working memory task, which correlated with subsequent gains in both working memory and occupational functioning (Subramaniam et al., 2014). Activation during working memory tasks has also been shown to increase in dorsolateral PFC, anterior cingulate cortex, and frontopolar cortex following CT for SZ, and such effects have been positively associated with working memory performance (Haut, Lim, & MacDonald, 2010; Ramsay, Nienow, Marggraf, & MacDonald, 2017). An activation likelihood estimate meta-analysis of 14 task-based fMRI studies of CT for SZ did not identify any brain subregions that consistently showed increased activation across studies, which may be attributable to the heterogeneous nature of CT intervention protocols and/or their diffuse neural mechanisms (Mothersill & Donohoe, 2019). However, systematic reviews and meta-analyses indicate that studies of CT in SZ have widely reported increased activation in bilateral prefrontal, frontal, and parietal regions, and some have reported subcortical effects in caudate and thalamus (Mothersill & Donohoe, 2019; Ramsay & Macdonald, 2015; Wei et al., 2016). Furthermore, by identifying changes in neural activity during cognitive tasks that are not explicitly rehearsed during CT, task-based fMRI studies have demonstrated that both the behavioral and the neural effects of CT can generalize to different contexts that require similar cognitive engagement (Ramsay & Macdonald, 2015).

Alongside regional, task-based activation, intrinsic (i.e., resting-state) activation and connectivity have evidenced change following CT for SZ in several studies. A study comparing CT to a placebo control in chronic SZ reported that in CT exclusively, patients demonstrated increased connectivity between thalamus and right MFG at rest, which predicted cognitive gains (Ramsay, Nienow, & MacDonald, 2017). Similarly, a separate study found that CT, but not a treatment-as-usual intervention, was associated with both increased cognitive performance and increased resting-state activity in medial PFC and anterior cingulate cortex (Fan, Zou, Tan, Hong, & Tan, 2017). In the magnetoencephalography (MEG) literature, CT for SZ has been associated with change in resting-state neural oscillations, including increased gamma activity within the default mode network, which has been found to predict gains in cognitive function (Popova et al., 2018). Although these initial findings align with trends from task-based fMRI, there is a need for broader, network-based exploration of resting-state change following CT that goes beyond measuring activity in individual regions or connectivity between pairs of regions.

Another limitation of recent literature is its emphasis on evaluating neural mechanisms known to support cognitive function in healthy individuals. Although functional networks have widely demonstrated dysconnectivity in SZ, the broader picture of functional disorganization (or lack of typical functional specialization) in SZ is less understood. In particular, relatively little is known about compensatory engagement of alternative functional networks or network-related processes in SZ. Some evidence suggests that, although dorsal PFC is preferentially engaged by healthy adults during working memory tasks, those with SZ exhibit hypo-activation of dorsal PFC and elevated, potentially compensatory activation of ventral PFC (Tan et al., 2006). Other evidence suggests that posterior parietal cortex exhibits compensatory activation in SZ during cue anticipation in working memory tasks (Quintana et al., 2003), such that hypo-activation of

task-relevant regions in SZ is coupled with compensatory hyper-activation of less functionally-specialized regions (Crossley et al., 2016). Based on these findings, further investigation of the relationship between network connectivity and cognitive function in SZ is warranted in order to clarify how certain aspects of atypical network organization may promote rather than detract from cognitive function.

The study of compensatory network processes has important clinical applications, as targeted enhancement of compensation may be a mechanism of existing cognitive interventions and/or an important objective for future interventions. Thus far, there has been minimal exploration of the potential for interventions to modulate compensatory network engagement in SZ. However, emerging evidence suggests that CT for SZ may enhance naturalistic compensatory mechanisms related to cognitive function. In a recent study, individuals with early-course SZ demonstrated resting-state hyperconnectivity between thalamus and left superior temporal gyrus, which increased after CT but decreased after a computer gaming intervention. Enhanced hyperconnectivity after CT was associated with gains in overall cognitive function, indicating that thalamo-temporal hyperconnectivity may serve a compensatory function that benefits cognition in SZ (Ramsay et al., 2020). Likewise, a meta-analysis of nine task-based fMRI studies noted that although neural mechanisms of CT across studies appeared to reflect normalization in regions that have shown aberrant activity in SZ (e.g., PFC and thalamus), there was also evidence of potential compensation in the form of enhanced activity in inferior frontal gyrus, precentral gyrus, and postcentral gyrus following CT (Ramsay & Macdonald, 2015). Thus, compensatory network engagement both before and after CT represents a promising area for continued study that may increase understanding of intervention mechanisms and, more

broadly, the contributions of alternative network processes to cognitive function in SZ.

Graph Theory Approaches to Connectivity

Graph theory is an approach to quantifying complex network characteristics that is quickly gaining traction in studies of neural network connectivity (Bullmore & Sporns, 2009; Guye, Bettus, Bartolomei, & Cozzone, 2010; Spielberg, Miller, Heller, & Banich, 2015). Graph-theory analysis of BOLD fMRI time series data is used to derive probabilistic maps of the significant connections (also referred to as 'edges' or 'links') between pairs of pre-defined 'nodes' (i.e., brain regions of interest) and to estimate intra-network parameters (properties) (Bullmore & Sporns, 2009). Unlike other approaches to connectivity analysis, which typically focus on pairwise connections, graph theory analysis examines the functional organization of networks by quantifying multiple distinct properties of both networks and nodes, including the role of individual nodes or connections within a larger network. Categories of graph-theory properties include those related to i) segregation, which refers to a network's capacity for functional specialization; ii) integration, or the capacity within a network for effective communication between distal nodes; iii) resilience, or the degree to which the network can maintain functioning when aspects of it are disrupted; and iv) centrality, or the degree to which a node contributes to different aspects of network functioning (e.g., how much a node contributes to communication efficiency) (Rubinov & Sporns, 2010). Each of these four qualities is quantifiable in multiple graph-theory properties, allowing for a multifaceted and highly specific characterization of each network.

Several studies have investigated neural network organization and cognitive function in SZ through the lens of graph theory. Graph-theory analysis of white matter tracts in SZ via diffusion tensor imaging has found reduced centrality of frontal hubs (i.e., nodes with high

numbers of connections to other nodes), suggesting reduced structural support for complex integration of executive function (van den Heuvel, Mandl, Stam, Kahn, & Hulshoff Pol, 2010). In childhood-onset SZ, graph-theory analysis of resting-state fMRI has evidenced reduced network segregation and increased global integration (Alexander-Bloch et al., 2010), aligning with the aforementioned reports of loss of specialization and compensatory recruitment of less-specialized networks in SZ (Crossley et al., 2016; Quintana et al., 2003; Tan et al., 2006). Similarly, several studies of adult-onset SZ have identified reduced functional segregation (Vecchio et al., 2023; Fornito, Zalesky, Pantelis, & Bullmore, 2012; Lynall et al.., 2010), although some have conversely reported increased functional segregation in SZ (Gao et al., 2023; Hadley et al., 2016). In both healthy adults and adults with SZ, graph-theory analysis of fMRI has linked local and global efficiency of the frontoparietal network (FPN) and cingulo-opercular network (CON), as well as whole-brain global efficiency and centrality (participation coefficient) of right anterior insula, to generalized cognitive ability (Sheffield et al., 2015). Reduced centrality of right anterior insula and lower global efficiency of CON, but not FPN, appear to partially mediate the relationship between psychotic-like experiences and lower cognitive ability (Sheffield, Kandala, Burgess, Harms, & Barch, 2016), suggesting a mechanistic role for altered network organization in cognitive impairment. Given the demonstrated utility of graph-theory principles for clarifying complex network organization in SZ, such methods have significant potential to improve understanding of neural network changes that occur during CT interventions for SZ.

Project Overview

The objective of the present studies was to identify, via graph-theory analysis of resting-state (rs) functional network organization, 1) neural mechanisms involved in cognitive impairment in first-episode SZ and 2) neural mechanisms by which CT promotes cognitive recovery in first-episode SZ. A secondary objective was to examine whether features of functional network organization corresponded with generalized or domain-specific cognitive impairment and/or recovery.

Participants with first-episode SZ were enrolled in a randomized controlled trial (RCT) in which they received 24 weeks of a Posit Science/BrainHQ CT intervention at the UCLA Aftercare Research Program. Initial results from the RCT indicate that the CT intervention was highly efficacious and that efficacy was enhanced among a subset of participants who completed an aerobic exercise program alongside CT (Nuechterlein et al., 2023). As the present studies focused on mechanisms of CT more broadly, participants in the CT and CT + exercise conditions were collapsed into a single group. Prior to beginning CT and again after six months of CT, SZ participants completed an rs-fMRI scan and the MATRICS Consensus Cognitive Battery (MCCB; Kern et al., 2008; Nuechterlein et al., 2008), a clinician-administered measure of cognitive function. Cognitive and rs-fMRI data were also collected at two time points, spaced six months apart, from demographically matched healthy comparison participants (HC) who did not undergo any intervention. Analyses focused on identifying features of intrinsic functional networks that were associated with cognitive function and impairment prior to intervention (Study 1), as well as changes in network features that were associated with cognitive change following CT (Study 2).

The present studies introduce a novel framework for differentiating between restoration of typical neural network organization (i.e., *normalization*) and development of alternative network processes that support cognition (i.e., *compensation*) (**Figure 1**). In this framework, changes in neural network properties that occur from pre- to post-intervention are considered *normalization* if they consist of a) decreases in network features that differentiate pre-intervention SZ from HC and predict cognitive impairment in pre-intervention SZ or b) increases in network features that differentiate HC from pre-intervention SZ and positively predict cognitive function in HC. Neural network changes from pre- to post-intervention are considered *compensation* if they are significantly associated with cognitive gains but do not involve a connection or property that predicts cognitive impairment in pre-intervention SZ or that positively predicts cognitive function in HC. Normalization and compensation are not positioned as mutually exclusive processes and may co-occur within individuals and groups.

The *normalization vs. compensation* framework is informed by evidence of naturalistic and treatment-induced compensatory network function in SZ, as reviewed above. It also draws from neurodiversity theory, which calls for recognition of alternative modes of neurocognitive functioning as legitimate and not necessarily pathological (e.g., Chapman, 2019), and provides an initial model for extending such theory to the study of neurobiological processes. As such, studying functional connectivity using a framework that incorporates both normalization and compensation may provide additional context for understanding SZ according to an ecological model (Chapman, 2021) that acknowledges strengths of minority cognitive styles and considers impairment as deriving from social context as well as intra-individual processes (Diehl, Heller, Yee, & Miller, 2023).

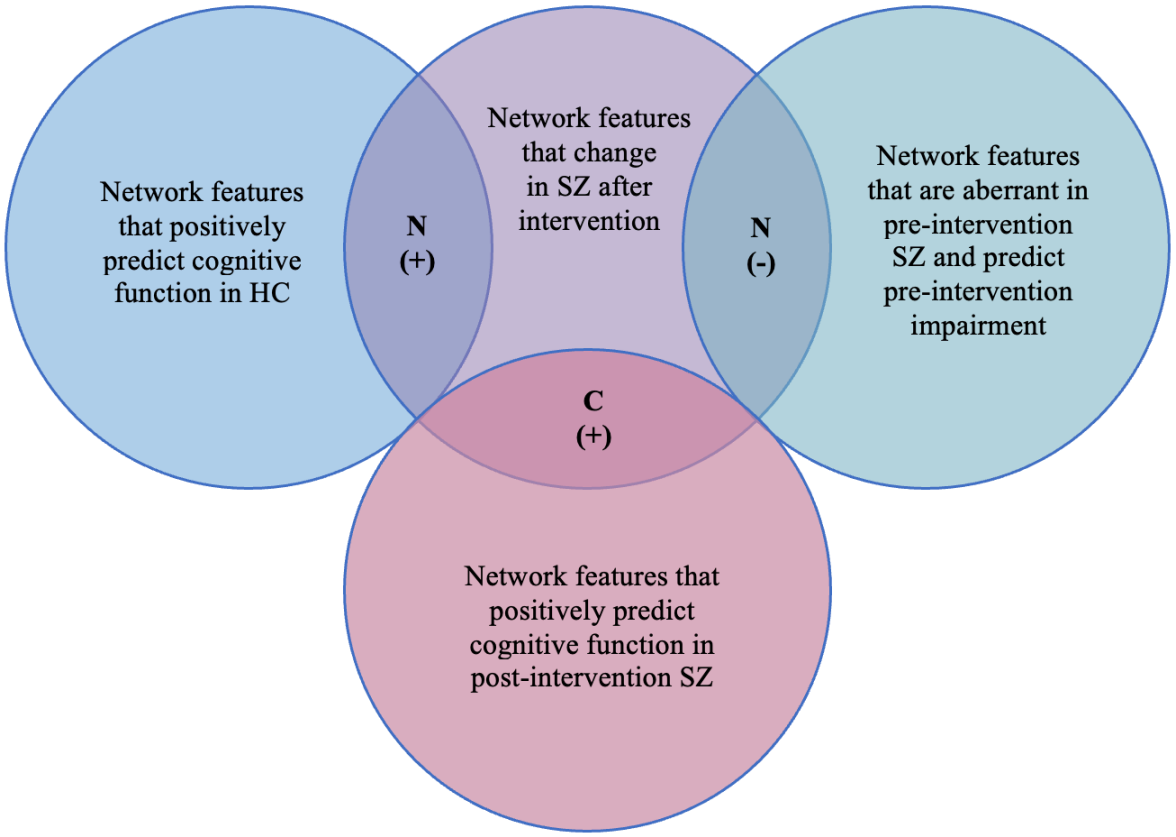


Figure 1. Conceptual diagram: Normalization and compensation. N(+): area where change in the positive direction indicates normalization. N(-): area where change in the negative direction indicates normalization. C(+): area where change in the positive direction indicates compensation.

The present studies quantified change in neural network organization by employing graph-theory methods to examine resting-state functional connectivity. The ability of graph-theory methods to differentially quantify multiple components of network organization is particularly well suited to addressing outstanding questions about mechanisms of cognitive recovery in SZ. Research on network engagement in SZ during cognitive tasks has suggested that functional network specialization is disrupted in SZ and has identified engagement of less specialized networks as a compensatory phenomenon, suggesting reduced network segregation and compensatory global integration (Crossley et al., 2016; Quintana et al., 2003; Tan et al.,

2006). Such phenomena may not be fully captured by analytic approaches that focus on identifying positive, negative, or effective connectivity, as these approaches produce a less granular picture of intra-network organization. Therefore, graph-theory quantification of pre- to post-intervention changes provides a particularly appropriate framework for differentiating between normalization and compensation. This approach also provides an avenue for differentiating between compensatory mechanisms that are engaged naturalistically in SZ (i.e., those engaged prior to intervention, possibly including elevated global integration [Alexander-Bloch et al., 2010]) and those that are introduced or enhanced by intervention.

Study 1: Prior to intervention, identify associations between resting-state neural network aberrations and cognitive function in first-episode SZ.

Prior studies point to an overall pattern of reduced functional specialization of nodes and networks in SZ coupled with increased reliance on less-specialized nodes and networks (Crossley et al., 2016; Quintana et al., 2003; Tan et al., 2006). Likewise, several graph-theory studies have found reduced network modularity and clustering (i.e., reduced segregation) and/or increased global efficiency and robustness (global integration) in SZ (Alexander- Bloch et al., 2010; Vecchio et al., 2023; Fornito, Zalesky, Pantelis, & Bullmore, 2012; Lynall et al., 2010), although results have been inconsistent across studies (Gao et al., 2023; Hadley et al., 2016). Reduced local and global efficiency of CON has been linked to cognitive impairment in SZ (Sheffield et al., 2016, 2017), although in some studies, SZ have not differed from HC on efficiency or other properties of CON (Sheffield et al., 2015). Centrality of right anterior insula, a key hub in CON, has previously been associated with cognitive function in SZ and healthy adults (Sheffield et al., 2015), and reduced centrality of this hub may be implicated in cognitive impairment associated with psychotic-like experiences (Sheffield, Kandala, Burgess, Harms, &

Barch, 2016). Dorsal anterior cingulate cortex (dACC), also considered a CON hub, is known to contribute to cognitive control and error monitoring in healthy adults (Brockett & Roesch, 2021), has been implicated in SZ pathophysiology (Fornito, Yücel, Dean, Wood, & Pantelis, 2009), and has demonstrated reduced connectivity in SZ, although the same study found that dACC centrality was intact (Becerril, Repovš, & Barch, 2011).

Aim 1a. We expected a similar pattern of reduced network segregation and increased global (whole-brain) integration in SZ as reported by Alexander-Bloch et al. (2010) and others. Consistent with a pattern of reduced functional specialization, we hypothesized that first-episode SZ patients would exhibit one or more of the following effects: i) intact or elevated whole-brain global efficiency and robustness (assortativity), yet ii) reduced clustering coefficient and transitivity, iii) reduced centrality of right anterior insula and bilateral dACC, and iv) within CON, reduced intra-network global efficiency and clustering coefficient.

Aim 1b. We hypothesized that an individual SZ participant's degree of aberrance in network segregation, CON efficiency, and CON hub centrality would correspond with the severity of that individual's generalized cognitive impairment, as assessed by the MCCB composite score. On an exploratory basis, we also planned to test for associations between aberrant network features and domain-specific cognitive function, as assessed by the MCCB working memory, attention/vigilance, and processing speed summary scores.

