Neural Impact of Cognitive Remediation for Schizophrenia in a Randomized Controlled Trial

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Dedication

I first want to dedicate this to my friends and family. I also want to dedicate this to the schizophrenia patients who participated in this and other studies. Their hard work is helping us better understand treatments for future generations of individuals who may suffer from serious mental illness.

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Chapter 1: Review and Background on Cognitive Remediation for Schizophrenia

Foreword: Portions of this introduction were written in collaboration with Angus W. MacDonald and Tasha M. Nienow who provided edits and revision. A later version of this introduction and review will be found in *The Oxford Primer for Schizophrenia and Related Disorders*.

Introduction

Schizophrenia and related psychotic illnesses are characterized by a heterogeneous presentation of hallucinations, delusions, and disorganization. While these symptoms are treatable by modern anti-psychotic medications, cognitive deficits associated with the illness have only shown marginal improvements associated with pharmacotherapy (Choi, Wykes, & Kurtz, 2013). The cognitive impairments observed in schizophrenia are found to be broad and pervasive (Heinrichs & Zakzanis, 1998) and associated with functional disability in this population (Green et al., 2004), making them critical targets for emerging psychiatric interventions. Currently, cognitive remediation training (CRT) is a behavioral training approach that is becoming a popular and useful class of interventions to treat cognitive impairments in schizophrenia and related illnesses. These treatments largely focus their efforts to improve problems with impaired attention, problem solving, and memory, using behavioral learning strategies (Keefe et al., 2011). Meta-analytic findings indicate that CRT for patients with schizophrenia

provides modest benefits that generalize to cognitive and functional improvements (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011), however the neural mechanisms that support these types of improvements from CRT are only just beginning to be understood. The current dissertation seeks to clarify the neural changes that coincide with CRT for schizophrenia, and how they may relate to improvements in cognition and psychosocial functioning.

History of CRT

The development of modern cognitive training interventions for people with schizophrenia began in the 1960s and 70s. As an understanding emerged of the cognitive difficulties faced by people with schizophrenia, so did efforts to improve cognitive faculties in areas of attentional control, concept formation, and reinforcement learning. Many early intervention studies borrowed techniques from previously successful studies with stroke and traumatic brain injury (TBI) patients, and offered either a repeated practice or a strategy-based intervention (Kurtz et al., 2001). Typically, these studies targeted a specific cognitive domain such as attention or memory, and change in performance on the training task was used to assess improvement in cognitive performance. While the majority of these studies lacked the methodological rigor of a randomized clinical trial, they demonstrated that people with schizophrenia could learn new skills, and showed that cognitive impairments in schizophrenia were modifiable. By and large, more carefully controlled trials examining CRT for schizophrenia did not begin until the 1990s. Studies began to conduct cognitive exercises in targeted domains,

and assess changes on related neuropsychological measures; thereby measuring whether training could "generalize" to untrained tasks or skills.

Training Approaches

As the number of controlled trials examining CRT for schizophrenia grew, so too did the different approaches for these types of training. CRT has historically differed with regards to the approaches and training techniques used. One important distinction is between drill-and-practice approaches versus strategy coaching interventions. Drill-and-practice approaches have generally relied on computerized implementation of adaptive training programs that modify their difficulty based on the performance of the participant. These programs generally use errorless-learning principles to ensure that a participant stays at an accuracy level that maximizes cognitive challenge, while also learning from their mistakes and limiting subsequent frustration. These approaches generally offer concentrated practice to train cognitive skills individually, though many domains of cognition could be exercised in the course of a session (Saperstein & Kurtz, 2013). In contrast, strategy coaching approaches provide practice applying techniques such as mnemonics, chunking, goal setting, and self-monitoring to performance on cognitive tasks of graded difficulty (Wykes & van der Gaag, 2001).

These two approaches hold different assumptions with regards to their theoretical mechanisms, as drill-and-practice approaches are hypothesized to exercise disrupted brain circuitry to support rehabilitated skills, while strategy coaching utilizes intact neural processing to develop compensatory strategies to circumvent existing deficits. In practice

these two approaches are often used together, as both targeted cognitive training and strategy coaching likely compliment one another to initiate functional improvements in patients with schizophrenia. This is often achieved through the use of a "bridging group," which is generally included in addition to computerized drill-and-practice trainings (Medalia & Choi, 2009; Medalia & Saperstein, 2011, 2013). These groups focus on translating the skills obtained during computerized training to real-world goals and situations, and have been shown to be efficacious in improving functional outcomes (Keefe et al., 2011; Medalia & Choi, 2009).

Another critical domain on which restorative drill-and-practice CRT interventions vary is whether they use a "top-down" or "bottom-up" approach. Top-down approaches target domains of ability, such as reasoning, problem-solving, working memory, or attention, while "bottom-up" approaches target the early perceptual processes hypothesized to support these domains of functioning. The Neuropsychological and Educational Approach to Cognitive Remediation (NEAR) is an example of a top down approach. This approach is predicated on the idea that cognitive abilities are used together in everyday life to accomplish tasks; therefore, training will be most effective if abilities are trained in coordination with one another. Training immediately begins with higher order executive processes with the assumption that more foundational abilities such as attention are being trained simultaneously (Medalia & Choi, 2009; Medalia & Richardson, 2005a). In contrast, "bottom-up" approaches exercise cognitive processes in relative isolation, and often focus on more basic cognitive processes such as attention, motor skills, and perceptual processes initially, and then incorporate higher order

cognitive processes such as memory and executive processes later in the training program (Vinogradov, Fisher, & de Villers-Sidani, 2012). Though these approaches target separate systems, their distinction may be loose, and many investigators have sought to capitalize on the benefits of each approach by incorporating aspects of both into their training protocols.

CRT has traditionally, and continues to be a therapist guided intervention, but as computers have begun to take a more prominent role in cognitive training, questions have arisen regarding the role of the therapist, and the setting in which CRT is best delivered. The majority of trials examining CRT have been conducted in a laboratory, with patients coming in multiple days a week to participate in therapist supervised training. This can in some ways be a barrier to treatment, placing burden on patients who would need to frequently commute to a clinic or hospital for treatment. However, clinic-based training does offer regular client-therapist interaction, bridging sessions to translate training goals to real world experiences, and exposure to adjunct treatments which all likely have therapeutic benefits in their own right (Wykes et al., 2011).

Other crucial factors may include patient motivation, ability to stay on task, and attrition, which are difficult to monitor and manage when participants are not in the laboratory or clinic being supervised during training. This is notable, as the therapist's job during CRT is not exclusively to supervise the administration, but perhaps more importantly to facilitate the engagement of participants in the process of learning, to enhance self-awareness, to promote personal growth, and to facilitate transfer of learning to application in other settings (Medalia & Choi, 2009). One trial has demonstrated that

computerized CRT could be effectively administered with positive results from home with minimal client-therapist interaction (Fisher et al., 2014), suggesting that this treatment could be efficacious outside of a clinical setting. However, it is worth noting that this study was conducted in younger first-episode patients who may have already had competency and motivation to use computers. These types of interventions are likely much more susceptible to attrition effects, and should be carefully considered with regards to their implementation. With these factors in mind, it is important to consider individual patient variability in regards to training setting, though general guidelines suggest that primary training most optimally takes place in the clinic with a trained clinical psychologist (Keefe et al., 2011). When possible and appropriate, training in the clinic can be supplemented by homework, and perhaps some combination of a clinic-based and self-guided intervention will largely characterize the future of these types of interventions.

Other important theoretic factors concern the breadth and duration (i.e. dose or frequency) of engaging in CRT. The duration of training has varied by approach, ranging anywhere from 12 weeks to up to two years of weekly training, with consensus indicating that 40 sessions over a three to four month time period being optimal (Keefe et al., 2011). Review of the neuroscience work done in both animals and humans suggests that CRT must be both of a sufficient intensity and duration to evince enduring changes in both behavior and neural plasticity (Vinogradov et al., 2012). This has been observed behaviorally, as engaging in CRT with insufficient duration or intensity (frequency) may moderately improve behavior in the short term, but will be less likely to generalize or

endure beyond the training itself. As a result, most interventions propose that the best results will be observed with multiple training sessions in a week as opposed to spread out over longer periods of time. Though meta-analytic findings show no preference for longer compared with shorter CRT trials (Wykes et al., 2011), further work will be required to identify and understand the optimal duration and frequency of training, as well as the potential benefit of 'booster sessions' beyond the initial training period to help further maintain cognitive gains in the long-term.

While drill and practice CRT programs are thought to exercise neural systems impacting dysfunctional cognitive domains, some propose that these acquired skills do not always lead to functional gains outside of their trained context (Medalia & Saperstein, 2013). To do so, CRT has also been paired with a number of complimentary therapeutic interventions, including structured employment and both functional and social skills training. To include these adjunct treatments, programs have demonstrated that providing work therapy in conjunction with CRT has benefits for both cognition and prospects of long-term employment (Bell, Bryson, Greig, Fiszdon, & Wexler, 2005; McGurk et al., 2005). Patients who underwent CRT along with supported employment were more likely to hold a job, worked more hours, and earned more compared to patients who underwent supported employment alone. Wexler and Bell (2005) propose a symbiotic relationship between cognitive and vocational training, hypothesizing that productivity in the work place may allow patients to use and maintain their skills in a meaningful way. Similar findings were observed in the context of supported education, with psychosis patients showing improvements in concentration and memory when CRT was paired with

postsecondary education courses (Kidd, Kaur Bajwa, McKenzie, Ganguli, & Haji Khamneh, 2012).

Social skills training has also become a widely accepted complimentary therapy associated with CRT, as many interventions utilize traditional group social skills training (Eack et al., 2009; Hogarty et al., 2013), while others have relied on computerized programs to exercise the neural substrates of social cognition (Hooker et al., 2013). One study demonstrated that combining cognitive training with a socially focused functional skills training had the greatest capacity to improve both social competence and real-world behavior compared to either of these interventions alone (Bowie et al., 2012). This offers support for the notion that the synergistic effects of combining CRT with adjunct therapies holds great promise for improving functional outcomes in schizophrenia, compared to using these approaches in isolation. An increasingly wider range of complimentary therapeutics is also being incorporated into CRT, as the potential additive benefits of things like exercise, neuromodulation, and cognitive enhancing medications are currently being examined in this context.

Measurement and Efficacy of Cognitive Remediation

Numerous meta-analyses have examined the efficacy of CRT over the course of its development in the last three decades. The most recent meta-analysis in this field was conducted by Wykes and colleagues (2011), and included a total of 40 studies with 2,104 total subjects. As both the largest and most recent meta-analysis to date, they observe mean overall effect sizes in the moderate range for global cognition (d=.45), global

cognition at follow-up (*d*=.43), overall functioning (*d*=.42), and overall functioning at follow-up (*d*=.37). This group also painstakingly determined whether any of these effects were being moderated by variables related to methodological rigor (not all CRT trials have been randomized or placebo-controlled), patient population, or intervention type. They concluded that none of these effects could be accounted for by these factors. Critically, studies where CRT has been directly compared to a cognitively stimulating control condition demonstrate that this treatment, and not merely the effect of engagement or interaction with a therapist, can lead to substantive cognitive gains (Bell et al., 2005; Fisher, Holland, Merzenich, & Vinogradov, 2009; Kurtz, Seltzer, Shagan, Thime, & Wexler, 2007; Mcgurk, Ph, Mueser, et al., 2007).

However, the efficacy of computerized CRT interventions appears less consistent when these programs are compared to other types of computer-based activities or training. Two studies demonstrated that CRT initiated greater overall cognitive improvements when compared to a computer games control condition (Fisher et al., 2014, 2009), suggesting that the training was able to target and improve cognition specific to the intervention. However, studies with similar computerized interventions and controls showed that participants in the CRT group only showed improvements in the tasks (Dickinson et al., 2010) or domains (Kurtz et al., 2007) on which they were trained. This may suggest that computerized CRT has limited capacity to generalize to untrained domains of cognition. As such, the disparate findings in this field will continue to require scrutiny, and future controlled trials will be called on to establish a consensus on how best to implement computerized CRT for schizophrenia.

Wykes et al. (2011) also examined studies measuring psychosocial outcomes. They were able to demonstrate that studies have shown small to moderate effects from CRT on these abilities, though it is still unclear which aspects of cognitive training positively impact this broad psychosocial domain. They also demonstrate that the few studies that have begun to follow these individuals longitudinally show that individuals who functionally improve can maintain these gains well beyond the duration of training. And while it seems that adjunctive therapies coupled with CRT can be practically utilized to promote functional skills, it is not yet clear whether active employment, social skills training, or a combination of these kinds of treatments best translates to abilities in real-world settings. Future studies will be needed to clarify why and how these interventions have modest generalizable effects on cognition and functional outcome or ability. Overall, meta-analytic findings in this area lead to an increasingly accepted conclusion: CRT for schizophrenia, regardless of its approach or theoretic basis, has moderate cognitive and psychosocial benefits. It also seems clear that there are incremental improvements when combining CRT with additional forms of rehabilitation (i.e. social skills training, supported employment, supported education) and strategy coaching (McGurk, 2012; McGurk et al., 2007).

Moderators of Treatment Response

One challenge of CRT for schizophrenia is determining factors predictive of treatment response and outcome. Considerable variability in response to CRT has been previously observed, with some patients who underwent treatment exhibiting large

improvements in specific cognitive domains while others make little no improvements at all (Kurtz et al., 2007; Medalia & Richardson, 2005). This inter-participant variability may in some cases be masking larger effects of CRT, potentially blurring the relationship between treatment and cognitive improvement. For this reason, a clearer understanding of individual differences in response to CRT may help to guide the development of better treatment programs, as well as personalized medicine tailored to a patient's specific needs.

Efforts to predict patient response to CRT have examined whether baseline cognitive ability predicted neuropsychological or psychosocial improvements. Fiszdon and colleagues (2005) demonstrated that baseline performance on tasks of working memory and attention predicted normalization of performance on a digit sequence recall task after CRT. This indicates that basal levels of cognition may be crucial factors in treatment participation. Another study used a measure of verbal learning to categorize patients based on their learning potential (Fiszdon et al., 2006). Results showed that patients who scored high on this test at baseline also showed higher scores on a test of functional capacity, suggesting that certain patients may be more ready or likely to respond to cognitive treatments based on their pre-treatment psychosocial functioning.

Other approaches have used linear regression to examine functional outcome predictors at baseline. Kurtz and colleagues (2009) examined whether baseline neurocognitive functioning, symptomology, or treatment characteristics predicted patient outcome. Their findings demonstrated that higher auditory sustained attention capacity and stronger working memory, even when controlled for by all other variables, were the

only two cognitive factors predictive of response to CRT. This finding largely indicates that stronger baseline cognitive abilities, as well as those who are more functionally intact, are most likely to benefit from CRT. However all is not lost for lower functioning patients. Work by Twamley et al., (2011) indicates that patients with poorer baseline working memory and overall cognitive functioning may have better response to strategy training approaches to CRT. This may suggest that using these approaches in tandem could have useful benefits for patients with weaker initial attention and working memory skills. Additionally, Bell and colleagues (2014) showed that individuals with lower community functioning showed a better response when receiving supported employment in addition to CRT, further suggesting that special consideration should be given to lower functioning individuals in the context of cognitive training.

Medalia and Richardson (2005) examined whether non-cognitive patient characteristics, illness factors, or treatment factors differed between patients who showed functional improvement from CRT and those who did not. Factors related to the illness itself, such as positive symptom acuity and extent, were not shown to differ between improvers and non-improvers. However, patients with stronger work behavior skills and more intrinsic motivation at baseline showed greater gains from CRT. Other factors predictive of functional improvement in their study included having a Ph.D. level clinician, and having sufficient treatment intensity (at least two sessions per week). Another study examining response to CRT showed that functional improvements were greater in patients who were younger, had fewer symptoms, were on lower doses of anti-psychotics, and had higher baseline neurocognitive functioning (Vita et al., 2013). While

these results suggest that those with less severe illness are more likely to respond positively to CRT, there are other factors that can contribute to cognitive and functional improvements.

Findings by Medalia and Richardson (2005) also indicate that motivation and perceived competence may be critical factors predictive of functional change. This may be especially relevant as deficits in motivation are thought to be a core feature to the pathology of schizophrenia and related psychotic illnesses, as well as a strong predictor of functional outcome (Nakagami, Hoe, & Brekke, 2010). In the case of cognitive training, motivation may serve to translate cognitive gains to functional ones (Velligan, Kern, & Gold, 2006), potentially helping patients to work harder and better tolerate stress. Not surprisingly, motivation has been shown to impact various functional outcomes including overall functioning, cognition, and social cognition (Gard, Fisher, Garrett, Genevsky, & Vinogradov, 2009). Higher pre-treatment motivation may also bode well for a patient's response to CRT interventions, but the consensus is that motivation in schizophrenia patients is dynamic, and that CRT interventions may aim to enhance it in treatment settings to facilitate learning (Medalia & Saperstein, 2011).

Brain Changes Associated with Cognitive Remediation and Potential Neural Targets

While measures of cognition and psychosocial functioning serve as the primary indices of improvement in response to CRT, changes in neural functioning are theorized to underlie these behavioral changes. Translational research has established that neural plasticity is feasible well into adulthood (Buonomano & Merzenich, 1998), and CRT is

hypothesized to work through this mechanism. Meta-analytic findings demonstrate that hypoactivation in areas of the prefrontal cortex play a role in the cognitive dysfunction observed in schizophrenia (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). As such, CRT interventions that exercise these brain regions are theorized to promote neural plasticity restoring cognitive and neural functioning. Findings by Haut, Lim, and MacDonald (2010) demonstrated that the dorsolateral prefrontal cortex (DLPFC), in addition to the anterior cingulate cortex (ACC), increased in activation in response to the n-back task after undergoing a working memory focused CRT. As the DLPFC and ACC are two regions intimately involved in executive control and attention respectively, it stands to reason that improving the activation patterns in these areas should hold great benefits to patients suffering from cognitive dysfunction. Findings by Subramaniam and colleagues (Subramaniam et al., 2014) demonstrated similar results using a bottom up auditory drill and practice training and facial emotion recognition training regimen, showing that patients who underwent CRT had increased lateral prefrontal activation on an n-back working memory task. These lateral prefrontal improvements were also predictive of improved occupational functioning six months after training.

Cognitive training has also been demonstrated to impact limbic brain areas crucial for affective, social, and emotional functioning. In a trial that utilized an auditory CRT, patients in the active treatment group showed improved reality monitoring skills, which correlated to activation in the medial PFC (Subramaniam, Luks, Fisher, Simpson, Nagarajan, et al., 2012). This activity was also correlated with improved social functioning six months after training. Another study utilized a combination of working

memory exercises, auditory CRT, and a computerized a social skills training program. Patients in the active treatment showed increased activation in the amygdala, putamen, and medial PFC during an emotional recognition task following training (Hooker et al., 2013). These findings provide support for the notion that functional changes in response to CRT are not merely limited to prefrontal brain activity, and influence more than just traditionally cognitive abilities. Further examination of the neural processes that are impacted by CRT will guide the continuing development of this treatment. As we develop a clearer understanding of the brain areas most strongly associated with cognitive and psychosocial change, future interventions can be designed to have maximal impact on these systems. One important goal will be to meta-analyze the existing studies that have examined functional activation changes associated with CRT, thereby identifying specific neural targets that can be engaged by focused training, as well as examined in future experiments.

Increasing functional activation may be a crucial mechanism by which CRT influences improved cognition and functional outcomes, especially as observed hypoactivation patterns may in part characterize disrupted functioning (Glahn et al., 2005; Minzenberg et al., 2009). However, other hypotheses suggest that neural dysconnectivity (both hypo- and hyperconnections), characterized by aberrant connections within and between brain regions, may also characterize these disruptions (Andreasen, Paradiso, & O'Leary, 1998; Anticevic et al., 2013; Atluri, Steinbach, Lim, Kumar, & MacDonald, 2014; Cole, Anticevic, Repovs, & Barch, 2011; Friston & Frith, 1995; Lynall et al., 2010). Therefore, both functional and structural connectivity

disruptions may be important neural targets for improving cognition in schizophrenia, though few studies have measured these neural systems in response to CRT.