Study 2: Following 6 months of CT, evaluate resting-state neural network normalization and compensation as mechanisms of cognitive change.

In order to determine whether functional neural mechanisms of cognitive improvement in CT for SZ consist primarily of normalization or compensation, we examined normalization and compensation as competing hypotheses. However, normalization and compensation were not

expected to be mutually exclusive processes across networks, nor are network segregation and integration mutually exclusive within networks (e.g., "small-world" networks are high on both) (Rubinov & Sporns, 2010).

Aim 2a. To evaluate the hypothesis that improvement in CT is driven by network normalization, we tested for network properties that i) were aberrant in SZ (relative to HC) prior to intervention, ii) predicted impaired cognitive performance in SZ prior to intervention, and iii) became less aberrant in SZ post-intervention. It was expected that such properties could correlate positively or negatively with post-intervention cognitive performance, as normalization might be incomplete (i.e., a property could predict cognitive impairment in SZ both before and after CT, but its effect could be significantly attenuated following CT). We also allowed for the possibility of no correlation between a normalized property and post-intervention cognitive performance, as normalization might decouple a given property from cognitive function. Normalization was also evaluated by testing for network properties that i) were more pronounced in HC than SZ prior to intervention, ii) were positively associated with cognitive targets in HC, and iii) became more pronounced in SZ following intervention.

In line with research described above, we expected that normalization from pre- to post-intervention in SZ would consist primarily of increased PFC functional specialization, manifesting as increased segregation within networks that involve PFC hubs. Specifically, we hypothesized that normalization would occur primarily within CON and would involve one or more of the following effects: i) increased centrality of right anterior insula and bilateral dACC within the whole-brain network, and ii) within CON, increased intra-network clustering coefficient and global efficiency, given prior reports (Sheffield et al., 2015, 2016, 2017).

Aim 2b. To evaluate the alternative hypothesis that improvement in CT is driven by network compensation, we tested for network properties that i) changed from pre- to post-intervention and ii) were relevant to cognitive performance in SZ post-intervention, but iii) did not predict cognitive impairment in SZ prior to intervention or positively predict cognitive function in HC. We expected that because compensatory mechanisms fostered by CT may build upon naturalistic compensatory engagement that is present prior to intervention, properties involved in compensation might or might not distinguish SZ from HC prior to CT. Changes in network properties were only eligible to be considered compensatory if their association with post-intervention cognitive targets was positive, since a negative association would indicate a decline in cognitive function following intervention.

Given evidence that efficiency of FPN may predict cognitive performance (Sheffield et al., 2015) but does not appear to be compromised in SZ (Sheffield et al., 2016, 2017), as well as evidence that posterior parietal cortex (involved in FPN) may exhibit compensatory activation during working memory tasks (Quintana et al., 2003), we hypothesized that compensation would occur primarily within FPN. Specifically, we hypothesized that within FPN, SZ would demonstrate increased intra-network global efficiency following CT. Compensation was also expected to involve increased global integration, evidenced by increased whole-brain global efficiency and robustness. We did not anticipate any significant changes in neural network properties in HC from baseline to six-month follow-up.

Study 1: Functional Network Organization in First-Episode Schizophrenia and its Relationship to Cognitive Function

Method

Participants and Screening Procedures

Participants with first-episode SZ were recruited through a randomized controlled trial (RCT) conducted by the UCLA Aftercare Research Program (Nuechterlein et al., 2023). SZ participants met DSM-5 criteria for SZ, schizophreniform disorder, or schizoaffective disorder, depressed type, with onset within the last two years, and received comprehensive care through the Aftercare Research Program throughout their participation in the RCT and the present studies. Additional inclusion criteria for SZ participants were as follows: i) between 18 and 45 years old, ii) no history of neurological disorder or significant head injury, iii) no substance use disorder within the six months prior to SZ onset, iv) premorbid IQ ≥ 70, v) fluent in English, vi) able to commute to UCLA regularly for appointments, and vii) not pregnant or lactating at the time of study participation. All participants were stabilized on antipsychotic medication prior to beginning study procedures. A total of 69 participants with SZ completed MRI scanning. Of these, six were scanned using a beta rs-fMRI protocol incompatible with later scanner protocols; 13 did not complete the rs-fMRI portion of the scan due to time constraints or early termination of scanning; two were missing spin echo fieldmap files; one was excluded due to severe metal-induced artifact; one did not complete a cognitive assessment (MCCB); and one was an outlier on the MCCB (composite score more than two standard deviations below the group mean) and was excluded, resulting in a final sample of N = 45 SZ participants included in analyses.

HC participants were recruited from the greater Los Angeles community and were demographically matched to the SZ sample on age, gender, race/ethnicity, and parental education. HC completed the Structured Clinical Interview for DSM-5, Research Version (SCID-5-RV; First, Williams, Karg, & Spitzer, 2015) prior to enrollment and were eligible for inclusion if they met the following criteria: i) between 18 and 45 years old, ii) no history of neurological disorder or significant head injury, iii) no current or past psychotic disorder, bipolar

disorder, obsessive-compulsive disorder, post-traumatic stress disorder, or substance use disorder, iv) no current major depressive disorder or past major depressive episode with a duration greater than one year; v) no history of psychotic disorder among first-degree relatives; vi) fluent in English, and vii) no pregnancy at the time of study participation. A total of 38 HC participants completed MRI scanning. Of these, two later endorsed exclusion criteria and were retroactively excluded; one did not complete the rs-fMRI portion of the scan due to time constraints; one was excluded following preprocessing and quality checking due to faulty registration of imaging data (see Preprocessing of MRI Data); one did not complete the MCCB; and one was an outlier on the MCCB (composite score more than two standard deviations below the group mean) and was excluded, resulting in a final sample of N = 32 HC included in analyses.

Data were collected from March 2017 to April 2023. Due to the COVID-19 pandemic, data collection was paused for parts of 2020-2021. Study procedures were continuously approved and overseen by the UCLA Institutional Review Board (IRB). All participants provided written informed consent prior to their participation and were compensated for their time at the conclusion of each study visit. All procedures were in accordance with the Nuremburg Code and the Declaration of Helsinki.

Cognitive Assessment

Cognitive function was assessed using the MATRICS Consensus Cognitive Battery (MCCB; Kern et al., 2008; Nuechterlein et al., 2008), a clinician-administered neuropsychological battery developed by Nuechterlein and colleagues for the purpose of evaluating the efficacy of interventions for SZ. The MCCB assesses functioning in seven domains: processing speed, attention/vigilance, working memory, verbal learning, visual

learning, reasoning/problem solving, and social cognition. A composite score is computed based on summary scores for each of these domains. In the present studies, the MCCB composite score was used to test for associations between functional connectivity and generalized cognitive function. Summary scores for processing speed, attention/vigilance, and working memory were used to probe for relationships between functional connectivity and specific domains of cognitive function. Among SZ participants, the MCCB was completed prior to the initiation of any RCT intervention components that targeted cognitive function.

Neuroimaging Data Acquisition

All neuroimaging data were acquired at the UCLA Staglin Center for Cognitive Neuroscience using a 3T Siemens Prisma scanner. A high-resolution T1-weighted anatomical scan was acquired using an MPRAGE sequence with 208 interleaved slices (TR = 2500 ms, TE = 1.81 ms, flip angle = 8°, FOV = 208 mm anterior-to-posterior x 144 mm inferior-to-superior x 208 mm right-to-left, voxel size = 0.8 mm x 0.8 mm x 0.8 mm). Two spin echo fieldmap images, one anterior-to-posterior and one posterior-to-anterior, were collected with 72 interleaved slices (TR = 8000 ms, TE = 66 ms, flip angle = 90°, FOV = 208 mm anterior-to-posterior x 144 mm inferior-to-superior x 208 mm right-to-left, voxel size = 2 mm x 2 mm x 2 mm). Resting-state BOLD data were acquired using a 6.5-minute sequence with 488 volumes and 72 interleaved slices (TR = 800 ms, TE = 37 ms, flip angle = 52°, FOV = 208 mm anterior-to-posterior x 144 mm inferior-to-superior x 208 mm right-to-left, voxel size = 2 mm x 2 mm x 2 mm). Foam padding was used to minimize participant head movement. During rs-fMRI, participants were asked to remain awake with their eyes open and to focus on a neutral stimulus. rs-fMRI data were collected approximately 30-40 minutes after the start of each scan, allowing ample time for

participants to acclimate to scanning conditions.

Preprocessing of MRI Data

Raw data in DICOM format were converted to NIfTI format using dcm2niix version 1.0.20210317 (Li, Morgan, Ashburner, Smith, & Rorden, 2016). Data were then preprocessed using the FMRIB Software Library (FSL; https://fsl.fmrib.ox.ac.uk/fsl/) version 6.0.4 (Smith et al., 2004), Advanced Normalization Tools (ANTs; http://stnava.github.io/ANTs/; Tustison et al., 2014), HD-BET (https://github.com/MIC-DKFZ/HD-BET; Isensee et al., 2019), and the Graph Theory GLM (GTG) MATLAB toolbox (https://www.nitrc.org/projects/metalab_gtg; Spielberg, 2014), which draws from the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/; Rubinov & Sporns, 2010). GNU Parallel (https://www.gnu.org/software/parallel/; Tange, 2020) was used to speed up processing by parallelizing computations to multiple CPU cores.

Preprocessing of T1-weighted images consisted of signal intensity normalization using the ANTs N4BiasFieldCorrection tool (Tustison et al., 2010) and brain extraction using antsBrainExtraction.sh to create participant-specific brain masks. An initial brain mask was generated for each participant by summing masks created using the OASIS and Kirby brain templates provided by ANTs (Avants & Tustison, 2018). Following visual inspection, brain masks were regenerated using HD-BET for a subset of participants with faulty ANTs extractions (i.e., excess skull inclusion or problematic brain exclusion). On a case-by-case basis, custom brain masks were created to address problematic inclusion and/or exclusion by summing the masks created by ANTs and HD-BET, using a single ANTs template instead of a sum of multiple, or incorporating additional ANTs templates (i.e., NKI).

Spin echo fieldmaps in the anterior-to-posterior and posterior-to-anterior directions were merged into a single file, and the TOPUP function in FSL was used to correct for distortions

caused by the susceptibility-induced field (Andersson, Skare, & Ashburner, 2003). A mean unwarped fieldmap image was computed, and signal intensity normalization was applied using the ANTs N4BiasFieldCorrection tool. Brain extraction was then performed using several methods, including HD-BET and FSL BET (Smith, 2002) with variable parameters. The resulting brain masks were visually inspected, and the best quality mask was selected for each participant.

Masks capturing signal from white matter and cerebrospinal fluid (CSF) were generated for each participant using FSL FAST and eroded using FSLMATHS to prevent overlap with gray matter. Masks were visually inspected for quality.

Initial preprocessing of rs-fMRI timeseries data was performed using FSL FMRI Expert Analysis Tool (FEAT) version 6.00. Preprocessing steps included grand-mean intensity normalization, correction of susceptibility-induced field distortions using the unwarped fieldmap image, motion correction using rigid-body transformations via MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), brain extraction using BET, FLIRT linear registration (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady, & Smith, 2002) to the T1-weighted image, and FNIRT nonlinear registration (Andersson, Jenkinson, & Smith, 2007a, 2007b) to the Montreal Neurologic Institute (MNI) 2 mm standard brain. FEAT outputs were visually inspected for quality. Motion censoring was then performed using ICA-based Automatic Removal of Motion Artifacts (ICA-AROMA; Pruim et al., 2015). As spatial smoothing is required for ICA-AROMA, FEAT was run once with spatial smoothing (5 mm Gaussian kernel) and once without smoothing, and motion censoring was initially performed on smoothed timeseries. The unsmoothed timeseries for each participant was then regressed on the motion components obtained from that participant's smoothed data. A DVARS value (Smyser, Snyder, & Neil, 2011;

Power, Barnes, Snyder, Schlaggar, & Petersen, 2012) was computed for each volume of the motion-censored unsmoothed data. For participants with more than five DVARS outlier volumes, motion-censored data were visually inspected, and data with visible motion artifacts were subjected to spike regression. Additional preprocessing of rs-fMRI data was completed using the GTG toolbox (Spielberg, 2014) and consisted of regressing each participant's timeseries data on participant-specific white matter, ventricular, and global signal and their first derivatives.

Region of Interest (ROI) Selection

Cortical regions of interest (ROIs) were defined for each participant using the 360-region Human Connectome Project (HCP) atlas derived from a multimodal parcellation by Glasser et al. (2016). Fifteen participant-specific subcortical ROIs were generated using FSL FIRST (Patenaude, Smith, Kennedy, & Jenkinson, 2011). For each participant, cortical ROIs and 14 non-brainstem subcortical ROIs were concatenated using MATLAB, and areas of overlap (i.e., two hippocampal ROIs included in the HCP atlas) were eliminated. The resulting 372 ROIs were applied to rs-fMRI data and used to compute connectivity matrices. Following this computation, four ROIs (L_OFC, L_pOFC, L_TGv, and R_TGv) representing left orbitofrontal cortex, left posterior OFC complex, left temporal pole, and right temporal pole, respectively, were removed for all participants due to insufficient signal in some participants. One additional ROI (R_LIPd) representing a section of right superior parietal lobule (SPL) had insufficient signal in one SZ participant. This participant was excluded from analyses of whole-brain graph properties, as removal of R_LIPd was inadvisable due to the demonstrated relevance of SPL to cognitive processes such as visuospatial attention (e.g., Wu et al., 2016). The remaining 368 ROIs were used to calculate whole-brain graph properties (see Study 1 Analyses).

To address hypotheses related to *a priori* networks of interest (CON and FPN), subsets of HCP cortical ROIs were identified as members of CON and FPN according to Ji et al.'s (2019b) classification (https://github.com/ColeLab/ColeAnticevicNetPartition). A total of 56 cortical ROIs across hemispheres were identified as members of CON, and 50 were identified as members of FPN. To limit the number of ROIs included in the present studies, and because specific hypotheses involved only cortical regions, we did not include subcortical ROIs in CON or FPN analyses, despite the inclusion of subcortical ROIs in Ji et al.'s (2019b) classification.

Table 1. Cingulo-opercular network (CON) regions of interest (ROIs). ROIs from the Glasser et al. (2016) Human Connectome Project (HCP) parcellation were classified as members of CON based on Ji et al. (2019b).

Hemisphere	Label	Description
Left	L_FEF	Frontal Eye Fields
Left	L_5mv	Area 5m ventral (SPL)
Left	L_23c	Area 23c (PCC)
Left	L_SCEF	Supplementary and Cingulate Eye Field
Left	L_6ma	Area 6m anterior (SMA)
Left	L_7Am	Medial Area 7A (superior precuneous)
Left	L_p24pr	Area Posterior 24 prime (mid-cingulate)
Left	L_33pr	Area 33 prime (dACC)
Left	L_a24pr	Anterior 24 prime (dACC)
Left	L_p32pr	Area p32 prime (dACC)
Left	L_6r	Rostral Area 6 (premotor)
Left	L_46	Area 46 (central dlPFC)
Left	L_9_46d	Area 9-46d (central dlPFC)
Left	L_43	Area 43 (posterior operculum)
Left	L_PFcm	Area PFcm (posterior operculum)
Left	L_PoI2	Posterior Insular Area 2
Left	L_FOP4	Frontal Opercular Area 4
Left	L_MI	Middle Insular Area
Left	L_FOP1	Frontal Opercular Area 1 (posterior operculum)
Left	L_FOP3	Frontal Opercular Area 3
Left	L_PFop	Area PF opercular (supramarginal)
Left	L_PF	Area PF Complex (supramarginal)
Left	L_PoI1	Area Posterior Insular 1
Left	L_FOP5	Area Frontal Opercular 5
Left	L_PI	Para-Insular Area

Left	L_a32pr	Area anterior 32 prime (dACC)
Left	L_p24	Area posterior 24 (dACC/rACC boundary)
Right	R_FEF	Frontal Eye Fields
Right	R_PEF	Premotor Eye Field
Right	R_PSL	PeriSylvian Language Area
Right	R_5mv	Area 5m ventral (SPL)
Right	R_23c	Area 23c (PCC)
Right	R_SCEF	Supplementary and Cingulate Eye Field
Right	R_6ma	Area 6m anterior (SMA)
Right	R_7Am	Medial Area 7A (superior precuneous)
Right	R_p24pr	Area Posterior 24 prime (mid-cingulate)
Right	R_a24pr	Anterior 24 prime (dACC)
Right	R_p32pr	Area p32 prime (dACC)
Right	R_6r	Rostral Area 6 (premotor)
Right	R_IFSa	Inferior frontal sulcus area IFSa (IFC)
Right	R_46	Area 46 (central dlPFC)
Right	R_9_46d	Area 9-46d (central dlPFC)
Right	R_43	Area 43 (posterior operculum)
Right	R_PFcm	Area PFcm (posterior operculum)
Right	R_PoI2	Posterior Insular Area 2
Right	R_FOP4	Frontal Opercular Area 4
Right	R_MI	Middle Insular Area
Right	R_FOP1	Frontal Opercular Area 1 (posterior operculum)
Right	R_FOP3	Frontal Opercular Area 3
Right	R_PFop	Area PF opercular (supramarginal)
Right	R_PF	Area PF Complex (supramarginal)
Right	R_PoI1	Area Posterior Insular 1
Right	R_FOP5	Area Frontal Opercular 5
Right	R_PI	Para-Insular Area
Right	R_a32pr	Area anterior 32 prime (dACC)
Right	R_p24	Area posterior 24 (dACC/rACC boundary)

Figure 2. Cingulo-opercular network (CON) regions of interest (ROIs). Figure was created using BrainNet Viewer (http://www.nitrc.org/projects/bnv/; Xia, Wang, & He, 2013).