Diffusion Tensor Imaging (DTI) is one such method for assessing structural connectivity by measuring fractional anisotropy and mean diffusivity to characterize white matter microstructure *in vivo*. Numerous studies have used DTI to examine structural connectivity in both chronic and first-episode schizophrenia, indicating widespread reductions in white matter fiber integrity, but also an overall lack of convergence in these findings (Melonakos et al., 2011). More consistent findings have been observed when combining DTI with functional activation measures, and have largely implicated frontal and temporal regions having reduced structural connectivity (Fitzsimmons, Kubicki, & Shenton, 2013). Abnormal structural connections have been shown to relate to symptom profile (Camchong, MacDonald, Bell, Mueller, & Lim, 2011) as well as working memory performance (Marenco et al., 2012), suggesting that disrupted tractography could underlie a broad array psychiatric symptomology in schizophrenia. However, these disrupted connections may be malleable in response to CRT, as one study demonstrated increased structural connectivity in the genu and body of the corpus callosum as well as the right posterior thalamic radiation following training (Penadés et al., 2013a).

Independent component analysis (ICA) is another novel tool that uses a blind-source separation procedure to identify neural networks in functional imaging data. The functional integration or "coherence" of these networks is becoming an increasingly common and useful method for examining functional connectivity, and is emerging as an

important way to characterize the pathophysiology of a variety of neuropsychiatric disorders (M. Greicius, 2008). Patients with schizophrenia have been observed to have widespread differences in functional components observed both during task (Dae et al., 2009; Garrity et al., 2007; Meda, Stevens, Folley, Calhoun, & Pearlson, 2009) and at rest (Mingoia et al., 2012; Rotarska-Jagiela et al., 2010). Particular focus has been on the default mode network (DMN) and fronto-parietal executive network (EN) that are thought to be negatively and positively related to cognitive engagement respectively. These networks therefore may be critical targets for investigation with regards to CRT, especially as previous studies have demonstrated that they are plastic in response to neural stimulation (Venkatakrishnan, Contreras-Vidal, Sandrini, & Cohen, 2011).

One study demonstrated that patients who underwent CRT showed improved functional connectivity in the DMN and a fronto-parietal EN during a working memory task (Penadés et al., 2013b). Following training, patients who underwent CRT showed functional connectivity patterns more like that of healthy controls, supporting theories that this type of training may restore healthy neural functioning. Other studies have observed gray matter preservation in the hippocampus, amygdala, and fusiform gyrus as the result of CRT, suggesting that this treatment may confer neuroprotective factors to support improved cognitive functioning (Eack et al., 2010). Many of these studies demonstrate task-related changes that appear to restore functioning to that of healthy controls, and while current findings show that CRT impacts both functional activation and neural connectivity, it is unclear whether one better account for treatment related improvements.

Another potential neural target concerns frontal and subcortical brain areas together. Previous reviews have highlighted both prefrontal (Glahn et al., 2005) and thalamic disruptions (Pergola, Selvaggi, Trizio, Bertolino, & Blasi, 2015) associated with schizophrenia, but more recently connections *between* these regions have emerged as potential markers associated with the pathophysiology of this illness. Numerous resting state fMRI (rsfMRI) studies have identified aberrant thalamocortical connections in schizophrenia, wherein patients show both reduced prefrontal-thalamic connectivity, and hyper-connectivity between the thalamus and temporal, parietal, somatosensory/motor, and visual cortices (Anticevic et al., 2013; Atluri et al., 2014; Klingner et al., 2014; Welsh, Chen, & Taylor, 2010; Woodward, Karbasforoushan, & Heckers, 2012). Findings by Anticevic and colleagues showed that overall symptom severity was correlated to observed hyperconnectivity between the thalamus and sensory cortices (Anticevic et al., 2013), but the role of reduced thalamus-PFC connections may be more nuanced. Emerging evidence suggests that structural and functional interrelationships within cortico-striatal-thalamal circuits are linked to overall cognitive performance (Sui et al., 2015). Furthermore, animal models have demonstrated that perturbations to the thalamic nuclei within this network may influence working memory function (Duan et al., 2015). These findings may indicate that disrupted connections from thalamus to the prefrontal cortex may be involved in the widely observed cognitive deficits associated with schizophrenia. However, while these widespread intrinsic dysconnections may characterize patients in a disease state, it is unclear whether they are malleable in

response to psychiatric recovery. This will be another critical target of investigation for future studies examining neural changes associated with CRT.

Future Directions and Specific Aims

Despite the increasing prominence of CRT for schizophrenia in the last 2-3 decades, many questions remain about the neural mechanisms supporting this treatment. A number of studies have examined functional activation changes associated with CRT in schizophrenia, and it now may be the case that these studies can be usefully meta-analyzed. This type of analysis may be particularly critical to both organize thinking about the hypothesized mechanisms of CRT, but also understand its overall impact. Additionally, the promising results of CRT demonstrated by Haut and colleagues (2010) have never been systematically replicated, and only examined cognitive improvement as it related to improvements on a working memory task. We therefore sought to replicate these results, but also expand this inquiry to examine whether changes in functional activation also relate to improvements in measures of cognition, psychosocial functioning, and symptom profile. This is of critical importance, as behavioral findings indicate that cognitive and psychological factors are predictive of response to CRT (Kurtz et al., 2009), but it is currently unclear whether individual neural activity also predicts improvement. This highlights the first goal of the current dissertation, which is to replicate previous findings, identify specific brain areas responsive to CRT in schizophrenia, and predict treatment response from baseline brain functioning patterns.

In addition to examining whether functional activation increases are associated with CRT, this dissertation will also evaluate other forms of neural activation change; especially as evidence indicates that strict patterns of hypoactivation do not fully characterize the cognitive disruptions associated with schizophrenia, and rather a combination of hyper- and hypoactivation is associated with this dysfunction (Glahn et al., 2005; Minzenberg et al., 2009). This may suggest that as opposed to increasing functional activation, more complex patterns of activation may better capture the improvements associated with CRT, especially as the PFC has widespread cortical and subcortical connections that support cognitive functioning (Miller & Cohen, 2001). In light of this functional connectedness, some have proposed that disruptions in functional connectivity may characterize the pathophysiology of the illness (Andreasen et al., 1998; Anticevic et al., 2013; Atluri et al., 2014; Cole et al., 2011; Friston & Frith, 1995; Garrity et al., 2007; Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011), and may also better characterize cognitive disruptions (Lynall et al., 2010; Sui et al., 2015).

Current evidence suggests that CRT affects both functional activation and neural connectivity (Haut et al., 2010; Penadés et al., 2013b; Subramaniam, Luks, Fisher, Simpson, & Nagarajan, 2012), but it is unclear whether one better accounts for treatment related improvements. In the current dissertation**,** I also aim to identify whether cognitive and functional improvement from CRT in schizophrenia is better predicted by changes in functional activation (BOLD signal) versus functional connectivity (as measured by ICA and seed-based methods). Last, it is not known whether neural changes from CRT generalize beyond task-based cognitive states to influence intrinsic brain functioning. To

examine this I will measure functional connectivity changes at rest using both ICA and seed-based connectivity techniques. Specifically, I will examine hypothesized disruptions in default mode, executive, and thalamocortical networks. These orthogonal approaches could elucidate important mechanisms that underlie CRT, which could be systematically targeted by emerging interventions.

To carry out these aims, I am collaborating in a blinded clinical trial at the Minneapolis VA, wherein schizophrenia patients undergo either 48 hours of a working memory-focused CRT or a computer skills training control condition. Before and after treatment, eligible patients complete neurocognitive testing, are evaluated on measures of psychosocial functioning, and undergo a fMRI scan. Scanning procedures include two n-back tasks and an eight-minute resting scan. In this sample I sought to address the following specific aims:

Aim 1. Conduct a meta-analysis to (a) identify common brain regions influenced by CRT for schizophrenia, and (b) compare these regions to previously established areas of dysfunction to determine whether CRT invokes target engagement of these brain areas.

Aim 2. Test the hypotheses that (a) patients in the active treatment group will show greater BOLD activation change in areas of the lateral PFC and ACC, as well as task-related increases in functional connectivity within a fronto-parietal executive control network and the default mode network (DMN). Second, I hypothesize that (b) change in functional connectivity is a psychometrically better predictor of improved psychosocial

functioning compared to change in BOLD signal. To test this, I will compare the correlations of BOLD activity and functional connectivity with psychosocial outcome. Last, I will test the prediction that (c) patients in the CRT group will have increased resting state functional connectivity in the default mode and fronto-parietal executive control networks, compared to those in the control condition.

Aim 3. Test the hypothesis that (a) cognition, psychosocial functioning, symptoms, and motivation at baseline, before administering CRT, are predictive of neural changes in response to the treatment, particularly in areas of the PFC. Second, I hypothesize that (b) modulation of prefrontal areas before the CRT intervention will predict *improvements* in cognition, psychosocial functioning, and psychiatric symptomology, and that they provide unique information over and above baseline behavioral and self-report measures.

As our understanding of cognition in schizophrenia evolves, so too should CRT, and insights about the neural mechanisms of dysfunction should continue to guide the way we treat them. The current dissertation seeks to be a part of this conversation, and will shed light on these emerging potential mechanisms. Currently, we know there is considerable variability in the presentation and course of schizophrenia (Carpenter & Kirkpatrick, 1988), and that cognitive symptoms may be particularly heterogeneous (Joyce, Hutton, Mutsatsa, & Barnes, 2005). This may indicate that a "one size fits all" approach to cognitive remediation may be haphazard, and potentially explains largely modest efficacy as a whole. Tailored approaches to CRT may be able to offer a better

course of treatment, guided not only by the patient's presenting symptoms, but also the neuroscience supporting changes to these systems. Examining the specific neural changes spurred by these interventions will be an important step in this emerging field.