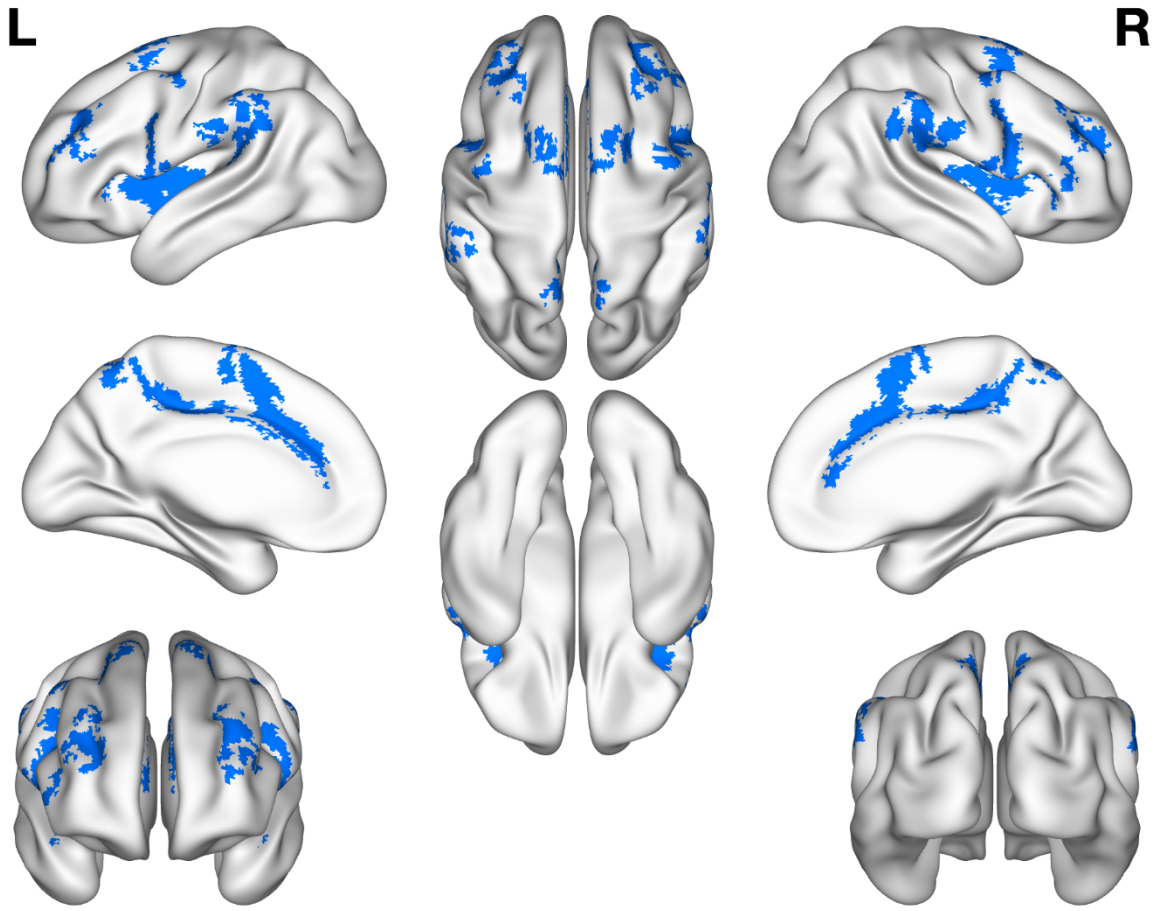
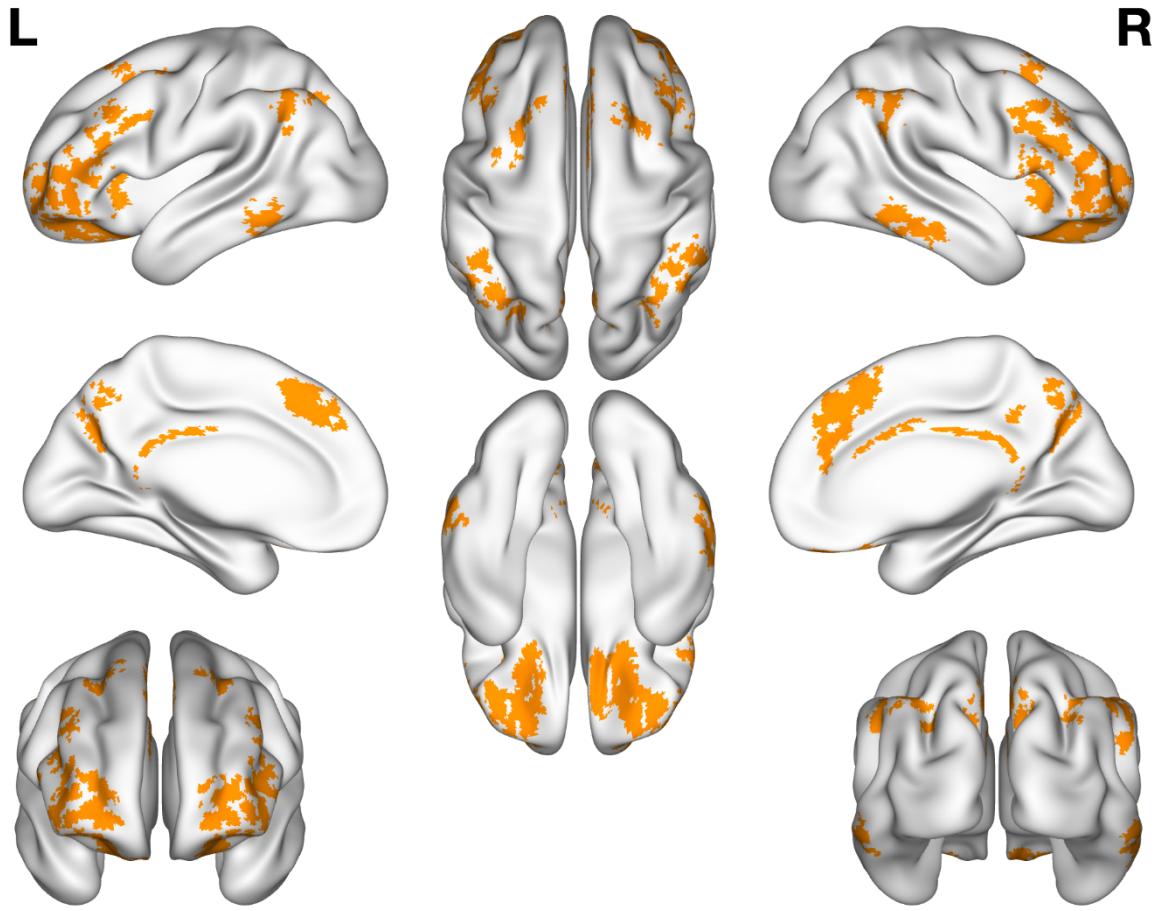


Table 2. Frontoparietal network (FPN) regions of interest. ROIs from the Glasser et al. (2016) Human Connectome Project (HCP) parcellation were classified as members of FPN based on Ji et al. (2019b).

Hemisphere	Label	Description
Left	L_RSC	RetroSplenial Complex
Left	L_POS2	Parieto-Occipital Sulcus Area 2
Left	L_7Pm	Medial Area 7P (SPL)
Left	L_8BM	Area 8BM (superior paracingulate)
Left	L_8C	Area 8C (dlPFC)
Left	L_a47r	Area anterior 47r (anterior lateral OFC)
Left	L_IFJp	Inferior frontal sulcus area IFJp (IFC)
Left	L_IFSa	Inferior frontal sulcus area IFSa (IFC)
Left	L_p9_46v	Area posterior 9-46v (central dlPFC)
Left	L_a9_46v	Area anterior 9-46v (central dlPFC)
Left	L_a10p	Area anterior 10p (fronto-polar)

Left	L_11l	Area 11l (anterior middle OFC)
Left	L_13l	Area 13l (middle OFC)
Left	L_i6_8	Inferior 6-8 Transitional Area (dlPFC)
Left	L_s6_8	Superior 6-8 Transitional Area (dlPFC)
Left	L_AVI	Anterior Ventral Insular Area
Left	L_TE1p	Area TE1 posterior (MTG)
Left	L_IP2	Area IntraParietal 2 (supramarginal)
Left	L_IP1	Area IntraParietal 1 (LOC)
Left	L_PFm	Area PFm Complex (supramarginal)
Left	L_p10p	Area posterior 10p (fronto-polar)
Left	L_p47r	Area posterior 47r (IFC)
Right	R_RSC	RetroSplenial Complex
Right	R_POS2	Parieto-Occipital Sulcus Area 2
Right	R_7Pm	Medial Area 7P (SPL)
Right	R_33pr	Area 33 prime (dACC)
Right	R_d32	Area dorsal 32 (superior rACC)
Right	R_8BM	Area 8BM (superior paracingulate)
Right	R_8C	Area 8C (dlPFC)
Right	R_44	Area 44 (IFC)
Right	R_a47r	Area anterior 47r (anterior lateral OFC)
Right	R_IFJp	Inferior frontal sulcus area IFJp (IFC)
Right	R_IFSp	Inferior frontal sulcus area IFSp (IFC)
Right	R_p9_46v	Area posterior 9-46v (central dlPFC)
Right	R_a9_46v	Area anterior 9-46v (central dlPFC)
Right	R_a10p	Area anterior 10p (fronto-polar)
Right	R_11l	Area 11l (anterior middle OFC)
Right	R_13l	Area 13l (middle OFC)
Right	R_OFC	Orbitofrontal
Right	R_i6_8	Inferior 6-8 Transitional Area (dlPFC)
Right	R_s6_8	Superior 6-8 Transitional Area (dlPFC)
Right	R_AVI	Anterior Ventral Insular Area
Right	R_TE1p	Area TE1 posterior (MTG)
Right	R_IP2	Area IntraParietal 2 (supramarginal)
Right	R_IP1	Area IntraParietal 1 (LOC)
Right	R_PFm	Area PFm Complex (supramarginal)
Right	R_31a	Area 31a (PCC)
Right	R_p10p	Area posterior 10p (fronto-polar)
Right	R_p47r	Area posterior 47r (IFC)
Right	R_TE1m	Area TE1 Middle (MTG)

Figure 3. Frontoparietal network (FPN) regions of interest (ROIs). Figure was created using BrainNet Viewer (http://www.nitrc.org/projects/bnv/; Xia, Wang, & He, 2013).



Selection of Graph Properties

A subset of graph properties was selected for analysis based on study hypotheses related to functional network segregation, integration, and robustness and node centrality (**Table 3**). The following brief definitions are based on Rubinov and Sporns (2010, 2011) and GTG documentation (Spielberg, 2014).

Clustering Coefficient: A measure of functional segregation that quantifies the extent to which nodes are organized into clusters of multiple interconnected nodes. In the present study,

we examined mean clustering coefficient across all nodes in the whole-brain network, CON, and FPN.

Current-Flow Global Efficiency: A measure of functional integration that represents the extent to which nodes can efficiently communicate with other nodes distributed throughout a network as opposed to communicating primarily within isolated subnetworks.

Assortativity: A measure of network robustness (i.e., resilience) that quantifies the extent to which highly connected nodes (also known as hubs) are connected to each other.

Transitivity: A measure of functional segregation that is computed by normalizing a network's mean clustering coefficient in order to avoid bias toward less connected nodes.

Node Strength: A measure of node centrality that quantifies the overall connectedness of a node to other nodes in the network.

Communicability Betweenness Centrality: A measure of node centrality that quantifies the extent to which a node facilitates connections between other nodes.

Eigenvector Centrality: A measure of node centrality that quantifies the extent to which a node is connected to other nodes that are highly connected (i.e., hubs).

Of the 368 ROIs included in whole-brain analyses, a subset of 10 ROIs located in right anterior insula and bilateral dACC were selected for analyses of node centrality. We focused on these regions based on their previously established role as hubs within CON and their demonstrated relevance to cognitive function (Wu et al., 2019; Brockett & Roesch, 2021). Although right anterior insula and dACC are typically characterized as members of CON, we evaluated their centrality in the context of the whole-brain network rather than within CON because 1) in the Ji et al. (2019b) classification that was used to identify CON and FPN ROIs in the present study, the regions we selected for centrality analyses were not classified as members

of CON, and 2) analyzing centrality in the whole-brain context allows for a more complete characterization of nodes' behavior as hubs, since hubs may participate in multiple networks or facilitate inter-network connections. A similar approach has been taken in other studies (e.g., Sheffield et al., 2015). For analyses focused on CON and FPN, rather than examining the centrality of specific nodes within each network, we computed total node strength across each network as a measure of the overall connectedness of nodes classified as network members.

Study 1 Analyses

Aim 1a. Connectivity matrices with robust correlations were computed using the GTG toolbox. For each participant, we generated a 368 x 368 whole-brain connectivity matrix, a 56 x 56 CON matrix, and a 50 x 50 FPN matrix. The GTG toolbox was then used to compute selected graph properties of the whole-brain network, CON, and FPN (**Table 3**) using positive weights only. To test for hypothesized group differences in graph properties, non-parametric permutation-based GLMs were computed within the GTG toolbox, with whole-brain and network-specific graph properties as dependent variables and group membership (SZ vs. HC) as the predictor.

Aim 1b. Graph properties were evaluated as predictors of cognitive performance in SZ and HC. Using the GTG toolbox, another series of GLMs was run with group (SZ vs. HC) and MCCB composite score entered simultaneously as independent variables, such that the test of the main effect of MCCB involved only its unique contribution to DV variance. A separate model tested a Group x MCCB interaction with main effects of group and MCCB partialed out. On an exploratory basis, separate models were used to test each domain-specific cognitive measure (MCCB working memory, attention/vigilance, and processing speed summary scores) as a predictor of graph properties, as well as the interaction of each domain-specific measure with

group. Effects were visualized using the ggplot2 function (Wickham, 2016) in R Statistical Software version 4.3.0 (R Core Team, 2023).

Correction for multiple comparisons. At each step of analysis, the set of tests associated with a single graph property was considered one family, and Bonferroni correction was used to control the family-wise error rate. For global (i.e., non-node-specific) properties that were evaluated for CON, FPN, and the whole-brain network (clustering coefficient, current-flow global efficiency, and assortativity), we divided our baseline significance threshold of .05 by the number of networks (three) to obtain a corrected critical α of .017. Total node strength was evaluated only for CON and FPN, so α was set at .05 / 2 = .025. The remaining global property, transitivity, was only evaluated for the whole-brain network, so no correction was applied, and α was set at .05. Node-specific properties (node strength, communicability betweenness centrality, and eigenvector centrality) were each evaluated for 10 nodes, so α was set at .05 / 10 = .005 (**Table 3**). A similar approach to correcting for multiple comparisons involving graph-theory properties has been taken in other studies (e.g., Sheffield et al., 2015).

Study 1 was intended to lay the foundation for Study 2 by informing our conceptualization of normalization and compensation following CT. Given this objective, as well as a lack of consensus in the literature regarding the relationship of graph properties to cognitive function in SZ, we tested a wide-ranging set of hypotheses in Study 1. Bonferroni correction is an overly conservative method for correcting for multiple comparisons when the comparisons are not independent. At the same time, we took a lenient approach by applying Bonferroni only within families of tests associated with each graph property rather than across the entire set of tests involved in each study aim. With this approach, we did not adjust significance thresholds or *p* values to account for the number of graph properties we examined (N = 8). Furthermore, since

MCCB composite score was our primary cognitive variable of interest, and tests of domain-specific MCCB summary scores (working memory, attention/vigilance, and processing speed) were considered exploratory, we treated tests associated with each MCCB subscore as separate families rather than correcting for the total number of tests performed across all four MCCB subscores. Thus, our application of Bonferroni was intended to strike a balance between minimizing Type I error and preserving the exploratory potential of Study 1, given our limited sample size.

Although effects were considered statistically significant only if they met Bonferroni-corrected critical α thresholds, all effects with uncorrected $p < .05$ are reported and discussed in the Study 1 Results and Discussion sections below. Although effects with critical $\alpha < p < .05$ should be interpreted with caution, they provide a basis for hypothesis testing in future studies with higher statistical power.

Table 3. Graph properties computed for the whole-brain network, CON, and FPN.