Chapter 2: Brain Correlates of Cognitive Remediation In Schizophrenia: Activation Likelihood Analysis Shows Preliminary Evidence Of Neural Target Engagement

Foreword: This chapter was written in collaboration with Angus W. MacDonald, who edited and revised versions of the manuscript. The text of this chapter can also be found in press at *Schizophrenia Bulletin*.

Abstract

Cognitive remediation training (CRT) for schizophrenia has been found to improve cognitive functioning and influence neural plasticity. However, with various training approaches and mixed findings, the mechanisms driving generalization of cognitive skills from CRT are unclear. In this meta-analysis of extant imaging studies examining CRT's effects we sought to clarify whether varying approaches to CRT suggest common neural changes, and whether such mechanisms are restorative or compensatory. We conducted a literature search to identify studies appropriate for inclusion in an activation likelihood estimation (ALE) meta-analysis. Our criteria required studies to consist of training-based interventions designed to improve patients' cognitive or social functioning, including generalization to untrained circumstances. Studies were also required to examine changes in pre- versus post-training functional activation using fMRI or PET. The literature search identified 162 articles, nine of which were appropriate for inclusion. ALE analyses comparing pre- and post-training brain activation showed increased activity in the lateral and medial PFC, parietal cortex, insula, as well as the caudate and thalamus. Notably,

activation associated with CRT in the left PFC and thalamus partially overlapped with previous meta-analytically identified areas associated with deficits in working memory, executive control, and facial emotion processing in schizophrenia. We conclude that CRT interventions from varying theoretic modalities elicit plasticity in areas that support cognitive and socio-emotional processes in this early set of studies. While preliminary, these changes appear to be both restorative and compensatory, though thalamo-coritcal areas previously associated with dysfunction may be common sources of plasticity for cognitive remediation in schizophrenia.

Introduction

Schizophrenia is characterized by broad and pervasive cognitive deficits (Heinrichs & Zakzanis, 1998) affecting functional ability and contributing to poor outcomes in this population (Green et al., 2000). Because these impairments respond only mildly to antipsychotic treatments (Harvey, 2009), clinical researchers have examined psychological approaches to ameliorate these cognitive problems. Cognitive remediation training (CRT) is an increasingly viable strategy for treating the cognitive and functional deficits experienced by patients with schizophrenia. These interventions consist of clinician-led or computerized training that utilize a mix of cognitive exercises and generalization strategies to improve the attention, problem solving, and memory skills that support daily functioning.

Meta-analytic findings spanning various CRT approaches and domains indicate that this treatment has modest effects on global cognition and functioning, and that these

changes may persist beyond the acute training period (Wykes et al., 2011). Still, much remains unclear about the neurobiology underlying CRT, and whether increases, decreases, or functional reorganization of brain activity reflect improvements in cognition. Randomized trials studying CRT in schizophrenia have approached these questions by adding pre- and post-treatment neuroimaging protocols. Numerous studies have observed training-related synaptic plasticity, which is broadly characterized in this context by functional activation changes associated with cognitive training. However, with small sample sizes, various CRT approaches, and heterogeneity among findings, it is useful at this point to integrate these studies and provide a set of modal findings to guide future hypothesis tests.

In the current study we used a spatial meta-analytic approach known as activation likelihood estimate (ALE) to examine whether CRT across training modalities influences common neuroanatomical regions. This approach examines the cumulative evidence of activation for various brain locations across published studies. Though CRT treatments often differ, they share a common aim of generalization beyond their training domain, to transfer cognitive and psychosocial abilities to untrained circumstances. In the context of the current study, we sought to understand generalization as it related to performance on untrained tasks to measure the transfer of trained skills. Identifying the neural substrates associated with generalization of cognitive skill transfer to untrained abilities will be crucial to an emerging understanding of neural plasticity in schizophrenia, and may identify candidate neural targets supported by these mechanisms. This is of timely importance, as it will provide direction toward candidate brain areas of interest in

ongoing investigations of cognitive training. Furthermore, this study hoped to clarify discrepancies in this field to determine whether CRT interventions invoke compensatory or rehabilitative neuroplastic changes.

Impairments in executive functioning, cognitive control, working memory, and emotional processing are believed to be core cognitive deficits in schizophrenia, and a number of studies have identified neural disruptions associated with these disabilities (Barch & Ceaser, 2011; Eisenberg & Berman, 2010; Glahn et al., 2005; Kohler, Walker, Martin, Healey, & Moberg, 2010). Meta-analyses indicate that though patients and healthy individuals recruit the same neural networks in response to executive and working memory tasks, patients have disrupted activity in these areas(Glahn et al., 2005; Minzenberg et al., 2009). Using an ALE approach, Minzenberg and colleagues (Minzenberg et al., 2009) demonstrated that both patient and control groups activated prefrontal regions including dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and anterior cingulate cortex (ACC), as well as lateral temporal areas, parietal areas, and motor areas in response to cognitive tasks. However, differences were observed between groups, wherein patients showed less activation in areas including the lateral prefrontal cortex (PFC), ACC, and thalamus. Some of these same regions have shown abnormal responses during working memory tasks in patients' healthy siblings, suggesting they may also mark an unexpressed genetic liability for schizophrenia (Callicott et al., 2003).

ALE meta-analyses have also demonstrated that patients with schizophrenia show patterns of impairment associated with facial affect processing (Delvecchio, Sugranyes,

& Frangou, 2013). Frontal areas including the medial PFC and precentral gyrus, limbic areas such as the amygdala and insula, and midbrain areas including the caudate and thalamus were shown to activate less in response to emotional faces in patients compared to controls. As such, these aberrant patterns of prefrontal, limbic, and midbrain neural activations are thought to underlie the cognitive and socio-emotional deficits observed in schizophrenia, making them critical targets for cognitive interventions in schizophrenia.

Efforts to develop treatments for cognitive dysfunction in schizophrenia have not only looked towards biological markers of pathology, but have also built on a literature demonstrating the brain's ability to change. Research over the last three decades has indicated that the brain is 'plastic' well into adulthood, and studies examining synaptic and cortical map plasticity have demonstrated that long-term potentiation may underlie the implicit reorganization of the brain when it learns new material (Buonomano & Merzenich, 1998). Plasticity and potential skill transfer are thought to occur as the result of practice-driven coordination at multiple processing levels. Like in the case of working memory, engagement of both perceptual processes and top-down modulation of frontal brain areas are thought to impact cognitive processing (Gazzaley, 2011). Rewarded behavior is also known to promote plasticity, and is associated with neural activation in midbrain areas such as the ventral tegmental area, nucleus accumbens, and hippocampus (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006).

Though evidence for plasticity is strong, the argument that cognitive training can promote meaningful plasticity in healthy adults remains controversial. Cognitive training studies have been critiqued for their inability to demonstrate transfer to untrained tasks,

their lack of applicability to real-world skills, and a dearth of placebo controlled trials to examine their efficacy (Shipstead, Redick, & Engle, 2012). However, working memory training has been reported to increase activity in the lateral PFC and parietal cortices (Olesen, Westerberg, & Klingberg, 2004), along with other patterns of change (Dahlin, Nyberg, Bäckman, & Neely, 2008). Increases in activation may indicate strengthened cortical engagement resulting from training (Buschkuehl, Jaeggi, & Jonides, 2012), while decreases may be interpreted as improved neural efficiency, shifting neural processes from being effortful to more automatic (Kelly & Garavan, 2005). Redistribution and reorganization of neural activity in response to cognitive training may reflect both increases and decreases in activity, but also evokes activity in new areas as cognitive processes are learned or developed (Kelly & Garavan, 2005). Gray matter and other structural anomalies, which have been widely observed in schizophrenia (Glahn et al., 2008), are also worth considering in regards to functional changes, as compensatory versus rehabilitative activation changes may be related to the status of baseline atrophy and dysfunction. It is yet unclear which specific factors of cognitive training reflect changes in activity via improved cognition in healthy adults. An emerging picture suggests that areas susceptible to training-induced plasticity in healthy adults largely overlap with those implicated in cognitive deficits in schizophrenia (Minzenberg et al., 2009).

Emerging from findings in healthy adults, hypotheses about the neural systems influenced by cognitive training for schizophrenia largely implicate similar prefrontal mechanisms to support improved cognitive function. Individual studies examining CRT

in schizophrenia have primarily demonstrated increases in activation in cognitive control areas such as the lateral PFC (Haut et al., 2010). However, other trainings with both cognitive and social training components have demonstrated more nuanced patterns of activation change, with both increases and decreases in prefrontal and subcortical limbic areas (Hooker et al., 2013). Though these various approaches to CRT may have similar influences on cognition and psychosocial functioning, it is currently unclear whether they affect similar brain areas. A clearer understanding of the neural systems impacted by these interventions will be crucial as novel psychiatric treatments aim to intervene at the level of spatial and temporal neural dynamics.

The goal of the current study was to clarify the emerging understanding of CRT-induced plasticity in patients with schizophrenia, and characterize the observed functional activation changes evoked by training. Using an ALE approach, we examined whether CRT across training modalities change common neuroanatomical regions associated with interventions that influence the generalization of cognitive skill transfer. Additionally, we aimed to clarify whether CRT interventions invoke brain plasticity that is rehabilitative (change in areas previously shown to be disrupted) or compensatory (activation in new areas hypothesized to support cognitive functioning). In doing so, we examined "target engagement" by comparing the current findings to previous meta-analytic results to determine whether areas supporting CRT were similar to areas known to be deficient in this population. We hypothesized that CRT would show a restorative effect, increasing activation in areas previously shown to be dysfunctional, with maximal impact on areas of the brain that support cognition and social functioning. Predicted brain regions

included the lateral PFC supporting cognitive and executive control, and socio-emotional brain areas including the insula and medial PFC. To clarify whether specific aspects of the varying CRT approaches also support these hypotheses, we performed exploratory analyses to examine differences between extant studies based on the modality of training, intensity of the intervention, whether trainings were computerized, whether studies were placebo controlled, and differences in the task used to measure generalization of functioning and neural plasticity.

Methods

Literature Search

For this study we characterized cognitive remediation broadly, aiming to identify studies that examined any training-based intervention designed to improve schizophrenia patients' cognitive or social functioning, using data on generalization to untrained tasks, abilities, or circumstances. A literature search of English language speaking journals was conducted in PubMed using the following combinations of keywords: "Cognitive Remediation," or "Cognitive Training," or "Cognitive Rehabilitation," or "Psychiatric Rehabilitation," or "Working Memory Training," with "Schizophrenia," or "Psychosis," and with "fMRI," or "Imaging," or "Neural Activation." Inclusion criteria required studies to (A) be part of a clinical trial examining cognitive remediation in schizophrenia; (B) examine change in hemodynamic response on a fMRI or PET task both before and after training using a general linear model (GLM); (C) rely on a generalization task that

was not used for cognitive training; and (D) report findings in either Montreal Neurologic Institute (MNI) or Talairach space.

ALE Analysis

ALE analysis was conducted in GingerALE v2.3 (Eickhoff et al., 2009; Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Turkeltaub et al., 2012) in the BrainMap environment. Study coordinates were entered into the database in Talairach space. Coordinates reported in Montreal Neurologic Institute (MNI) space were transformed to Talairach space based on the icbm2tal algorithm (Lancaster et al., 2007). GingerALE calculations are carried out in multiple steps: First, modeled activation (MA) maps are created for each experiment by modeling individual foci within experiments as gaussians, with widths calculated based on the group Ns (Eickhoff et al., 2009). Next, an unthresholded ALE map is calculated based on the union of these MA maps, with the probabilities of finding a given value within a map combined across studies to build a 3D *p*-value image. The *p*-value image is then thresholded using a false discovery rate (FDR) correction, and then cluster-thresholded by simulating random data given the characteristics of the entered data set. In the cluster-level inference, contiguous voxels of the simulated data that exceed the set FDR threshold form a final cluster-corrected image. In the current analysis, we employed a FDR correction of $p<.05$, 1,000 permutations of simulated data, and a cluster-level inference threshold of $p<.05$. To control for within subject effects, separate investigations that contained the same subjects were treated as single studies in the ALE model, with foci from both experiments pooled into one study entry. Therefore,

interventions with multiple studies or imaging protocols were treated as one experiment in this investigation.

Results

Literature Search Results

Search results identified 163 unique articles, 19 of which were studies that used neuroimaging measures associated with CRT (See Figure 2.1). Of these, nine met the inclusion criteria, with a total of 128 subjects and 74 foci. Two pairs of included studies were conducted on the same subjects using a different fMRI task, and were treated as random effects in the ALE. As such, the final ALE contained seven experiments modeled as random effects.

The theoretic approach to cognitive remediation varied among the nine included studies (See Table 2.1). Two relied on an auditory training approach (Subramaniam et al., 2014; Subramaniam, Luks, Fisher, Simpson, & Nagarajan, 2012) (which utilizes errorless-learning strategies to improve the speed and accuracy of auditory information processing), while two others relied on an auditory training plus social cognition training program (Hooker et al., 2012, 2013). These four studies used a computer game active placebo control condition. Wykes and colleagues (Wykes et al., 2002) used an approach that relied on paper and pencil tasks to practice information processing strategies in areas of executive functioning and memory. Their study used an occupational therapy as the control condition. Two studies used computerized cognitive training to target broad areas of cognitive functioning including attention, verbal working memory, logical reasoning,

and executive functioning, and were compared to treatment as usual (TAU) as the control condition (Bor et al., 2011; Vianin et al., 2014). One study used a computerized working memory-focused cognitive training program with a cognitive behavioral social skills training control group (Haut et al., 2010). Finally, one study trained affective and social cognition more specifically using various facial emotion and affect recognition tasks, and used TAU as a control (Habel et al., 2010).

Of the nine studies summarized on Table 1, four relied on an n-back task to assess activation associated with cognitive functioning (Bor et al., 2011; Haut et al., 2010; Subramaniam et al., 2014; Til Wykes et al., 2002). Three studies used facial emotion assessment tasks to examine brain activation (Habel et al., 2010; Hooker et al., 2012, 2013). One study used a verbal fluency task (Vianin et al., 2014), and the last used a reality-monitoring task (Subramaniam et al., 2014). All nine studies observed increases in activation as a result of training, but only two of these studies also reported decreases in activation as a result of training (Hooker et al., 2012, 2013). All studies reported a group by time interaction except for Vianin and colleagues (Vianin et al., 2014), which reported comparisons of Time 2 versus Time 1 in the CRT condition, and CRT versus TAU during Time 2. For the purposes of this meta-analysis, only coordinates and the subject N from the Time 2 versus Time 1 in the active CRT condition were included in the ALE.

ALE Results

Cluster-thresholded ALE results identified eight distinct brain area clusters that significantly increased in response to cognitive remediation (See Table 2.2 and

Supplemental Figure 2.1). Increases from Time 1 to Time 2 occurred in the left middle frontal gyrus (MFG), left inferior frontal gyrus (IFG), left superior frontal gyrus (SFG), pre- and postcentral gyrus, bilateral insula, parietal lobe, and medial frontal gyrus. Target engagement was examined by comparing this pattern to previous ALE meta-analyses contrasting healthy controls versus schizophrenia patients on tasks of executive control and working memory (Minzenberg et al., 2009) and facial affect recognition (Delvecchio et al., 2013). Areas that increased in activation in response to CRT in the left MFG and precentral gyrus were shown to partially overlap with similar areas previously found to be impaired during both cognitive and emotion recognition tasks (Figure 2.2A). A similar pattern was found in the thalamus and caudate nucleus, with substantial overlap between areas associated with CRT and deficits in emotional processing, and a non-overlapping but adjacent region associated with deficits in cognition (Figure 2.2B). These a priori comparisons suggested that CRT increased task-related activity in areas of the brain previously shown to exhibit impairments in schizophrenia. These findings were consistent with the hypothesis that cognitive remediation works toward normalization of brain functioning among patients with schizophrenia.

To further clarify the relationship between increased task-based activity resulting from training and the characteristics of the interventions themselves, we contrasted ALE maps on the basis of training intensity, theoretic CRT approach used, whether or not the approach was computerized, whether it was placebo-controlled, and the fMRI task used to measure change. Based on these comparisons we were unable to show any group

differences. However, power for these analyses was low, and continued study will be required to clarify more subtle differences.

Discussion

Nine studies were identified for the current ALE meta-analysis, with a total of 128 subjects and 74 foci. We observed that across studies, schizophrenia patients who undergo CRT interventions generally increased neural activation in areas of the lateral and medial PFC, parietal cortex, the insula, as well as the caudate and thalamus. In spite of heterogeneous treatment approaches, this review demonstrated that broadly speaking, CRT influences brain regions known to support working memory, cognitive control, and socio-emotional functioning in healthy individuals. Critically, these observed functional changes are in response to previously untrained tasks, showing that improved cognition may generalize not only to untrained tasks, but also to the brain areas that support those tasks. Of note, CRT was shown to increase task-based activity in areas of the left MFG and thalamus/caudate that were previously found to show impairment on working memory, executive functioning, and emotion recognition processing tasks. This is preliminary, but suggestive evidence to indicate that CRT restores activation in the thalamo-cortical circuits that potentially support improved cognition and psychosocial functioning. While it is important to note that the areas associated with pathology only partially overlapped with the current ALE results, it underscores the need to specifically examine the engagement of these neural targets in future CRT studies. Also, no relationships were observed when comparing studies on the basis of training intensity,

training approach, computerization, or on the basis of the task used to measure neural activity. However, the small number of available studies meant we were sensitive to only large effects if they were present.

Critically, the current findings indicate that among studies using various CRT approaches, neural activity increased in prefrontal, insular, and thalamic areas previously demonstrated to be disrupted in patients with schizophrenia (Delvecchio et al., 2013; Minzenberg et al., 2009). Increased activity in the left MFG as well as posterior cortex in response to CRT may support improvements in working memory and executive functioning, while increases in insular activation may support improved socio-emotional processing. Furthermore, despite the links among some of these brain areas and genetic liability for schizophrenia, the current findings support the notion that there remains residual neural plasticity to support functional recovery among these patients. Though increased activity in these areas suggests that patients who undergo cognitive training normalize neural activity to reflect that of healthy individuals, increases in other brain areas may also reflect compensatory brain activation as a result of training. Robust increases in the left IFG may support compensatory integration of cognitive and socio-emotional information, as this area was not shown to be impaired in either of the previous meta-analyses. Other areas exhibiting change include the pre- and post-central gyrus, where increased activation could be indicative of improved motoric functioning in response to cognitive training, as well as strengthened somatosensory representations of task goals. This may be the result of improved confidence or practice associated with prolonged training on a computer or other laboratory tools.

Restorative activity observed in the left PFC and thalamus/caudate may be particularly relevant in light of recent observations demonstrating that patients with schizophrenia show both structural and functional irregularities in the thalamo-cortical circuit (Atluri et al., 2014; Marenco et al., 2012). We propose that increased activity in these connected areas as a result of cognitive training could be an underlying mechanism that supports the efficacy of CRT in schizophrenia. Future studies should investigate this functional circuit to determine whether improved co-engagement of these areas supports specific cognitive and psychosocial improvements from CRT. It will also be critical for these studies to examine these neural targets both at baseline and over the course of training, as individual differences in various neural systems may be predictive of positive outcomes.

Of the included studies, only two (Hooker et al., 2012, 2013) reported deactivations as the result of training, identifying areas of the bilateral thalamus, MFG, ACC, and superior frontal gyrus. Decreased engagement of these areas may reflect neural efficiency (Kelly & Garavan, 2005), especially in areas crucial to attention, as well as both cognitive and emotional control (Bush, Luu, & Posner, 2000). It is unclear whether other studies included in this ALE analysis did not evoke deactivations as a result of training, observed but did not report these negative deflections, or simply did not examine non-hypothesized contrasts. Future studies should examine time one versus time two contrasts more closely to further clarify the relationships between neural deactivation in response to CRT in schizophrenia. This is relevant, as a combination of increases and

decreases in neural activity in response to a task may characterize the brain patterns associated with functional improvement.