Graph Property	**Relevance**	**Critical α**
Whole Brain, CON, and FPN		
Clustering Coefficient	Functional segregation	.017
Current-Flow Global Efficiency	Functional integration	.017
Assortativity	Network robustness	.017
Whole Brain		
Transitivity	Functional segregation	.05
Node Strength		
R_AVI (anterior ventral insular area)	Centrality of right anterior insula	.005
R_AAIC (anterior agranular insula complex)		.005
L_33pr (area 33 prime)	Centrality of left dACC	.005
L_a24pr (area anterior 24 prime)		.005
L_p32pr (area posterior 32 prime)		.005
L_a32pr (area anterior 32 prime)		.005
R_33pr (area 33 prime)	Centrality of right dACC	.005
R_a24pr (area anterior 24 prime)		.005
R_p32pr (area posterior 32 prime)		.005
R_a32pr (area anterior 32 prime)		.005

Communicability Betweenness Centrality		
R_AVI (anterior ventral insular area)	Centrality of right anterior insula	.005
R_AAIC (anterior agranular insula complex)		.005
L_33pr (area 33 prime)	Centrality of left dACC	.005
L_a24pr (area anterior 24 prime)		.005
L_p32pr (area posterior 32 prime)		.005
L_a32pr (area anterior 32 prime)		.005
R_33pr (area 33 prime)	Centrality of right dACC	.005
R_a24pr (area anterior 24 prime)		.005
R_p32pr (area posterior 32 prime)		.005
R_a32pr (area anterior 32 prime)		.005
Eigenvector Centrality		
R_AVI (anterior ventral insular area)	Centrality of right anterior insula	.005
R_AAIC (anterior agranular insula complex)		.005
L_33pr (area 33 prime)	Centrality of left dACC	.005
L_a24pr (area anterior 24 prime)		.005
L_p32pr (area posterior 32 prime)		.005
L_a32pr (area anterior 32 prime)		.005
R_33pr (area 33 prime)	Centrality of right dACC	.005
R_a24pr (area anterior 24 prime)		.005
R_p32pr (area posterior 32 prime)		.005
R_a32pr (area anterior 32 prime)		.005
CON & FPN		
Total Node Strength	Overall node centrality	.025

Note. Critical α values listed in this table were used as significance thresholds for all tests in Aims 1a and 1b (i.e., main effect of group, main effect of MCCB subscores, and Group x MCCB interactions), as well as all tests in Study 2.

Results

Participants

Complete demographic, clinical, and cognitive data for Study 1 participants are provided in **Table 4**. SZ and HC did not differ in age ($t(72) = 1.37$, $p = .176$), sex ($t(75) = 1.26$, $p = .210$), race/ethnicity ($\chi^2(7) = 7.41$, $p = .388$), educational attainment ($t(75) = -1.76$, $p = .082$), or highest parental educational attainment ($t(75) = 0.23$, $p = .818$). As expected, SZ scored lower than HC on the MCCB composite score ($t(75) = -7.03$, $p < .001$, Cohen's $d = -1.63$) and working memory

($t(75) = -4.00$, $p < .001$, Cohen's $d = -0.92$), attention/vigilance ($t(75) = -2.69$, $p = .009$, Cohen's $d = -0.62$), and processing speed summary scores ($t(75) = -6.69$, $p < .001$, Cohen's $d = -1.55$).

Table 4. Demographic and clinical characteristics of participants, Study 1.

	Participants with First-Episode SZ (N = 45)	**Healthy Comparison Participants (N = 32)**
Demographics		
Age, years *M (SD)*[a]	22.95 (5.24)	21.50 (3.38)
Sex (female) *N (%)*	19 (42.22%)	9 (28.13%)
Race/Ethnicity *N (%)*		
Asian, Asian American, or Pacific Islander	10 (22.22%)	7 (21.88%)
Black or African American	6 (13.33%)	2 (6.25%)
White	10 (22.22%)	7 (21.88%)
Hispanic or Latinx	15 (33.33%)	12 (37.5%)
Southwest Asian/North African	0 (0%)	3 (9.38%)
Native American	1 (2.22%)	0 (0%)
Other or Multiracial	1 (2.22%)	1 (3.13%)
Unknown	2 (4.44%)	0 (0%)
Education, years *M (SD)*	13.42 (2.05)	14.19 (1.61)
Highest parental education, years *M (SD)*	15.24 (3.53)	15.05 (3.94)
Clinical Characteristics		
DSM-5 Diagnosis *N (%)*		
Schizophrenia	33 (73.33%)	--
Schizoaffective Disorder, depressed type	3 (6.67%)	--
Schizophreniform Disorder	9 (20.00%)	--
SAPS Total Score *M (SD)*[b]	10.39 (3.82)	--
SANS Total Score *M (SD)*[b]	12.80 (4.71)	--
BPRS Total Score *M (SD)*	42.73 (12.38)	--
MCCB Scores *M (SD)*		
Composite	34.13 (10.78)	50.94 (9.69)
Working Memory	43.00 (11.17)	53.06 (10.47)
Attention/Vigilance	40.69 (9.86)	46.56 (8.87)
Processing Speed	35.27 (12.01)	52.94 (10.56)

Note. SAPS, Scale for the Assessment of Positive Symptoms (Andreasen, 1984). SANS, Scale for the Assessment of Negative Symptoms (Andreasen, 1989). BPRS, Brief Psychiatric Rating Scale (Overall & Gorham, 1962). MCCB, MATRICS Consensus Cognitive Battery (Kern et al., 2008; Nuechterlein et al., 2008).

[a] Age: For SZ, N = 42 due to missing data.

[b] SAPS and SANS: N = 41 SZ due to missing data.

Group Differences in Graph Properties

To evaluate group differences in graph properties, the GTG toolbox was used to run robust GLMs with 5,000 non-parametric permutations. Group was dummy coded with HC as the reference group (SZ = 1 and HC = 0), and the intercept term occupied a second column in the design matrix. The contrast [1 0] was tested, with a two-tailed *t* test used to evaluate the beta coefficient for group. Separate GLMs were run for whole-brain properties, CON properties, and FPN properties. For global (non-node-specific) properties other than total node strength (i.e., clustering coefficient, current-flow global efficiency, assortativity, and transitivity), network density and total strength were included as covariates of no interest to remove variance related to overall intra-network connectivity. For node-specific properties other than node strength, covariates of no interest included network density, total strength, node degree, and node strength. For GLMs testing whole-brain node strength of individual nodes, only network density and total strength were included as covariates of no interest. For GLMs testing total node strength within CON and FPN, no covariates of no interest were included, as total node strength (a covariate in other analyses) was the DV in this case, and variance related to network density was expected to have excessive overlap with the DV.

SZ and HC did not differ on measures of whole-brain functional segregation (mean clustering coefficient, transitivity), whole-brain functional integration (current-flow global efficiency), whole-brain network robustness (assortativity), or whole-brain centrality of right anterior insula or dACC (node strength, communicability betweenness centrality, eigenvector centrality). SZ and HC also did not evidence any differences in segregation (mean clustering coefficient), integration (current-flow global efficiency), robustness (assortativity), or total node strength within CON or FPN.

Association of Graph Properties with Cognitive Performance

Given that SZ did not differ from HC on any of the graph metrics evaluated above, we tested for associations between graph metrics and cognitive function across groups (i.e., main effect of MCCB score with group-related variance partialed out). The series of GLMs described above was rerun, this time with both MCCB composite score and dummy-coded group entered simultaneously as independent variables and the intercept in the third column of the design matrix. All other specifications, including covariates, were the same as described above. The contrast [1 0 0] was used to test for the main effect of MCCB composite score, with two-tailed *t* tests used to evaluate the beta coefficient. GLMs were then repeated on an exploratory basis with each of the domain-specific MCCB scores (MCCB working memory, attention/vigilance, and processing speed) entered as an independent variable alongside group.

Across groups, node strength of R_p32pr (area posterior 32 prime in right dACC) was positively associated with MCCB composite score, $t = 2.92$, $p = .004$ (**Figure 4**). There was no significant main effect of MCCB composite score on measures of whole-brain functional segregation (mean clustering coefficient, transitivity), whole-brain functional integration (current-flow global efficiency), whole-brain network robustness (assortativity), whole-brain centrality of other nodes in right anterior insula or dACC (node strength, communicability betweenness centrality, eigenvector centrality), CON or FPN segregation (mean clustering coefficient), CON or FPN integration (current-flow global efficiency), CON or FPN robustness (assortativity), or total node strength within CON or FPN.

Exploratory analyses revealed a main effect of MCCB attention/vigilance on FPN current-flow global efficiency that did not survive correction for multiple comparisons, $t = -1.27$, $p = .028$ (n.s.) (**Figure 5**; an outlier may be driving the effect). There were no other main effects

of domain-specific MCCB scores (working memory, attention/vigilance, or processing speed) on any of the whole-brain or network-specific graph metrics that we evaluated.

Figure 4. Main effect of MCCB composite score on node strength of R_p32pr. Across groups, MCCB composite score was positively associated with node strength of area p32 prime in right dACC. Plotted node strength values are residuals following regression on two covariates of no interest, network density and total strength.

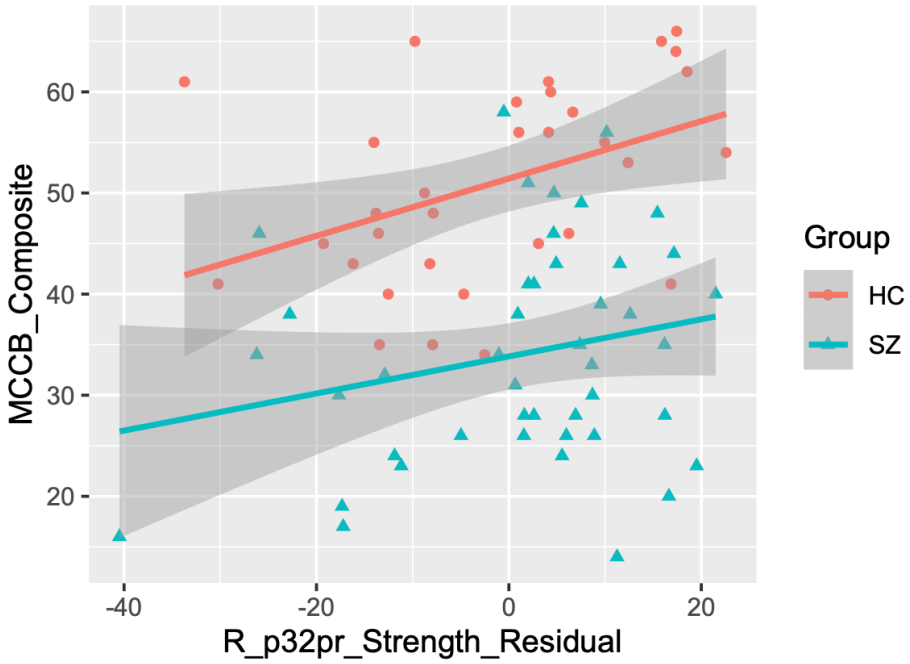
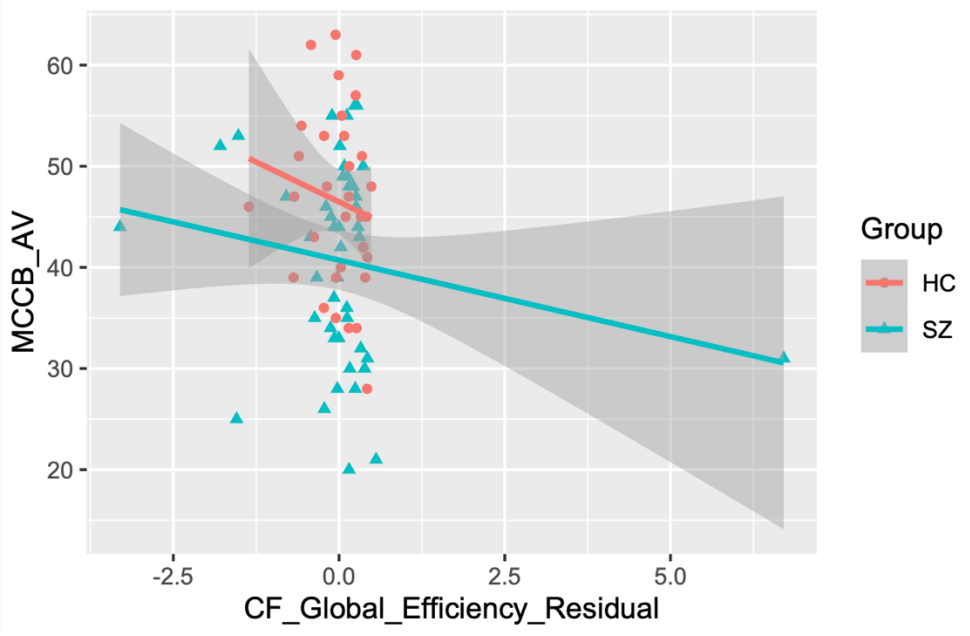


Figure 5. Main effect of MCCB attention/vigilance on current-flow global efficiency within FPN. Across groups, there was a non-significant negative association between attention/vigilance and FPN current-flow global efficiency, a measure of functional integration. Plotted current-flow global efficiency values are residuals following regression on two covariates of no interest, FPN network density and total strength.



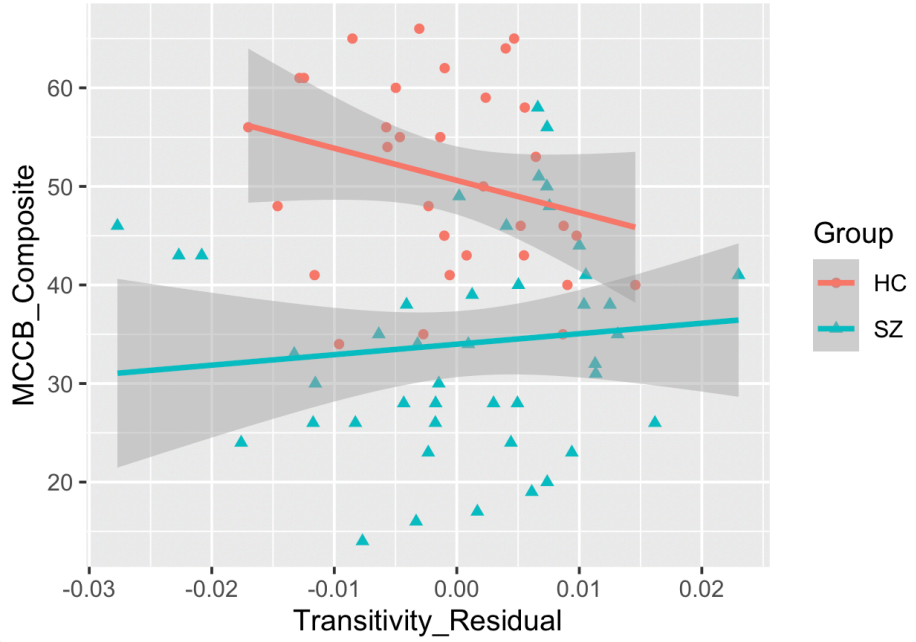
Group Differences in the Association of Graph Properties with Cognitive Performance

A final series of GLMs tested interactions between group and MCCB scores in predicting whole-brain, CON, and FPN graph properties. An interaction term was computed by multiplying the dummy-coded group variable by MCCB composite score. In each GLM, MCCB composite score, group, and the interaction term were entered as independent variables, with the intercept in the fourth column of the design matrix. The contrast [0 0 1 0] was tested, and two-tailed *t* tests were used to evaluate the beta coefficient for the interaction term. All other specifications, including covariates of no interest, were the same as described above. GLMs were repeated on an exploratory basis with domain-specific MCCB scores substituted for the composite score.

There was an interaction between group and MCCB composite score in predicting whole-brain transitivity, such that transitivity was more positively associated with MCCB composite

score among SZ than among HC, $t = 2.17$, $p = .028$ (**Figure 6**). There were no significant interactions between group and MCCB composite score for any of the other whole-brain, CON, or FPN metrics we evaluated.

Figure 6. Interaction of Group x MCCB composite score in relation to whole-brain transitivity. Plotted transitivity values are residuals following regression on two covariates of no interest, network density and total strength.



Exploratory analyses involving domain-specific MCCB scores revealed several interactions between group and MCCB working memory summary score that were non-significant after correcting for multiple comparisons. Group and MCCB working memory interacted to predict whole-brain assortativity, such that assortativity was less negatively associated with working memory for SZ than for HC, $t = 2.25$, $p = .023$ (n.s. after correcting for multiple comparisons) (**Figure 7**). There were also interactions between group and MCCB working memory in relation to several measures of dACC node centrality: node strength of R_p32pr (area posterior 32 prime in right dACC), $t = -2.11$, $p = .037$ (n.s.) (**Figure 8a**),

eigenvector centrality of L_a24pr (area anterior 24 prime in left dACC), t = -2.04, p = .048 (n.s.) (**Figure 8b**), eigenvector centrality of L_a32pr (area anterior 32 prime in left dACC), t = -2.00, p = .046 (n.s.) (**Figure 8c**), and eigenvector centrality of R_a24pr (area anterior 24 prime in right dACC), t = -2.14, p = .032 (n.s.) (**Figure 8d**). Each of these metrics was less positively associated with working memory in SZ than in HC.

Figure 7. Interaction of Group x MCCB working memory in relation to whole-brain assortativity. The relationship between whole-brain assortativity and MCCB working memory summary score was less negative for SZ than for HC, though this effect was not significant after correcting for multiple comparisons. Plotted assortativity values are residuals following regression on two covariates of no interest, network density and total strength.

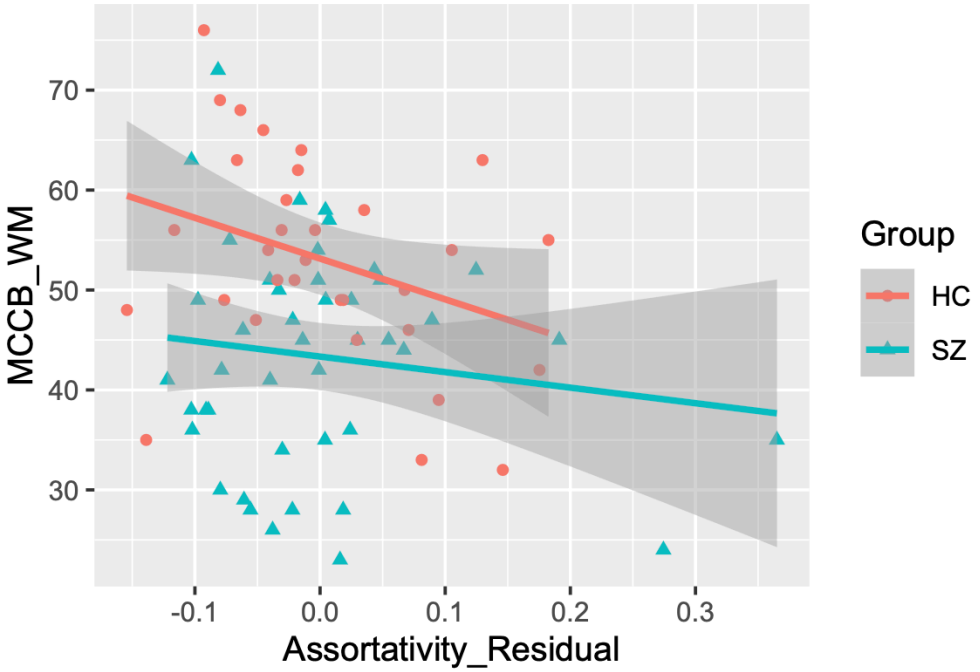
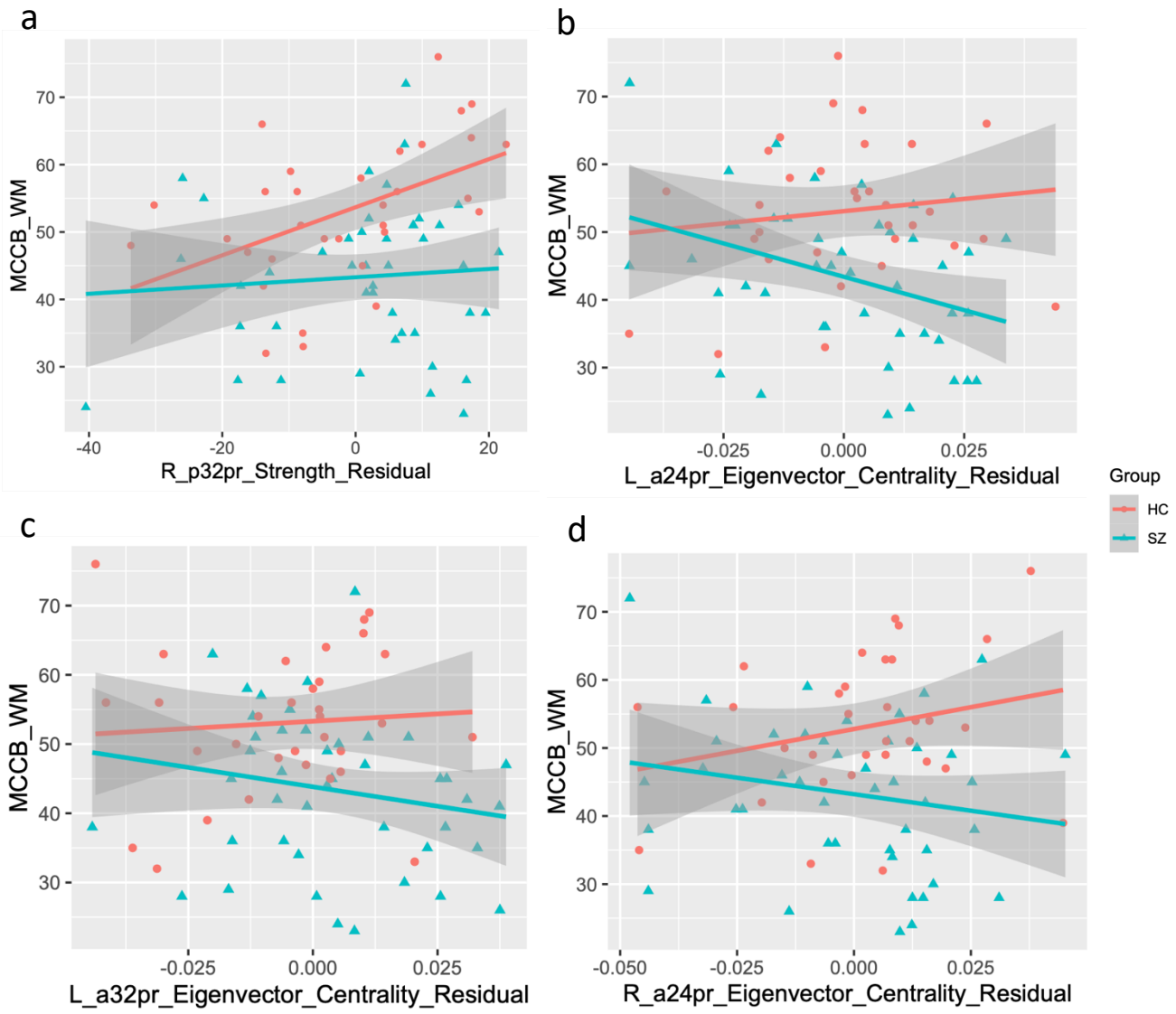
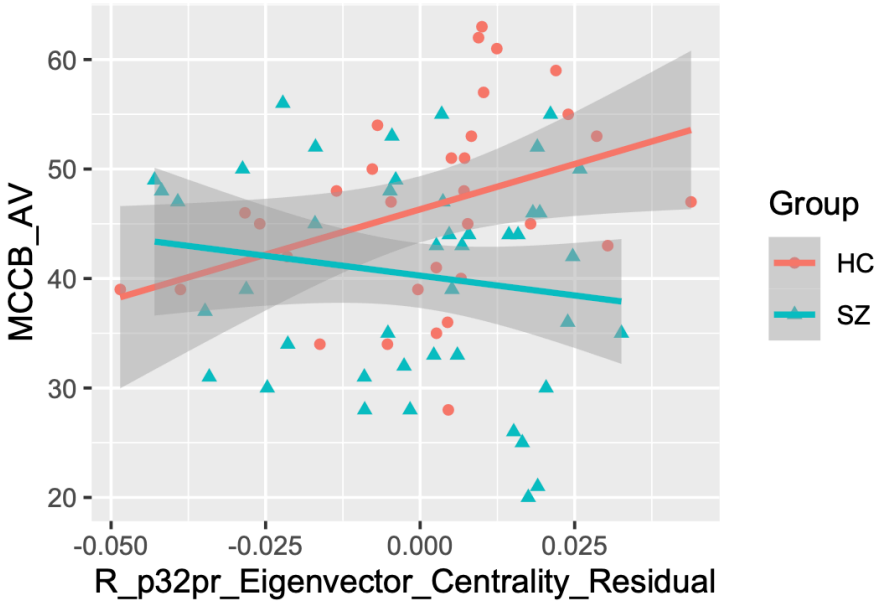


Figure 8. Interaction of Group x MCCB working memory in relation to dACC node centrality. 8a: Node strength of R_p32pr was more positively associated with working memory in HC than in SZ, though this effect was not significant after correcting for multiple comparisons. Plotted node strength values are residuals following regression on two covariates of no interest, network density and total strength. 8b-d: Eigenvector centrality of L_a24pr, L_a32pr, and R_a24pr was positively associated with working memory in HC but negatively associated with working memory in SZ, though these interaction effects were not significant after correcting for multiple comparisons. Plotted eigenvector centrality values are residuals following regression on four covariates of no interest: network density, total strength, node degree, and node strength.



Finally, there was an interaction between group and MCCB attention/vigilance summary score in relation to eigenvector centrality of R_p32pr that was not significant after correcting for multiple comparisons, t = -1.96, p = .05 (n.s.) (**Figure 9**). Attention/vigilance was less positively associated with eigenvector centrality of R_p32pr for SZ than for HC.

Figure 9. Interaction of Group x MCCB attention/vigilance in relation to eigenvector centrality of R_p32pr. The positive relationship between eigenvector centrality of R_p32pr and MCCB attention/vigilance summary score was less pronounced for SZ than for HC, though this effect was not significant after correcting for multiple comparisons. Plotted eigenvector centrality values are residuals following regression on four covariates of no interest: network density, total strength, node degree, and node strength.



There were no significant interactions of group with MCCB processing speed summary score for any of the whole-brain, CON, or FPN graph metrics examined here.

Discussion

The objective of Study 1 was to identify aberrant features of resting-state functional network organization in first-episode SZ and evaluate their relationship to generalized and domain-specific cognitive function. It was hypothesized that SZ would show altered network

organization consistent with a pattern of reduced functional segregation and intact or elevated global integration and robustness, as well as reduced centrality of CON hubs and reduced clustering and global efficiency within CON. We anticipated that most of these network features would be associated with cognitive impairment but that some (i.e., elevated global integration and robustness) might represent naturalistic compensation. Contrary to hypotheses, SZ did not differ from HC on any of the properties of functional network organization that we evaluated. However, results indicated that whole-brain functional segregation may be more beneficial to generalized cognitive performance in SZ than in HC, possibly reflecting a naturalistic compensatory mechanism. In addition, we found evidence that the strength of a node in right dACC is associated with generalized cognitive performance across SZ and HC, suggesting a shared mechanism of cognitive function that is intact in first-episode SZ. Conversely, we found that in SZ, certain features of functional network organization (including centrality of several nodes in bilateral dACC) may be decoupled from cognitive performance. These findings suggest that aspects of cognitive performance in SZ do not rely on the same functional network features as in HC, which may indirectly reflect the role of compensatory neural mechanisms of cognitive function. Alternatively or in addition, cognitive impairment in SZ may be more related to disrupted engagement of network processes than to disruptions in network organization itself, leading SZ to experience less cognitive benefit from network features that resemble those of HC. Notably, some effects were found only for a single domain of cognitive function (e.g., decoupling of dACC node centrality from cognitive performance was only found in the domain of working memory), suggesting relevance to specialized rather than generalized cognitive processes. However, the latter set of effects did not survive correction for multiple comparisons, so this interpretation must be regarded cautiously.

Based on prior literature (Alexander-Bloch et al., 2010; Fornito, Zalesky, Pantelis, & Bullmore, 2012; Vecchio et al., 2023), it was hypothesized that an overall reduction in functional network segregation would serve as a mechanism of cognitive impairment in SZ. However, SZ did not differ from HC on measures of network segregation (whole-brain transitivity; clustering coefficient of CON, FPN, and the whole-brain network), and across groups, these measures were not associated with cognitive performance. Surprisingly, a Group x MCCB interaction indicated that in SZ, whole-brain transitivity was more positively associated with generalized cognitive function than in HC. In other words, functional segregation appeared more beneficial to cognitive performance in SZ than in HC. Given previous literature suggesting that segregation is reduced in SZ, it is possible that this effect was related to illness severity and/or duration (i.e., both segregation and cognitive performance may have been higher among participants with less severe and/or more recent-onset illness). Alternatively, the present findings could be interpreted as evidence that, to the extent that functional segregation is present in SZ, it serves as a compensatory mechanism supporting cognitive function.

More broadly, the present findings raise questions about the role of functional segregation in SZ cognitive function and whether this role differs in HC. Studies of neurotypical adults have indicated that cognitive function is supported by a balance between functional segregation and integration and that different cognitive processes are optimized by each (Wang et al., 2021). In both SZ and non-psychosis samples, generalized cognitive function has been positively associated with measures of functional integration (Wang et al., 2021; Sheffield et al., 2015, 2016, 2017). Although in the present study, there were no significant effects related to whole-brain integration (i.e., current-flow global efficiency), it is possible that generalized cognitive function in HC relied on the coexistence of segregation and integration (i.e., small

worldness) or on an optimal balance between the two rather than benefitting linearly from segregation. In follow-up studies, it may be beneficial to examine the balance between segregation and integration (as has been done in other studies, e.g., Duan et al., 2019) and whether the optimal ratio is different in SZ than in HC.

We also hypothesized that two hubs associated with CON – right anterior insula and bilateral dACC – would demonstrate lower centrality in SZ than in HC. Although this hypothesis was not supported, we did find that across groups, node strength of R_p32pr (a dACC node representing right area posterior 32 prime) was positively associated with MCCB composite score. Contrary to hypotheses, this suggests that centrality of right posterior dACC is an intact mechanism of generalized cognitive function in SZ. This finding may have implications for understanding mechanisms of CT interventions. Specifically, enhancing connectivity of R_p32pr may not be a fruitful target for interventions seeking to normalize disruptions in network functioning, but it may be an appropriate target for interventions seeking to promote compensation by enhancing intact network processes.

A consistent pattern of effects emerged from exploratory analyses of dACC node centrality in relation to MCCB working memory summary score, although these effects were non-significant after correcting for multiple comparisons. The eigenvector centrality of three nodes in dACC (R_a24pr, L_a24pr, and L_a32pr, representing bilateral area anterior 24 prime and left area anterior 32 prime) was more positively associated with working memory in HC than in SZ. A similar effect was observed for node strength of a fourth dACC node (R_p32pr), despite its positive association with generalized cognitive function across groups. Taken together, these findings suggest that further research is warranted to determine whether working memory in SZ relies less on dACC hubs than it does in HC. If such a finding emerged in better-powered

studies, it would suggest that dACC hubs are less beneficial to working memory in SZ despite maintaining their centrality within the global network. This could be the result of reduced engagement of these regions during working memory tasks. Future studies may be able to provide further insight by examining dACC activation and centrality during working memory tasks in addition to during the resting state. It may also be beneficial to examine whether reduced reliance on dACC centrality is associated with increased, compensatory reliance on alternative nodes or hubs that were not evaluated in the present study (e.g., nodes in posterior parietal cortex, as suggested by Quintana et al., 2003).

Consistent with a pattern of network metrics becoming decoupled from cognitive performance, whole-brain network assortativity (a measure of robustness) was more negatively associated with cognitive function in HC than in SZ, although this effect was non-significant after correction for multiple comparisons. Notably, although some studies have reported elevated network robustness in SZ (e.g., Lynall et al., 2010), no group differences in assortativity emerged in the present study. It is possible that in SZ, widely distributed functional dysconnectivity (as has been demonstrated in a large body of literature) and/or reduced recruitment of specialized nodes during cognitive tasks (e.g., Crossley et al., 2016) makes network resilience less relevant to cognitive performance in SZ. Although the present findings do not provide any evidence of naturalistic compensation through elevated robustness in SZ, they do suggest that elevated robustness is less detrimental or perhaps less relevant to cognitive performance in SZ than in HC.

A secondary objective of the present study was to explore whether features of network organization corresponded with generalized or domain-specific cognitive function and impairment in SZ. Previous findings have been mixed, with few consistent associations emerging between specific patterns of functional dysconnectivity and individual cognitive domains

(Sheffield & Barch, 2016). In the present study, analyses involving domain-specific MCCB summary scores were considered exploratory. Furthermore, we did not make direct comparisons between different MCCB summary scores' associations with graph properties, so we cannot make inferences about the domain specificity of the observed effects. It is nonetheless notable that for three of the four dACC nodes that showed non-significant Group x MCCB working memory interactions in relation to measures of node centrality, similar effects did not emerge for generalized cognitive function, attention/vigilance, or processing speed. It is possible that decoupling of dACC centrality from cognitive function specifically impacts cognitive processes relevant to working memory, and it may be informative to formally test this hypothesis in future resting-state and task-based studies. Thus, the present non-significant findings can be seen as laying the groundwork for future, hypothesis-driven investigations of domain specificity.

In exploratory analyses of main effects, a non-significant relationship emerged between FPN global efficiency and the MCCB attention/vigilance summary score. Across both SZ and HC, higher FPN global efficiency was associated with lower attention/vigilance score. A specific relationship between FPN efficiency and the domain of attention/vigilance is plausible given FPN's established relationship to attention (Markett et al., 2014). However, the direction of the observed non-significant effect was unexpected, as we had hypothesized that in Study 2, compensation following CT might consist of increased FPN global efficiency accompanied by gains in cognitive function. Furthermore, previous studies have linked lower FPN efficiency to working memory impairment in major depressive disorder (Tan et al., 2021) and higher FPN efficiency to generalized cognitive performance in both SZ and HC (Sheffield et al., 2015). As discussed above, it may be useful in future studies to examine measures of functional segregation and integration in tandem and to clarify whether different ratios between these measures are

beneficial to different types of cognitive tasks in SZ and HC. In the case of FPN, further investigation is needed to determine whether integration (i.e., global efficiency) impacts attention/vigilance differently than other cognitive domains.

Although the lack of any group differences in whole-brain, CON, or FPN properties contradicts hypotheses, it aligns with a recent meta-analysis that found that SZ resembled HC on most graph metrics of functional networks (Gao et al., 2023). The lack of group differences in the present sample also aligns with Sheffield et al. (2015)'s findings. Taken together with the other results of Study 1, this lack of group differences highlights the importance of conceptualizing cognitive impairment as arising not necessarily from disruptions in network organization, but also potentially from dissociation of network features from key cognitive processes. It is also possible that graph properties do not distinguish SZ from HC as reliably as other measures of neural network disruption. In a machine learning study, Lei et al. (2020) demonstrated that individuals with SZ were more consistently differentiated from HC by overall functional connectivity than by graph properties of functional networks. As discussed by Gao et al. (2023), meaningful but poorly understood heterogeneity within SZ may account for contradictory effects and lack of effects at the group level when studying graph properties.