While the current study has examined change in functional activation measured by a GLM, other studies have examined neural responses to cognitive training with different imaging measures. One study that used single-photon emission computed tomography (SPECT) found increases in prefrontal activity in response to CRT with this method (Penadés et al., 2003), while another showed mixed results, with decreased ACC activity in one subject and increased temporal activity in another in response to a verbal fluency task following training (Wykes, 1998). More recently, near infrared spectroscopy has been used to examine CRT, with one study showing an increase in prefrontal activity on an n-back task and improved verbal fluency and memory following six months of CRT (Pu et al., 2014). Studies using these alternative methods largely support the current results, demonstrating that prefrontal areas may be particularly amenable to neuroplastic changes in response to CRT.

Emerging findings indicate that in addition to functional disruptions in specific brain regions, schizophrenia may also be characterized by disruptions in neural connectivity (Cole et al., 2011; Lynall et al., 2010), reflecting aberrant connections both between and within brain areas. One study used independent components analysis (ICA) to assess whether functional connectivity changed as a result of CRT (Penadés et al., 2013b). After patients underwent 40 hours of training, they showed functional connectivity patterns in a network comprised of prefrontal areas that looked more like that of healthy controls. They propose that this change in functional connectivity, which

coincided with improvement in global cognition, represents enhanced neural efficiency. By examining functional connectivity, their conclusions offer insights that may be useful for understanding dysconnectivity in the context of assessing cognitive deficits in schizophrenia, especially as network-based approaches to understanding the brain are becoming increasingly germane to our understanding of CRT, related interventions, and serious mental illness more broadly (Frangou, 2014; Kelly & Castellanos, 2014). This puts the current findings into perspective, as the present ALE may only be elucidating functional hubs associated with neural changes, and that connections to and from these regions may also support these functional and psychosocial changes. It also highlights that we are currently only able to examine a very limited aspect of "plasticity," and cannot further resolve its source, which may be structural as well as functional, gross or molecular. Future investigations will be required to examine plasticity more broadly to further our understanding of the mechanisms supporting CRT.

A limitation of the current investigation is that we were constrained by the number of studies that met criteria for inclusion in this kind of analysis. This also limited our ability to examine differences between approaches to training, intensity of training, whether the approach was computerized, and the task used to measure neural change. Though we anticipated potential differences between intervention types, it is also possible that the specific CRT approach is less important than patients participating in prolonged engagement in challenging activities over time more generally. Additionally, the small sample size limited our ability to examine the relationship between treatment-induced changes in cognition, symptoms, and functioning and regional activation changes across

studies. We also note that the control conditions in the included studies ranged in terms of engagement, which may be potentially biasing the current results. More placebo-controlled studies measuring pre- and post-CRT neural activation will be necessary to draw reliable conclusions about the nature of neural plasticity in response to training, though the current findings represent an important first step. A second and related limitation is that in addition to examining heterogeneous CRT approaches, there was heterogeneity among the fMRI tasks used to measure cognitive change, with some measuring various aspects of working memory (i.e. n-back) and others measuring socio-emotional cognition (facial recognition). Differences in evoked activity are obviously important to consider in the context of these findings. Despite this heterogeneity, we still observed coherent activity in both traditionally cognitive and limbic areas in our ALE analysis.

It will also be important to understand these findings in the context of motivational and meta-cognitive factors that influence response to cognitive remediation and learning more broadly (Tas, Brown, Esen-Danaci, Lysaker, & Brüne, 2012). Especially as cognitive improvement associated with training has been found to be dependent on factors related to intrinsic motivation (Medalia & Richardson, 2005a). Additionally, a number of the included studies offered payment for participation, indicating that extrinsic motivation might also have been a factor. Future studies will be called upon to disentangle the relationship between neural changes associated with cognition versus motivation or meta-cognition more specifically. Last, this investigation of the neural systems associated with plasticity from CRT was limited in that it can only

speak to cognitive changes that immediately follow an intervention, and those that relate to near transfer generalization effects. Moving forward, studies should examine the effects of both long-term changes from CRT in schizophrenia, as well as whether these long-term neural changes also associate with improved psychosocial functioning in this psychiatric population.

Despite these limitations, the current findings come at an important time for understanding how to direct future development and examinations of CRT. They may also have important implications in the context of other psychiatric populations, as successful CRT interventions in schizophrenia are being applied to other mental disorders (Keshavan, Vinogradov, Rumsey, Sherrill, & Wagner, 2014). To conclude, the current meta-analysis demonstrates that CRT for schizophrenia, irrespective of theoretical approach, shows target engagement for neural functions in brain regions crucial to cognitive and socio-emotional functions. These coherent patterns of increased activity indicate that the neural mechanisms supporting CRT are both restorative and compensatory in nature, and generalize to untrained circumstances. Notably, increases in activation associated with CRT partially overlap with prefrontal and thalamic regions previously shown to be impaired in schizophrenia, establishing this as a potential restorative mechanism. This also establishes the thalamo-cortical circuit as a specific target for CRT and other cognitive enhancing interventions in schizophrenia.

Table 2.1. Studies Included in ALE

Source	Active N	Control N	Treatment	Control Condition	Duration/ Dose	Intensity	Task	Direction of Activity
Wykes, 2002	6	6	Individualized CRT	Occupational Therapy	12/40	3.333	N-back	↑
Haut, 2010	9	9	Working Memory Training	Cognitive Behavioral Social Skills Training	4-6/25	5	N-back	↑
Habel, 2010	10	10	Training of Affect Recognition	TAU	6/9	1.5	Facial Emotion and Age Recognition Task	↑
Bor, 2011	8	9	Rehacom-CRT	TAU	7/28	4	N-back	↑
Hooker, 2012	11	11	Auditory Training + Social Cognition Training	Computer Game Placebo	10/50	5	Emotion Recognition Task	↑↓
Subramaniam, 2012	15	14	Auditory and Visual Training	Computer Game Placebo	16/90	5.625	Reality Monitoring Task	↑
Hooker, 2013	11	11	Auditory Training + Social Cognition Training	Computer Game Placebo	10/50	5	Facial Emotion Recognition Task	↑↓
Vianin, 2014	8	8	RECOS CRT	TAU	14/42	3	Verbal Fluency Task	↑
Subramaniam, 2014	16	15	Auditory Training and Visual Training	Computer Game Placebo	16/90	5.625	N-back	↑

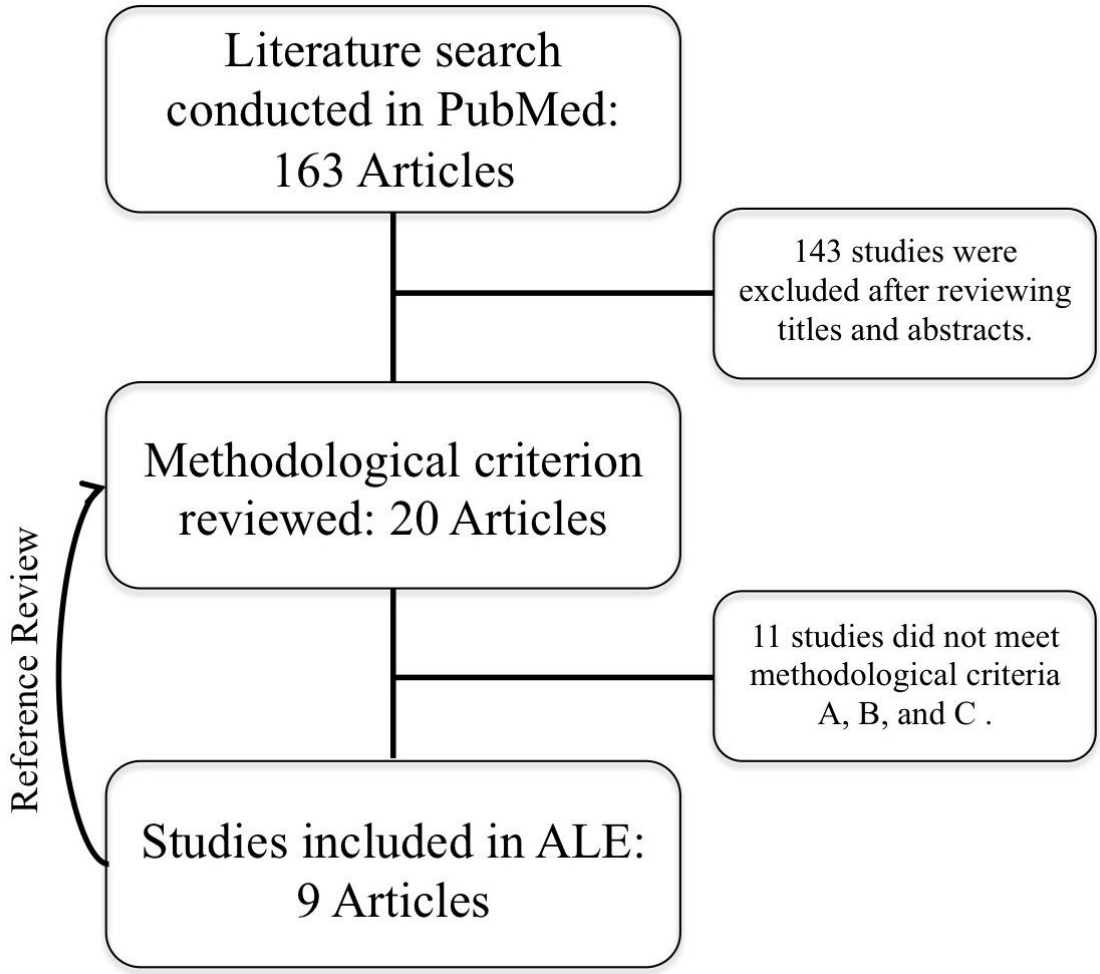
Note: The ALE included a total of 128 subjects (Active = 68; Control = 60). Participants underwent an average of 40 sessions (dose), an average of 10 weeks of training, and an average treatment intensity of 3.92 (calculated based on "Dose" divided by "Duration"). Notes: The two studies each by Hooker and colleagues and Subramaniam and colleagues were counted only once, as they constituted the same patient groups. We used the higher N from Subramaniam, 2014 (Subramaniam et al., 2014). The study by Vianin and colleagues measured Time 2 > Time 1 in active treatment group only and therefore only active treatment N was included; all others studies measured a Group x Task interaction. Abbreviations: N=Subject Number; TAU=Treatment as Usual, ↑=Increase, ↓= Decrease Intensity calculated based on Dose/Duration