Overall, the present study sheds light on both intact and altered neural mechanisms of cognitive function in first-episode SZ. Most notably, we found evidence that a hub in right dACC supports generalized cognitive function across SZ and HC but that whole-brain transitivity may have different implications in each group. Our findings highlight the need for cognitive neuroscience studies of SZ to consider not only network dysconnectivity itself, but also disruptions in the relationship between network organization and cognition. Results from the present study suggest that on a group level, the organization of key networks (CON and FPN)

and the global network in SZ resembles typical network organization. However, certain features of network organization may be decoupled from cognitive performance. This insight has implications for theorizing about mechanisms of CT interventions in SZ. Specifically, rather than targeting network organization itself, CT interventions may benefit from attempting to increase the extent to which individuals with SZ engage existing network processes or hubs while completing cognitive tasks. Future studies can expand on the present findings by formally investigating the domain-specificity of the observed effects and by exploring whether decoupling of network features from cognition is accompanied by naturalistic compensation in other nodes or networks in SZ.

Study 2: Normalization and Compensation in Functional Networks following Cognitive Training and Implications for Cognitive Recovery

Method

Participants

Participants with SZ from Study 1 were included in Study 2 if they 1) completed the 24-week CT intervention detailed below and 2) completed a follow-up MRI approximately six months after their initial MRI. HC participants from Study 1 were included in Study 2 if they completed a follow-up MRI approximately six months after their initial MRI and continued to meet all inclusion criteria. Of the participants included in Study 1, 17 SZ and 20 HC provided 6-month follow-up data and were included in Study 2.

Cognitive Training Intervention

Following their initial study visit, participants with SZ received a 24-week CT intervention as part of their participation in the RCT. SZ participants also attended a weekly bridging skills group, in which they discussed and practiced strategies for translating cognitive

skills from CT to everyday life. To promote adherence, participants received small monetary incentives for completing CT sessions. Intervention procedures are detailed by Nuechterlein and colleagues (2016, 2023).

The CT intervention consisted of 96 total hours of computerized CT, half of which specifically targeted neurocognitive domains (auditory discrimination, speed of processing, working memory, verbal memory, and verbal reasoning) and half of which targeted social and affective cognitive skills. This approach integrated aspects of bottom-up and top-down cognitive training (Nuechterlein et al., 2014) by beginning with training of fundamental sensory processes and progressing to training of complex cognitive skills. Intervention content was developed by BrainHQ of Posit Science Corporation. Initial results from the RCT associated with the present studies confirmed the efficacy of the CT intervention (Nuechterlein et al., 2023).

HC participants did not receive any intervention.

Cognitive Assessment

SZ and HC participants completed a second administration of the MCCB following procedures described in Study 1. SZ were administered the follow-up MCCB after completing the CT intervention (approximately six months following initial assessment). HC completed the follow-up MCCB approximately six months after their initial MCCB. In both groups, different forms of the Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997), which assesses visual learning, and the Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt & Benedict, 2001), which assesses verbal learning, were administered at six-month follow-up to minimize practice effects from the initial assessment.

Neuroimaging Data Acquisition & Preprocessing

Neuroimaging data collected at the six-month time point were acquired and preprocessed using procedures identical to those described in Study 1. As in Study 1, the Glasser et al. (2016) HCP cortical atlas was applied to each participant's rs-fMRI data and concatenated with participant-specific subcortical ROIs produced by FSL FIRST, resulting in 372 total ROIs. Four ROIs, consistent with those removed in Study 1, were removed for all participants, resulting in 368 ROIs that were used to compute whole-brain graph properties. The 56 CON ROIs and 50 FPN ROIs that were selected based on the Ji et al. (2019b) network classification (see Study 1) were used to evaluate intra-network properties for CON and FPN.

Study 2 Analyses

As in Study 1, the GTG toolbox was used to compute a 368 x 368 whole-brain connectivity matrix, a 56 x 56 CON matrix, and a 50 x 50 FPN matrix for each participant. Matrices from the six-month time point were concatenated with matrices from the pre-intervention time point to create a repeated-measures data structure for each participant. The same set of graph properties evaluated in Study 1 (**Table 3**) was computed for each participant at each time point using positive weights only. The GLM tool within the GTG toolbox was used to test for change in graph-theory properties from pre- to post-intervention in SZ. A separate repeated-measures GLM was run for each graph property of interest, with graph properties at the pre-intervention and six-month time points entered as repeated measures and group (SZ vs. HC) entered as a dummy-coded independent variable. A Group x Time interaction was tested to evaluate whether SZ experienced change in graph properties that differed from change experienced by HC. As we did not hypothesize any meaningful change in HC network properties given the lack of experimental intervention in this group, this design was intended to detect

change in SZ network properties that exceeded a level of variance in graph properties attributable to scanning participants at two different time points.

Associations between change in graph properties and change in cognitive performance in SZ were evaluated using a repeated-measures design with longitudinal data from SZ participants only. Change in cognitive performance was examined in relation to change in all graph properties of interest, even those that did not evidence change from pre- to post-intervention, because clinically relevant change could have occurred only in a subset of SZ participants. In other words, change in a given graph property could be associated with change in cognitive function even if, on a group level, SZ did not experience significant change in that property. MCCB change scores were computed for each participant by subtracting baseline scores from six-month scores. In a series of GLMs, MCCB composite change score was entered as a continuous predictor, with graph properties at the pre-intervention and six-month time points entered as repeated measures, and an MCCB x Time interaction was tested. The interaction term was used to evaluate whether change in MCCB composite score was associated with changes in graph properties from pre- to post-intervention. On an exploratory basis, analyses were repeated using domain-specific MCCB scores for working memory, attention/vigilance, and processing speed.

As in Study 1, network density and total strength were included as covariates of no interest in analyses of clustering coefficient, current-flow global efficiency, assortativity, and transitivity. Network density, total strength, node degree, and node strength were included as covariates of no interest in analyses of communicability betweenness centrality and eigenvector centrality. In analyses of individual nodes' strength within the whole-brain network, only network density and total strength were included as covariates of no interest. For GLMs testing

total node strength within CON and FPN, no covariates of no interest were included, as total node strength (a covariate in other analyses) was the DV in this case, and variance related to network density was expected to have excessive overlap with the DV.

To correct for multiple comparisons, Bonferroni-adjusted critical α values were selected for tests of each graph property following the same procedures described in Study 1 (α values are listed in **Table 3**). As in Study 1, all effects with uncorrected $p < .05$ are reported and discussed below, as effects that were non-significant after Bonferroni correction may inform the design of future studies with higher statistical power. Effects were visualized using the ggplot2 function (Wickham, 2016) in R Statistical Software version 4.3.0 (R Core Team, 2023).

Aim 2a. Normalization: As described above (see Project Overview), changes in network properties following CT were considered to reflect normalization if they i) involved decreases in properties that were aberrant in SZ prior to intervention and predictive of pre-intervention cognitive impairment or ii) involved increases in properties that differentiated HC from SZ prior to intervention and positively predicted cognitive targets in HC. Although no group differences in graph properties emerged in the larger Study 1 sample, it was unknown whether the Study 2 subsample displayed any group differences in graph properties at the pre-intervention time point. Therefore, normalization was not ruled out as a possibility in Study 2.

Aim 2b. Compensation: As described above (see Project Overview), changes in network properties following CT were considered compensation if they i) were positively associated with post-intervention cognitive performance, ii) involved properties that were not associated with cognitive impairment prior to intervention, and iii) did not involve properties that positively predicted cognitive performance in HC.

Results

Participants

Complete demographic, clinical, and cognitive data for Study 2 participants are provided in **Table 5**. SZ and HC did not differ in age ($t(34) = 1.01$, $p = .318$), sex ($t(35) = 0.65$, $p = .520$), race/ethnicity ($\chi^2(6) = 5.08$, $p = .533$), educational attainment ($t(35) = -0.70$, $p = .489$), or highest parental educational attainment ($t(35) = -0.02$, $p = .986$). As expected, prior to CT, SZ scored lower than HC on the MCCB composite score ($t(35) = -4.32$, $p < .001$, Cohen's $d = -1.43$) and working memory ($t(35) = -2.87$, $p = .007$, Cohen's $d = -0.95$), attention/vigilance ($t(35) = -2.10$, $p = .043$, Cohen's $d = -0.69$), and processing speed summary scores ($t(35) = -3.78$, $p < .001$, Cohen's $d = -1.25$).

Table 5. Demographic and clinical characteristics of participants, Study 2.

	Participants with First-Episode SZ (N = 17)	**Healthy Comparison Participants (N = 20)**
Demographics		
Age, years *M (SD)*[a]	23.38 (4.60)	21.95 (3.85)
Sex (female) *N (%)*	5 (29.41%)	4 (20.00%)
Race/Ethnicity *N (%)*		
Asian, Asian American, or Pacific Islander	5 (29.41%)	5 (25.00%)
Black or African American	3 (17.65%)	2 (10.00%)
White	3 (17.65%)	3 (15.00%)
Hispanic or Latinx	5 (29.41%)	6 (30.00%)
Southwest Asian/North African	0 (0%)	3 (15.00%)
Native American	0 (0%)	0 (0%)
Other or Multiracial	0 (0%)	1 (5.00%)
Unknown	1 (5.88%)	0 (0%)
Education, years *M (SD)*	13.82 (2.04)	14.25 (1.67)
Highest parental education, years *M (SD)*	15.35 (3.61)	15.38 (3.72)
Clinical Characteristics at Baseline		
DSM-5 Diagnosis *N (%)*		
Schizophrenia	14 (82.35%)	--
Schizoaffective Disorder, depressed type	0 (0%)	--
Schizophreniform Disorder	3 (17.65%)	--
SAPS Total Score *M (SD)*	10.88 (4.14)	--

SANS Total Score *M (SD)*	12.47 (4.29)	--
BPRS Total Score *M (SD)*	43.12 (13.74)	--
Clinical Characteristics at Six-Month Follow-Up		
SAPS Total Score *M (SD)*	5.88 (4.61)	--
SANS Total Score *M (SD)*	7.94 (4.66)	--
BPRS Total Score *M (SD)*	40.41 (14.88)	--
MCCB Scores at Baseline *M (SD)*		
Composite	32.88 (12.65)	48.25 (8.91)
Working Memory	40.59 (10.88)	51.25 (11.57)
Attention/Vigilance	38.18 (10.20)	44.55 (8.26)
Processing Speed	35.18 (13.59)	50.75 (11.50)
MCCB Scores at Six-Month Follow-Up *M (SD)*		
Composite	37.18 (13.09)	53.65 (9.86)
Working Memory	42.82 (10.00)	54.00 (11.66)
Attention/Vigilance	41.06 (9.60)	46.00 (9.98)
Processing Speed	38.35 (11.47)	56.45 (10.97)

Note. SAPS, Scale for the Assessment of Positive Symptoms (Andreasen, 1984). SANS, Scale for the Assessment of Negative Symptoms (Andreasen, 1989). BPRS, Brief Psychiatric Rating Scale (Overall & Gorham, 1962). MCCB, MATRICS Consensus Cognitive Battery (Kern et al., 2008; Nuechterlein et al., 2008).

[a] Age: For SZ, N = 16 due to missing data.

Change in Network Properties following CT

The GTG toolbox was used to implement an Ordinary Least Squares (OLS) repeated-measures GLM with 5,000 permutations for each graph property listed in **Table 3**. OLS regression was used because GTG is unable to calculate robust GLMs for repeated-measures designs. Graph properties at the baseline (pre-intervention) and six-month follow-up time points were entered as repeated DVs, and group was entered as a dummy-coded between-subjects IV with HC as the reference group (SZ = 1 and HC = 0). Two-tailed *t* tests were used to evaluate the beta coefficients for main effect of group and Group x Time interaction. The main effect of time was partialed out of the interaction term.

There was a main effect of group on communicability betweenness centrality of R_AVI (right anterior ventral insular area) that did not survive correction for multiple comparisons, t = 7.58, p = .010 (n.s.) (**Figure 10**). Across time points, R_AVI had higher communicability betweenness centrality among SZ than among HC. However, there was no significant Group x Time interaction for communicability betweenness centrality of R_AVI. There was a Group x Time interaction for node strength of R_AVI in which SZ experienced an increase in R_AVI strength from pre- to post-intervention, while HC showed a decrease, although this effect did not survive correction for multiple comparisons, t = 4.36, p = .043 (n.s.) (**Figure 11**).

Figure 10. Main effect of group on communicability betweenness centrality of R_AVI. Across time points, SZ had higher R_AVI communicability betweenness centrality than HC, although this effect was not statistically significant after correcting for multiple comparisons. Plotted communicability betweenness centrality values are mean residuals following regression on covariates of no interest (network density, total strength, node degree, and node strength, each measured at both time points).

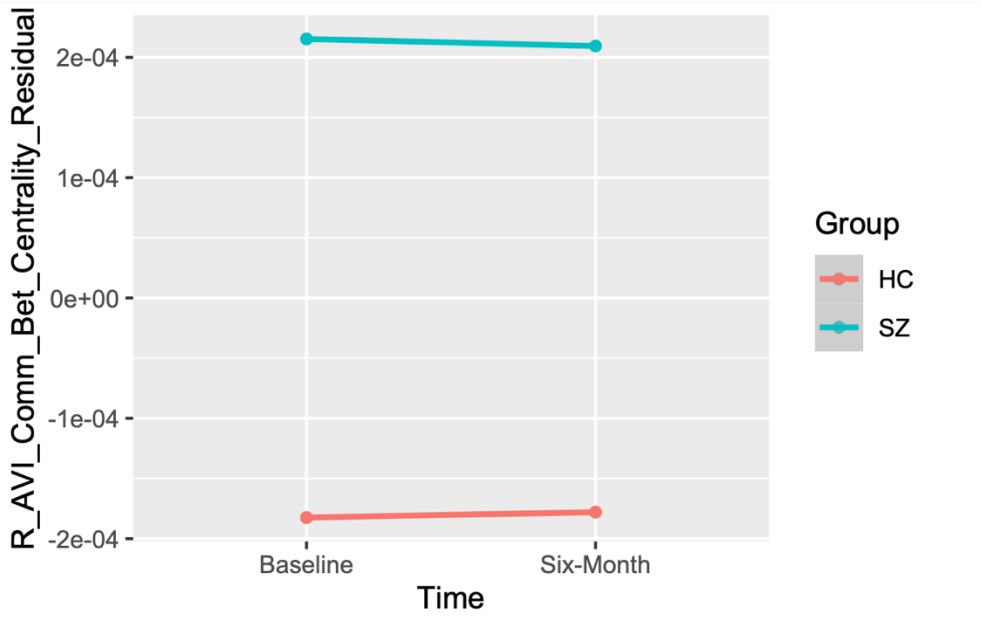
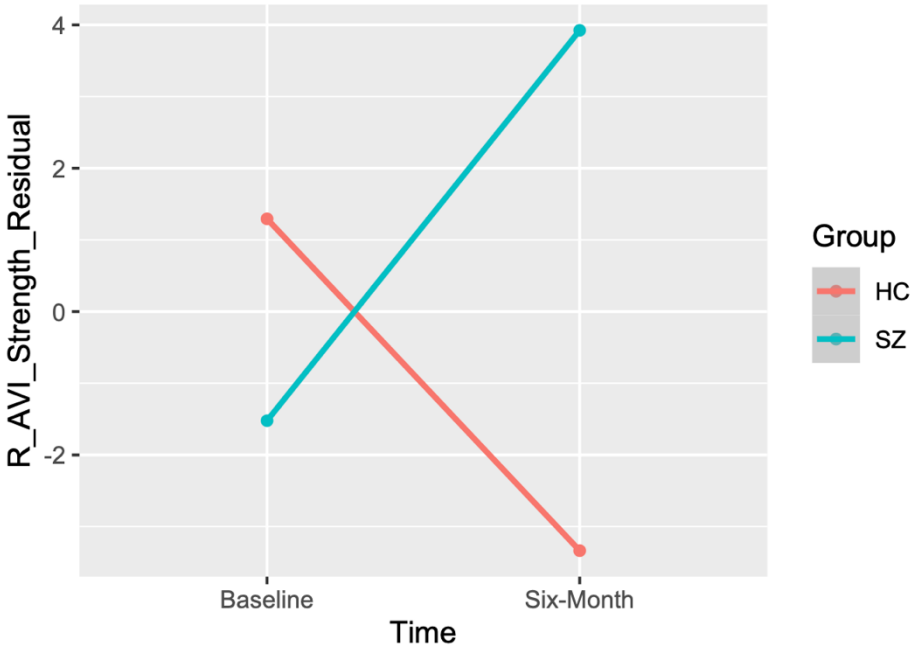


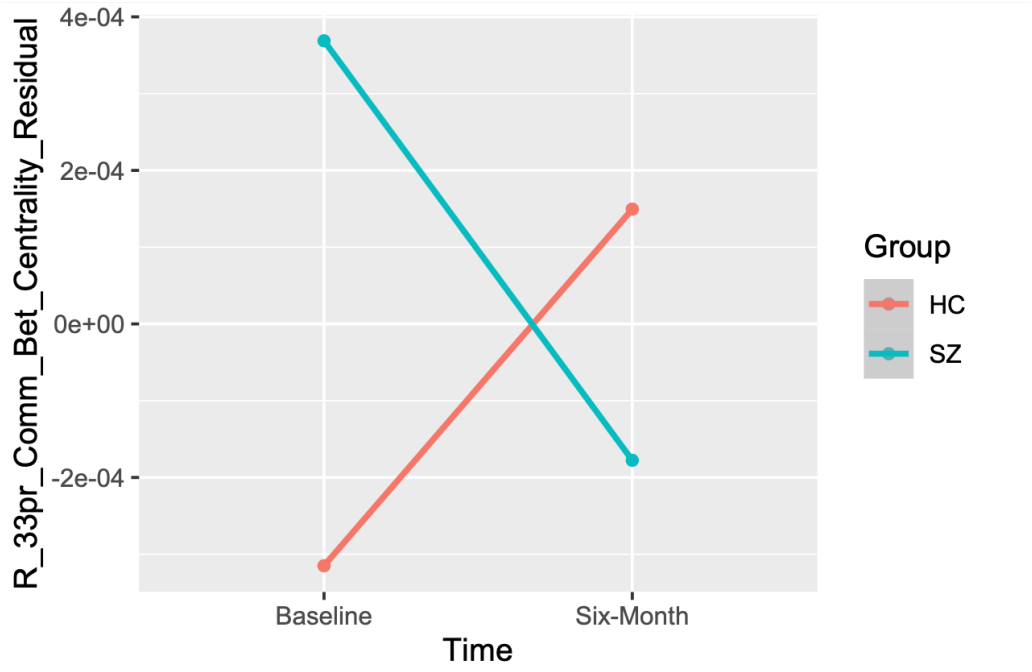
Figure 11. Interaction of Group x Time in relation to node strength of R_AVI. The interaction effect was non-significant after correcting for multiple comparisons. Plotted node strength values are mean residuals following regression on covariates of no interest (network density and total strength, each measured at both time points).