Table 2.2. Brain Areas Associated with Change from Cognitive Remediation Training

Brain Area	Brodmann Area	Volume (mm^3)	Maximum ALE-Value	x	y	z
Left Middle Frontal Gyrus, Left Precentral Gyrus	6	624	0.015	-40	-8	40
Left Inferior Frontal Gyrus, Left Insular Cortex, Left Precentral Gyrus	9	496	0.014	-44	6	24
Right Superior Parietal Lobe	7	448	0.012	32	-66	50
Right Postcentral Gyrus	2	440	0.017	38	-24	42
Thalamus, Lentiform Nucleus, Caudate	NA	312	0.013	-10	-2	0
Right Insular Cortex	13	264	0.013	38	16	4
Left Superior Frontal Gyrus, Left Middle Frontal Gyrus	10	264	0.012	-28	52	6
Left Medial Frontal Gyrus	6	248	0.012	-6	-8	68

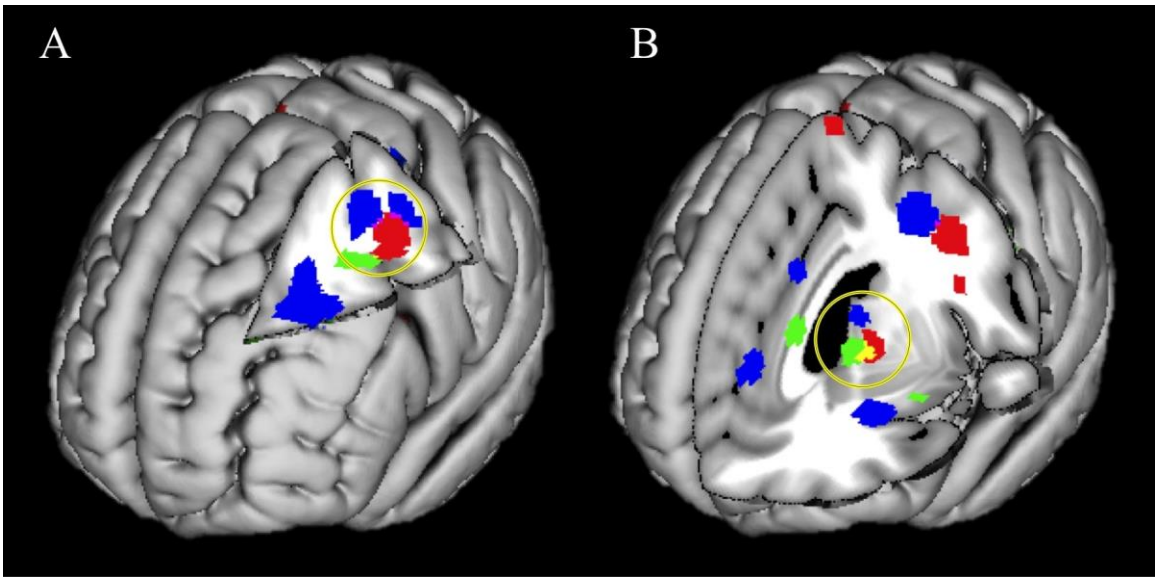
Note: All areas reported in Talairach Space. Brodmann Areas are defined by the Brain Map Talairach atlas.

Figure 2.1. Consort Diagram of Literature Search



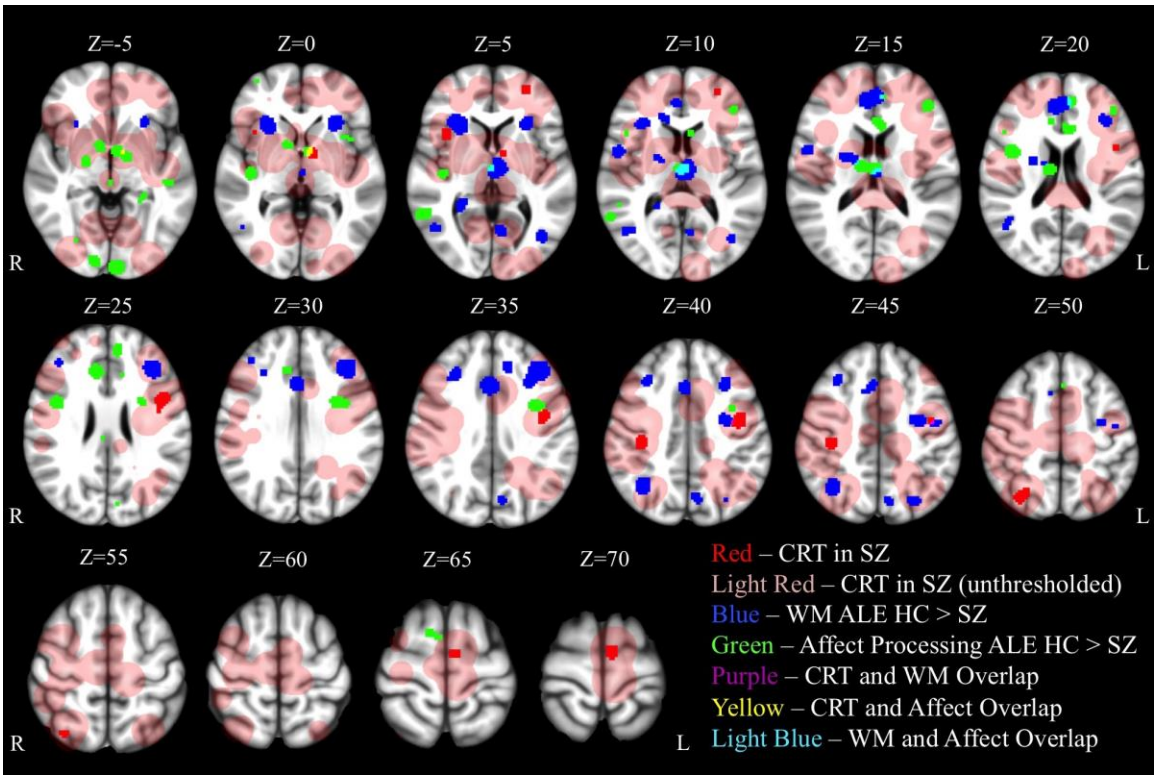
Note: No new articles were identified as the result of the reference review.

Figure 2.2. CRT Supports Restorative Functioning in Prefrontal and Thalamic Areas



Note: Areas in red depict brain regions that showed significant change as a result of CRT in the current ALE. Blue areas depict previously published results comparing controls > patients with schizophrenia (HC>SZ) on tasks measuring working memory (WM) and executive functioning. Green areas depict previously published results comparing HC>SZ on tasks measuring affective processing. Purple indicates overlap between CRT and the working memory ALE, and yellow indicates overlap between CRT and the affective processing ALE. (A) Increased functional activation as the result of CRT in the left PFC overlaps with areas shown to have dysfunctional processing in previous cognition and affective processing ALE meta-analyses. (B) Increased functional activation as the result of CRT in the thalamus and caudate nucleus overlaps with an area showing deficits in affective processing, and is adjacent to a thalamic area showing deficits in the WM ALE. Results from previous ALE studies are displayed here for comparison purposes with the kind permission of Minzenberg and colleagues (Minzenberg et al., 2009) and Delvecchio and colleagues (Delvecchio et al., 2013).

Supplemental Figure 2.1. Brain Areas Associated with Cognitive Remediation



Note: Brain Areas Associated with Cognitive Remediation. Areas in red depict brain regions that showed significant change as a result of training in the current ALE (CRT in SZ). Transparent red areas indicate unthresholded ALE results. Blue areas depict previously published results comparing controls > patients with schizophrenia (HC>SZ) on tasks measuring working memory and executive functioning. Green areas depict previously published results comparing HC>SZ on tasks measuring affective processing. Purple indicates overlap between CRT and the working memory (WM) ALE, yellow indicates overlap between CRT and the affective processing ALE, and light blue indicates overlap between the WM and affective processing ALEs. Results demonstrate that CRT impacts areas of the prefrontal cortex crucial for cognitive processing, limbic areas supporting socio-emotional functioning, and midbrain areas crucial for functional integration of these neural processes. Results from previous ALE studies are displayed here for comparison purposes with the kind permission of Minzenberg and colleagues (Minzenberg et al., 2009) and Delvecchio and colleagues (Delvecchio et al., 2013).

Chapter 3: General Methods

Foreword: This chapter outlines general methods common to three following studies. Each respective chapter will also outline these general methods as they relate to participants, trial design, training procedure, assessment procedure, and imaging procedure. Portions of this section were edited and revised by both Angus W. MacDonald and Tasha M. Nienow.

Participants

Patients with schizophrenia or schizoaffective disorder who had previously elected to participate in a clinical trial of a cognitive remediation intervention (Clinical Trial # NCT00995553) were recruited for the current study. Diagnosis was established using the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Spitzer, Gibbon, & Williams, 1997). Master's and doctoral level clinicians conducted the interviews, and the principal investigator (TMN) assigned a study diagnosis after review of available medical records, patient reports, and interviewer observations. All participants were between the ages of 18 and 60 years old, were clinically stable with no antipsychotic medication changes or hospitalizations in the previous four weeks, had a Weschsler Test of Adult Reading (WTAR) score of 70 or above, had no substance/alcohol dependence within the past six months and no substance/alcohol abuse in the past month, had no history of head injury with loss of consciousness for greater

than 20 minutes, and no known history of neurological conditions that could comprise cognitive functioning. All participants demonstrated capacity to give consent.