There was a Group x Time interaction for communicability betweenness centrality of R_33pr (area 33 prime in right dACC), such that HC experienced an increase in this measure and SZ experienced a decrease, although this effect did not remain significant after correcting for multiple comparisons, $t = 4.53$, $p = .040$ (n.s.) (**Figure 12**).

There were no group effects or Group x Time interactions for any of the CON or FPN properties we evaluated.

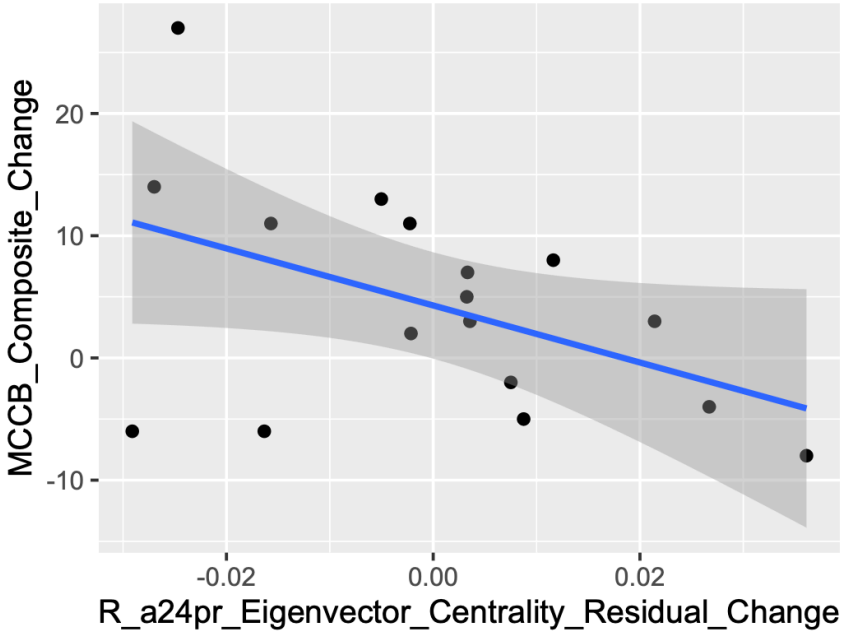
Figure 12. Interaction of Group x Time in relation to communicability betweenness centrality of R_33pr. The interaction effect was non-significant after correcting for multiple comparisons. Plotted communicability betweenness centrality values are mean residuals following regression on covariates of no interest (network density, total strength, node degree, and node strength, each measured at both time points).



Association of Network Changes with Change in MCCB

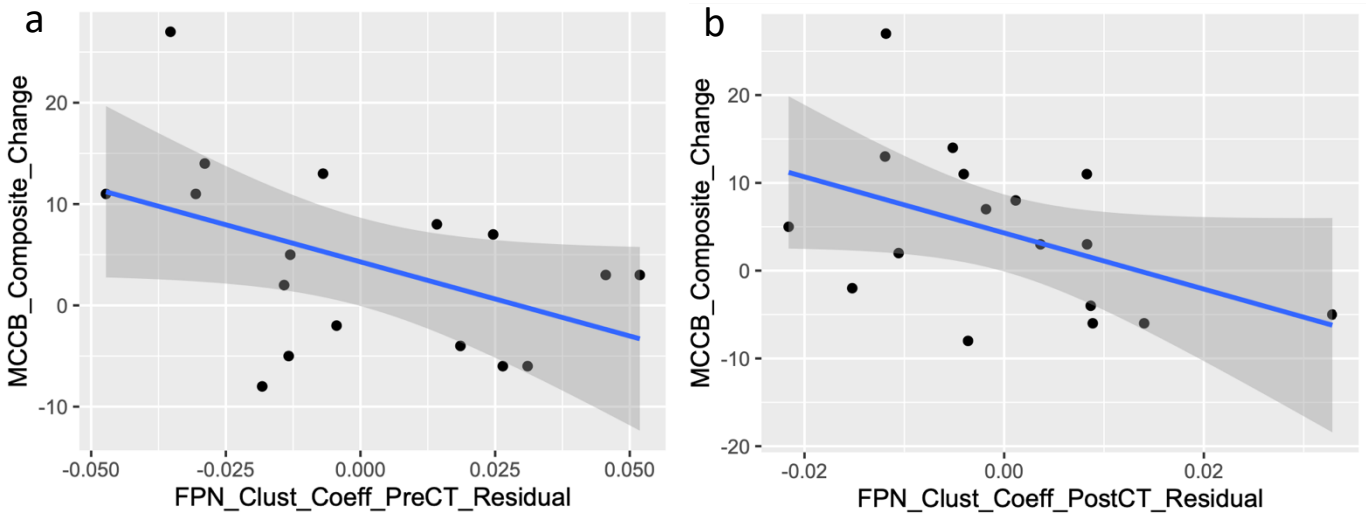
Among SZ, increased MCCB composite score from pre- to post-intervention was associated with decreased eigenvector centrality of R_a24pr (area anterior 24 prime in right dACC), as indicated by a Time x MCCB composite score interaction, although this effect did not survive correction for multiple comparisons, $t = 11.40$, $p = .013$ (n.s.) (**Figure 13**).

Figure 13. Association of change in MCCB composite score with change in eigenvector centrality of R_a24pr. The effect was non-significant after correcting for multiple comparisons. Plotted values for eigenvector centrality are pre-post differences in residuals following regression on covariates of no interest (network density, total strength, node degree, and node strength, each measured at both time points).



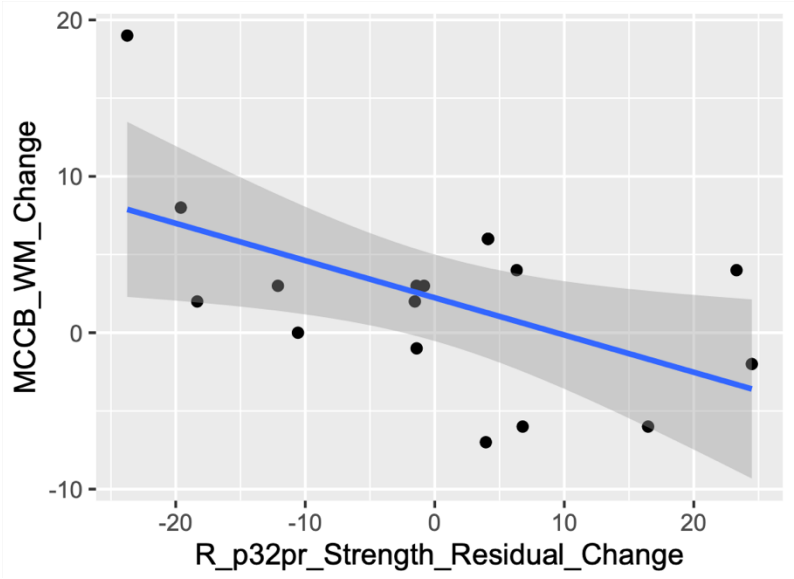
Across time points, there was a significant main effect of MCCB composite change score on FPN clustering coefficient, such that gains in MCCB composite performance were negatively associated with FPN clustering coefficient pre- and post-intervention ($t = 9.08$, $p = .010$) (**Figure 14**).

Figure 14. Main effect of MCCB composite change score on FPN clustering coefficient in SZ across time points. 14a: Negative association between pre-intervention FPN clustering coefficient and pre-post change in MCCB composite score in SZ. 14b: Negative association between post-intervention FPN clustering coefficient and pre-post change in MCCB composite score in SZ. Plotted values for FPN clustering coefficient are mean residuals following regression on covariates of no interest (network density and total strength, each measured at both time points).



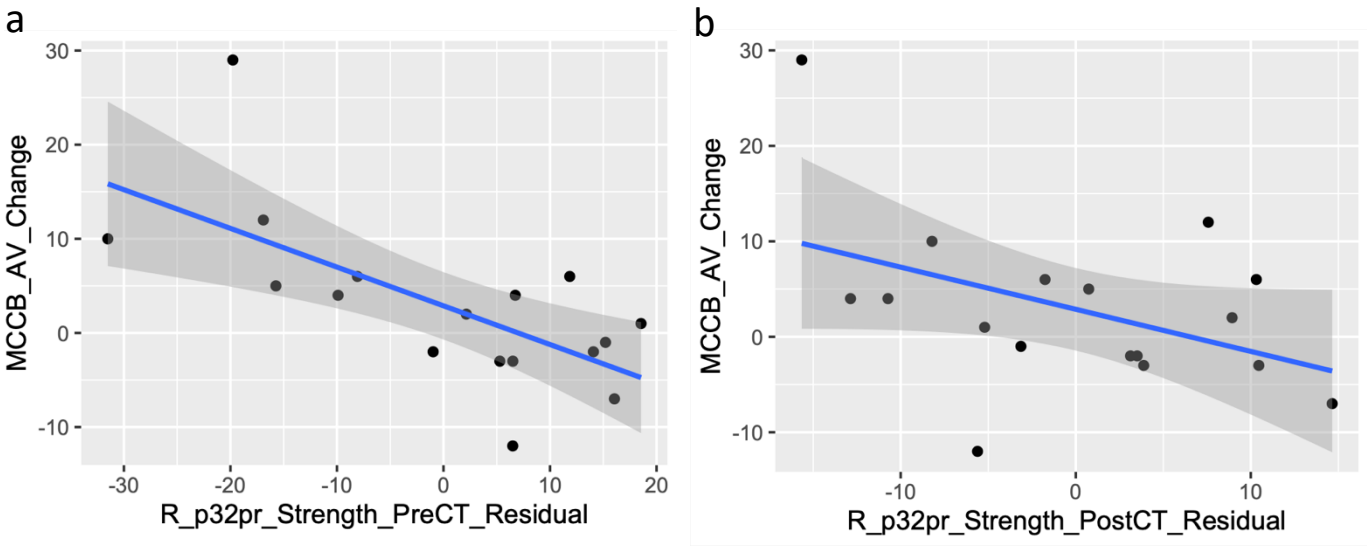
In exploratory analyses, gains in MCCB working memory among SZ were associated with decreased node strength of R_p32pr (area posterior 32 prime in right dACC) from pre- to post-intervention, $t = 5.48$, $p = .042$ (n.s.), although this effect was non-significant after correcting for multiple comparisons (**Figure 15**).

Figure 15. Association of change in MCCB working memory with change in node strength of R_p32pr. The effect was non-significant after correcting for multiple comparisons. Plotted node strength values are pre-post differences in residuals following regression on covariates of no interest (network density and total strength, each measured at both time points).



There were no significant associations between change in MCCB attention/vigilance and change in graph properties. However, there was a main effect of MCCB attention/vigilance difference score on node strength of R_p32pr, $t = 12.49$, $p = .004$, indicating that gains in attention/vigilance from pre- to post-intervention were negatively associated with R_p32pr node strength across time points (**Figure 16**). Several other main effects of MCCB attention/vigilance difference score became non-significant after correcting for multiple comparisons. Specifically, gains in attention/vigilance from pre- to post-intervention were associated with lower eigenvector centrality of R_p32pr, $t = 6.80$, $p = .037$ (n.s.), lower whole-brain transitivity, $t = 6.65$, $p = .032$ (n.s.), lower whole-brain clustering coefficient, $t = 6.87$, $p = .027$ (n.s.), and higher communicability betweenness centrality of L_a24pr (area anterior 24 prime in left dACC), $t = 11.80$, $p = .009$ (n.s.) across time points.

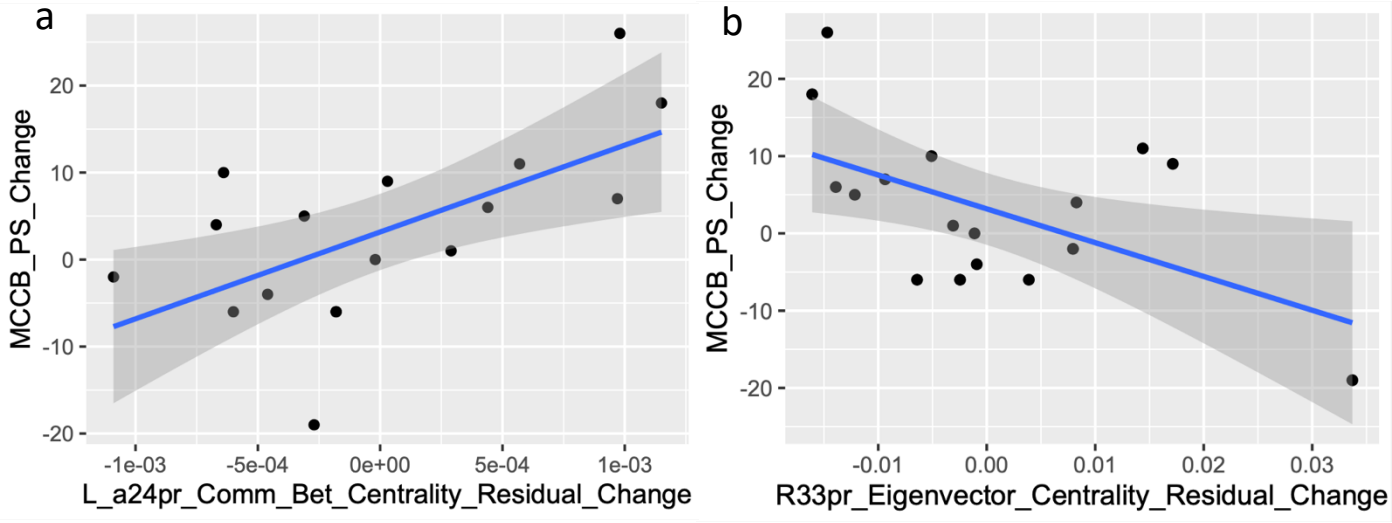
Figure 16. Main effect of MCCB attention/vigilance change score on node strength of R_p32pr in SZ across time points. 16a: Negative association between pre-intervention R_p32pr node strength and pre-post change in MCCB attention/vigilance score in SZ. 16b: Negative association between post-intervention R_p32pr node strength and pre-post change in MCCB attention/vigilance score in SZ. Plotted values for node strength are mean residuals following regression on covariates of no interest (network density and total strength, each measured at both time points).



Finally, gains in MCCB processing speed from pre- to post-intervention were associated with increased communicability betweenness centrality of L_a24pr, $t = 13.00$, $p = .010$ (n.s.) and decreased eigenvector centrality of R_33pr (area 33 prime in right dACC), $t = 6.28$, $p = .042$ (n.s.), although these effects did not survive correction for multiple comparisons (**Figure 17**).

There were no significant associations between change in CON graph properties and change in any of the MCCB subscores.

Figure 17. Association of change in MCCB processing speed with changes in dACC node centrality. 17a: Gains in processing speed were associated with increased communicability betweenness centrality of L_a24pr. 17b: Gains in processing speed were associated with decreased eigenvector centrality of R_33pr. Effects were non-significant after correcting for multiple comparisons. Plotted centrality values are pre-post differences in residuals following regression on covariates of no interest (network density, total strength, node degree, and node strength, each measured at both time points).



Parsing Normalization and Compensation

Based on results of Study 1 and Study 2, we identified network effects that appeared to be candidates for normalization and/or compensation according to our *a priori* definitions (**Figure 1**). In identifying candidate effects, we considered all findings from Studies 1 and 2 with uncorrected $p < .05$. This allowed for a more generative (though tentative) consideration of potential normalization and compensation effects, as most results did not reach significance according to Bonferroni-corrected thresholds. For each candidate effect, we determined whether additional tests would clarify whether the effect could be classified as normalization or compensation. **Table 6** summarizes candidate effects, relevant findings from Studies 1 and 2, and additional tests identified for each effect.

Table 6. Network effects identified as candidates for normalization and/or compensation.

Effect	Candidate For	Study 1 Evidence	Study 2 Evidence	Additional Tests
Increased R_AVI Centrality	Compensation	No group differences in centrality prior to CT No association with MCCB prior to CT	Communicability betweenness centrality: SZ > HC both pre- and post-CT Node strength increases after CT	Is centrality associated with cognitive performance in SZ after CT?
Decreased R_33pr Centrality	Compensation	No group differences in centrality prior to CT No association with MCCB prior to CT	Communicability betweenness centrality decreases after CT Decreased eigenvector centrality after CT is associated with increased processing speed	--
Decreased R_a24pr Centrality	Compensation	No group differences in centrality prior to CT Eigenvector centrality more negatively associated with working memory in SZ than in HC	Decreased eigenvector centrality after CT is associated with increased MCCB composite	--
Decreased R_p32pr Centrality	Compensation	No group differences in centrality prior to CT Node strength positively associated with MCCB composite across groups Node strength less positively associated	Decreased node strength after CT is associated with increased working memory Lower node strength pre- and post-CT is associated with greater gains in attention/vigilance after CT	--

		with working memory in SZ than in HC Eigenvector centrality more negatively associated with attention/ vigilance in SZ than in HC	Lower eigenvector centrality pre- and post-CT is associated with greater gains in attention/vigilance after CT	
Increased L_a24pr Centrality	Normalization and/or Compensation (inconclusive)	Eigenvector centrality more negatively associated with working memory in SZ than in HC	Increased communicability betweenness centrality after CT is associated with increased processing speed Higher communicability betweenness centrality pre- and post-CT is associated with greater gains in attention/vigilance after CT	--

To address the outstanding question identified for R_AVI centrality, we tested simple main effects of MCCB composite, working memory, attention/vigilance, and processing speed subscores on three measures of R_AVI centrality (node strength, communicability betweenness centrality, and eigenvector centrality) among SZ at the post-intervention time point. Effects were tested in GTG using robust GLMs with 5,000 permutations and covariates of no interest included in a manner consistent with previous analyses. Within the SZ group, there were no significant associations between post-intervention MCCB performance and any of the three measures of R_AVI centrality.

Discussion

In Study 2, we evaluated change in resting-state functional network properties as a mechanism of change in CT for first-episode SZ. We first tested for changes in graph properties of resting-state networks following a 24-week CT intervention. We then identified associations between changes in network properties and changes in cognitive performance as assessed by the MCCB. Our overarching goal was to determine whether CT promotes cognitive recovery by fostering normalization of functional networks, compensation via alternative network features, or a combination of both. Although no single graph property fully met our *a priori* criteria for normalization or compensation, we identified several intervention effects that are potentially consistent with compensation (**Table 6**). Tests of these effects were statistically significant at the $p < .05$ level but were non-significant after correcting for multiple comparisons. Thus, inferences about CT mechanisms in the present study should be treated with caution but provide an initial basis for further inquiry.

We hypothesized that normalizing effects of CT would include increased centrality of nodes that are considered CON hubs in HC, including right anterior insula and bilateral dACC. Surprisingly, results instead pointed to decreased centrality of several nodes in right dACC (R_33pr, R_a24pr, and R_p32pr) as a potential compensatory mechanism of intervention. Centrality of a fourth node located in left dACC (L_a24pr) was also identified as potentially relevant to intervention effects, but the pattern of effects for this node was not fully consistent with either normalization or compensation. In line with our hypotheses, centrality of a node in right anterior ventral insula (R_AVI) increased from pre- to post-intervention in SZ. However, we found no evidence that this increase contributed to cognitive recovery in the domains we examined, making its implications uncertain.

The observed dACC effects, though unexpected, may be explained by the variable role of dACC in cognitive tasks with differing demands. Prior task-based imaging studies have suggested that in healthy adults, dACC activity and connectivity increase during more complex cognitive tasks and are suppressed during less complex tasks (Xu, Calhoun, Pearlson, & Potenza, 2014; Aben, Calderon, Van den Bussche, & Verguts, 2020). Similarly, in healthy children and adolescents, degree centrality of dACC has been positively associated with performance on complex working memory tasks (i.e., Digit Span Backward) and negatively associated with performance on less complex tasks (Digit Span Forward) (Yang et al., 2015). As discussed by Yang et al. (2015), dACC centrality may therefore be adaptive for complex cognitive function but confer a disadvantage during less demanding cognitive tasks that are slowed by elevated performance monitoring. This pattern provides essential context for interpreting findings from the present study. Specifically, individuals with SZ may compensate for pervasive cognitive impairment by prioritizing neural processes that support essential and/or less demanding cognitive tasks, making dACC centrality less beneficial. Likewise, the "bottom-up" components of the present CT intervention focus on strengthening foundational cognitive processes before moving to complex processes (Nuechterlein et al., 2014), so CT may initially encourage neural network changes that promote cognitive performance on less complex tasks. Decreased dACC centrality may therefore be an effective compensatory mechanism both for coping with cognitive impairment prior to intervention and for harnessing the benefits of a bottom-up CT approach.

Of the three nodes in right dACC identified as potential sites of compensatory change, R_33pr (area 33 prime) was the only one that evidenced change in centrality at the group level following CT. As a group, SZ showed a decrease in communicability betweenness centrality of R_33pr from pre- to post-intervention. Although changes in communicability betweenness

centrality of R_33pr were not associated with changes in MCCB performance, decreases in a separate measure of R_33pr centrality – eigenvector centrality – were associated with gains in processing speed. Communicability betweenness centrality and eigenvector centrality do not index identical node characteristics, but they are closely related; betweenness quantifies a node's role in connecting other nodes to each other, and eigenvector centrality captures a node's degree of connectedness to other nodes that may serve as network hubs. As these two measures of centrality were implicated in our findings in different ways, the nuances of R_33pr's role remain unclear. However, CT appears to be associated with a decrease in the overall centrality of R_33pr, and this decrease corresponds with gains in processing speed. Since the SZ sample as a whole experienced a decrease in R_33pr centrality following intervention, CT may already be well designed to promote this potential mechanism of recovery across participants.

Two other nodes in right dACC, R_a24pr and R_p32pr, did not show changes in centrality at the group level following CT. However, within the SZ group, those who experienced greater decreases in the centrality of these nodes experienced more pronounced gains in cognitive function from pre- to post-intervention, suggesting a compensatory effect that was distributed unequally across participants. Based on Study 1 results, potential compensation involving R_a24pr and R_p32pr may build on naturalistic compensation that is present prior to intervention. In Study 1, we observed a decoupling of R_a24pr (area anterior 24 prime) eigenvector centrality from working memory performance in SZ, although this effect was non-significant after correcting for multiple comparisons. A normalizing intervention might have restored a positive relationship between R_a24pr centrality and working memory or increased centrality itself, given the apparent positive relationship between centrality and working memory in HC. However, we instead found that gains in generalized cognitive function were associated

with decreased eigenvector centrality of R_a24pr following intervention. This suggests that for individuals who benefitted most from CT, the intervention built upon the more negative centrality-cognition relationship that was observed in SZ prior to intervention. In other words, CT appeared to reduce a network feature that, unlike in HC, was potentially detrimental to cognitive function in SZ to begin with. This raises the question of whether SZ who experienced a decrease in R_a24pr centrality experienced a corresponding increase in centrality of one or more alternative nodes and, if so, whether this contributed to cognitive gains. Our limited focus on *a priori* CON hubs in the present study did not allow us to answer this question, but future studies should examine whether CT augments the centrality of alternative hubs (e.g., nodes in posterior parietal cortex, as suggested by Quintana et al., 2003).

A similar but more complicated pattern of results was observed for R_p32pr (area posterior 32 prime). In Study 1, node strength of R_p32pr was less positively associated with working memory in SZ than in HC, and eigenvector centrality was more negatively associated with attention/vigilance in SZ than in HC, although these effects were non-significant after correcting for multiple comparisons. CT did not appear to make cognitive performance more positively related to or reliant on R_p32pr centrality, as would be expected if normalization had occurred. Instead, SZ who experienced greater decreases in R_p32pr node strength experienced greater gains in working memory following CT. In addition, lower R_p32pr centrality prior to CT (as indexed by node strength and eigenvector centrality) appeared to predict a stronger treatment response in the domain of attention/vigilance, suggesting that SZ whose cognitive function already relied less on R_p32pr centrality may have been best positioned to harness compensatory benefits of CT. As discussed above, lower dACC centrality has been shown to facilitate performance on less complex cognitive tasks, so participants with lower R_p32pr

centrality prior to intervention may have had less difficulty engaging with "bottom-up" cognitive exercises involved in CT. Complicating this picture is the finding from Study 1 that across SZ and HC, node strength of R_p32pr was positively associated with MCCB composite score. The implications of R_p32pr centrality appear different for generalized cognitive performance than for domain-specific performance, potentially indicating that certain aspects of SZ cognitive function benefit from R_p32pr centrality, while others do not. The MCCB composite score incorporates several additional domains (verbal learning, visual learning, reasoning and problem solving, and social cognition) that were not examined individually in the present study, so it is possible that R_p32pr centrality is more beneficial to one or more of these domains than to the three examined here (working memory, attention/vigilance, and processing speed).

The SZ group as a whole did not experience a decrease in R_a24pr or R_p32pr centrality following CT. Thus, potential compensatory effects associated with these two nodes may have occurred only in a subset of participants who had already experienced some naturalistic compensation prior to intervention or who were otherwise more responsive to this potential mechanism of CT. It is also possible that decreases in centrality of these two nodes occurred naturalistically in some participants and were not attributable to CT. Given the lack of a group-wide effect, we cannot confidently infer that decreases in R_a24pr or R_p32pr centrality among some participants constituted intervention effects. However, the overall trend of our findings across R_33pr, R_a24pr, and R_p32pr suggests that reduced centrality of right dACC is a promising subject for future studies of potential compensatory mechanisms of CT.

We did not observe any pattern of effects that was clearly consistent with normalization. However, effects related to one node in left dACC were inconclusive, and neither normalization nor compensation can be fully ruled out. In Study 1, eigenvector centrality of L_a24pr (area

anterior 24 prime) was more negatively associated with working memory in SZ than in HC, although this effect was not statistically significant after correction for multiple comparisons. Following CT, increased communicability betweenness centrality of L_a24pr in SZ was associated with increased processing speed. Unlike centrality of the right dACC nodes discussed above, L_a24pr centrality appeared to have a different (i.e., more positive) relationship to cognitive change than it did to pre-CT cognitive function. However, the effects observed before and after CT pertained to different cognitive domains (working memory and processing speed, respectively), making this finding difficult to interpret. If the effect related to processing speed is indicative of a more positive relationship between L_a24pr centrality and overall cognitive function following CT, then it could represent normalization. Alternatively, the effects observed before and after CT may indicate that L_a24pr centrality has different relevance to different cognitive domains. It should also be noted that Study 2 involved only a subsample of Study 1 participants, and this subsample may or may not be representative of the full sample. As such, there are limitations to interpreting results from Study 1 and Study 2 in tandem, and secondary analyses of Study 2 results may be required to clarify interpretations of intervention effects.

In line with hypotheses, node strength of R_AVI (right anterior ventral insular area) increased in SZ following CT. This is particularly notable in light of previous studies that have linked centrality of right anterior insula to cognitive function in both SZ and HC (Sheffield et al., 2015). It is also notable that in Study 2, SZ exhibited higher communicability betweenness centrality of R_AVI than HC both before and after CT, whereas in the larger Study 1 sample, no group differences emerged for R_AVI centrality. Although Study 2 results for R_AVI centrality appear to align with compensation, R_AVI centrality was not associated with any of the MCCB outcome measures examined in SZ following intervention. This does not rule out the possibility

that increased R_AVI centrality is a form of compensation. For example, increases in R_AVI centrality may have been associated with intervention effects that were not captured by the MCCB subscores included in the present study. In SZ, connectivity of anterior ventral insula has previously been associated with negative symptoms (Sheffield et al., 2020). Therefore, it is possible that increased R_AVI centrality following CT serves as a mechanism of negative symptom alleviation or worsening rather than cognitive recovery.

Finally, although identifying predictors of treatment response was not an objective of the present study, several effects emerged that may speak to prediction of CT intervention response. As discussed above, lower node strength of R_p32pr across pre- and post-intervention time points was associated with greater gains in attention/vigilance following CT, and this was one of the few effects in Study 2 to survive correction for multiple comparisons. Within FPN, lower functional segregation (as indexed by clustering coefficient) across pre- and post-intervention time points was associated with greater gains in MCCB composite score, and this effect remained significant after correction for multiple comparisons. Similarly, lower whole-brain functional segregation (as indexed by transitivity and clustering coefficient) across time points predicted greater gains in attention/vigilance. These findings indicate that higher functional segregation might interfere with CT intervention response and/or that lower segregation allows participants to benefit more from CT. However, given the use of MCCB change scores in Study 2 analyses, secondary analyses may be needed to investigate whether ceiling effects played a role (i.e., if functional segregation was associated with cognitive benefits prior to CT, it might have also been associated with less pronounced change following CT due to ceiling effects). Communicability betweenness centrality of L_a24pr across pre- and post-intervention time points was also positively associated with gains in attention/vigilance following intervention.

Although predictors of treatment response do not speak directly to mechanisms of CT, follow-up investigations of such predictors may help identify neural network profiles that influence SZ participants' fit with the CT intervention as currently conceived. Such insights could lead to modifications to CT that improve its efficacy in a heterogenous population of SZ treatment-seekers.

In summary, the present study provides preliminary evidence that enhancing compensatory neural network function may be an influential component of CT. Past studies of neural mechanisms of CT and other SZ interventions have focused primarily on evaluating normalization of functional connectivity or other brain metrics. However, in light of the present findings, studies may benefit from considering the role of alternative, compensatory neural processes in cognitive recovery. Such an approach may also invite a reconceptualization of CT itself as an intervention that works in part by capitalizing on existing strengths. As understanding of compensation grows, efforts to improve or augment CT may benefit from targeting alternative neural network features that are not considered primary mechanisms of cognitive function in HC.

General Discussion

Several limitations are important to consider in contextualizing results from the present studies. First, the available sample was limited in size, particularly for analyses of intervention effects (Study 2). As there is no firm basis in the literature for anticipating the likely effect sizes of neural network changes following CT, we cannot confidently estimate the statistical power required to detect effects discussed in our hypotheses. However, the statistical power afforded by the present sample likely carried a significant risk of Type II error, especially given the wide-ranging hypotheses we tested and the subsequent need to correct for multiple comparisons. The present studies were intentionally broad and inclusive of exploratory analyses in response to the

field's still-nascent understanding of neural mechanisms of CT and cognitive recovery in SZ. Thus, future studies with greater statistical power will be important both for replicating the observed effects and for clarifying the amount of statistical power needed to reliably observe CT's effects on neural networks.

Another limitation was the lack of an SZ comparison group receiving medication only. The RCT did not include such a group because spontaneous gains in cognitive performance (beyond practice effects) are not typically observed in SZ, and even practice effects may be blunted (Goldberg et al., 2007; Hedman, van Haren, van Baal, Kahn, & Hulshoff Pol, 2013), suggesting that gains in cognitive function following CT can reasonably be attributed to the intervention. Variability in second-generation antipsychotics has also not been associated with significant variability in cognitive change over time in a first-episode SZ sample (Goldberg et al., 2007). Even so, in Study 2, a medication-only SZ group could have provided a desirable alternative to using the HC sample as a control in our analyses of change in network properties. In those analyses, we considered pre-post change in SZ network properties to be indicative of an intervention effect if it differed from longitudinal change observed in the HC sample. However, it is unknown whether HC longitudinal change is a valid control in this context, as fluctuations in network properties over a six-month period in HC may or may not be similar to those expected in SZ in the absence of intervention.

A final consideration is the present studies' focus on properties of resting-state neural networks rather than networks engaged during cognitive tasks. One advantage of this approach was our ability to analyze network properties in relation to the MCCB rather than relying on scanner-based tasks to measure cognitive performance. Since cognitive performance was evaluated outside the scanner environment, we were able to employ a robust, clinician-

administered measure that assesses cognitive performance in multiple distinct domains. However, our exclusive focus on intrinsic network organization prevented us from examining whether CT led to network changes that would have been evident only during pursuit of cognitive tasks. Thus, we were only able to observe normalizing and compensatory effects of CT if they were detectable even in the absence of cognitive demands. Both normalization and compensation may involve network changes that are observable only when task-positive networks are actively engaged. In future studies, collecting both task-based and resting-state data may help clarify whether normalizing and compensatory mechanisms of CT manifest differently during cognitive task engagement than during rest.

The present studies were innovative in their effort to distinguish between normalization and compensation components of cognitive recovery in SZ; their use of graph-theory methods to examine neural mechanisms of CT; and their objective of translating neural network modulation to cognitive outcomes in SZ. The *normalization vs. compensation* framework introduced here can be adapted to a wide variety of data modalities and study designs aimed at understanding intervention effects, both in SZ and transdiagnostically. Preliminary evidence of compensation in SZ following CT highlights the importance of considering the contributions of a broad range of intervention mechanisms to recovery from psychopathology.

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