Fifty-three of the 80 participants enrolled in the clinical trial were screened for MRI compatibility. Forty consented to the imaging study. Three participants were withdrawn by the principal investigator prior to scanning after additional review of their medical history found them to be ineligible. Two additional participants were withdrawn due to inability to complete the scans. Five participants chose to withdraw because lack of interest (N=3) or anxiety in the scanner (N=2). Thirty participants completed scanning but data was lost from three due to experimenter error. Twenty-seven participants completed all study procedures. No participants were removed after employing a 2mm mean displacement movement cutoff within each scan. There were no differences in sex, age, race, education, parental education, or chlorpromazine (CPZ)-equivalent medication dosage between those in the final sample and those who were removed for any of the above reasons (all p's>.13). Additionally, participants included in the present study did not differ between groups on factors related to age, education, parental education, WTAR IQ score, duration of illness, or total CPZ equivalence (see Table 3.1). Groups also did not differ based on sex (χ^2=.02, p=.88) or diagnosis (χ^2=1.94, p=.16). The protocol and consent process were approved by the Institutional Review Board at both the University of Minnesota and the Minneapolis VA Health Care System (VAHCS).

Study Design and Blinds

Participants were randomized to undergo either a working memory focused CRT (N=15) or a computer skills training (CST; N=12) active placebo condition (though 15 participants underwent CRT, one did not complete the picture n-back or resting scan at both time points, leaving N=14 in the CRT group for that task and rest). Data collection and analysis were conducted 'triple-blind,' wherein the participants, providers and technicians, as well as statisticians were unaware of group membership. All primary fMRI analyses were conducted blind to group status, and the blind was not broken until whole-ROI confirmatory analyses were completed as described in Chapter 4.

Training Procedure

All training took place at the Minneapolis VAHCS as part of a larger trial examining cognitive and behavioral outcomes associated with a working memory-focused CRT. Patients completed 48 hours of training over the course of 16 weeks (Three 1-hour sessions weekly) in either the CRT or CST condition. Groups did not statistically differ with regard to average number of training hours (CRT=48 (SD=0), CST=48 (SD=.28)), or the average number of training days needed to complete the protocol (CRT=40 (SD=4.09), CST=36 (SD=10.43)).

Participants randomized into the CRT group completed a computer-based training program that consisted of 21 adaptive computer exercises, which placed demands on working memory functions through verbal, visual, and spatial stimulus modalities. The tasks were selected from three sources: Psychological Software Services CogRehab program developed by Bracy (Indianapolis: Psychological Software Services; 1995),

Captain's Log educational software (Brain Train) developed by Sandford and colleagues (Sandford, Browne, & Turner, 1996), and variants of English word and picture n-back tasks used in experimental psychopathology research in patients with schizophrenia (Gevins & Cutillo, 1993). Approximately 1/3 of training time focused specifically on training with a version of the N-back task (0-2 back, 2-back, 3-back, or 4-back). Participants were advanced to a higher training level after demonstrating mastery performance (85% accuracy) at the previous level across three consecutive trial runs.

Participants randomized into the active placebo control group engaged in a computer skills training (CST) course, focusing on keyboarding skills and learning to use Microsoft Office 2007 for word processing, spreadsheet management, and presentation creation. The CST condition was designed to have the same level of training time, exposure to computers, and attention from treatment providers as the CRT condition, but did not rely on errorless-learning principles like that of the CRT condition.

CRT and CST interventions were both facilitated by Master's or Bachelor's level interventionists, who provided instruction, monitored progress, acknowledged effort, and intervened as necessary to minimize frustration. In addition, a doctoral level clinician (TMN) led weekly half hour bridging sessions where group members discussed the skills they were learning and how they could be applied in other real-life situations. Participants' reactions to the trainings were also processed in these meetings.

Assessment Procedure

Enrolled participants underwent clinical, cognitive, and functional assessment at baseline and after 16 weeks of training. Cognitive assessment included two variants of the n-back task: a word version featuring English language words, and a picture version featuring still-frame images of animals, both switching between blocks of 2-back and 0-back trials. Five variants of the word n-back task, including the version used at the pre and post-intervention assessment, were practiced throughout the training procedure in the CRT group, and were included as a manipulation check. A picture n-back task with novel stimuli was included to measure skill transfer and generalization (i.e. improving performance in untrained domains) to an untrained version of the working memory task. N-back task performance was assessed using the sensitivity measure D-prime (D'), which compared the number of 'hits' to 'false alarms' in the 2-back condition.

Other cognitive measures included the MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008), which was specifically developed to assess cognitive functioning in schizophrenia, and measures domains of attention/vigilance, speed of processing, working memory, verbal learning, visual learning, problem solving/reasoning, and social cognition. For this study, we specifically examined the working memory and overall cognitive functioning domains as dependent variables to measure near (generalization to related, though untrained task demands) and far transfer (generalization to unrelated skills with distinct task demands) in the context of our working memory-focused CRT intervention.

Functional capacity was measured using the University of California, San Diego Performance-Based Skills Assessment (UPSA) overall score which is a measure

assessing skillfulness on activities of daily living (Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001). Capacity for social competence was measured with the Social Skills Performance Assessment (SSPA) overall score, which rates domains including social competence and appropriateness, clarity, fluency, affect, interest/disinterest, grooming, and overall conversation skills based on role-plays of social interactions with a confederate (Patterson, Moscona, McKibbin, Davidson, & Jeste, 2001). This scale is significantly related to other social performance-based measures and self-report measures of quality of wellbeing. Inter-class correlation coefficients (ICC) amongst the clinical raters for the SSPA ranged from .82 to .95, with mean ICC for scaled scores ranging from .70 to .80 across raters. The composite score from the self-report Social Functioning Scale (SFS; six subscales that assess the frequency of engagement in social and recreational activities, independent living skills, and employment) was used to examine level of functioning in the community (Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990). ICCs for the SFS were .88 or higher for both the total scores and scaled scores.

Clinical symptoms were assessed using the expanded Brief Psychiatric Rating Scale (BPRS; Leukoff, Neuchterlein, & Ventura, 1986), which examines symptoms related to positive symptoms, negative symptoms, depression, mania, and disorientation. For the current study we relied on a total composite score to examine psychiatric symptomology. Mean ICCs from the BPRS ranged from .80 to .87, with the median ICC across items ranging from .84 to .89.

Imaging Procedure

In the scanner, participants completed the two previously described variants of the n-back task. Both versions of the task switched between 0-back trials and 2-back trials to measure baseline encoding and working memory or executive functioning respectively. Items were displayed on the screen for 500 ms with an inter-stimulus interval of 2,000 ms. Each task switched between blocks of 0-back trials and blocks of 2-back trials. All participants practiced the n-back tasks outside of the scanner before each imaging session. The whole scanning procedure including consenting, training, scanning, and debriefing procedures took approximately 1.5 hours.

FMRI scans were conducted at the University of Minnesota Center for Magnetic Resonance Research (CMRR). Participants were counterbalanced to receive either the word or picture n-back task first. Each n-back task was performed over two scanning blocks, each containing 212 functional scans, for a total of 424 functional scans per task. Images were collected using a 3 Tesla Siemens Trio MRI scanner, and a 32-channel head coil (repeat time (TR) = 1.5 seconds, echo time (TE) = 40, flip angle = 90 degrees, voxel size = 3.5 x 3.5 x 2 mm thickness, FOV= 22 cm, 35 axial slices). 240 resting scans used these same parameters. T1 reference images were also collected (voxel size = .86 x .86 x 1.5 mm thickness, 256 x 256 x 124 dimensions). Data were preprocessed using FSL (see: http://www.fmrib.ox.ac.uk/fsl/). Images were motion corrected using rigid body transformations (FLIRT) and a motion regression procedure. Scans were spatially smoothed at FWHM = 7 mm, normalized using the mean volume intensity, and filtered with a high pass frequency cutoff of 100 seconds. Field maps were collected to carry out

B0-unwarping. Mean average displacement (movement) across all scan sessions was .24mm (*SD*=.30).

Proposed Analyses

Study 1: This study will first replicate the findings of Haut and colleagues (2010) to determine whether a working memory focused CRT for schizophrenia influences areas of the lateral PFC, ACC, and frontal pole regions. Next we will examine whether observed changes associated with CRT relate to changes in measures of cognition, psychosocial functioning, or symptoms. Last we will measure whether baseline measures of cognition, psychosocial functioning or symptom profile are predictive of functional activation changes associated with CRT.

Study 2: This study will examine whether functional coherence measured by independent components analysis (ICA) is influenced by CRT. Analysis will focus on the default mode network (DMN) and executive network (EN) components, as we examine whether CRT influences changes in functional coherence during both the n-back task and during rest. Additionally we will determine whether coherence changes in these areas are associated with changes in measures of cognition, psychosocial functioning, or symptomology.

Study 3: We aim to examine whether CRT influences intrinsic thalamocortical connections with the MFG and ACC measured during rest. This study will also determine

whether changes in connectivity with theses brain areas are also related to changes in cognition. Last, we will determine whether observed changes in connectivity following CRT are also observed during the n-back task.

Table 3.1 Demographics

	CRT (SD)	CST (SD)	t-value	p-value
Age	42.93 (10.6)	45.75 (7.7)	0.8	0.4322
Education	13.47 (1.5)	12.42 (1.04)	1.2	0.2424
Parental Education	12.83 (4.3)	13.21 (1.79)	0.3	0.7628
WTAR IQ	104 (10.76)	101.42 (11.56)	0.6	0.5576
Duration of Illness	20.93 (12.73)	18.5 (11.11)	0.53	0.601
Total CPZ	551.8 (466.24)	320.75 (280.81)	1.6	0.1248
BPRS Total Time 1	42.53 (9.74)	45 (11.17)	0.6	0.5525

Table 1 Note: Pre-Treatment Group Demographics. CRT = Cognitive Remediation Training (N=15), CST = Computer Skills Training (N=12), WTAR IQ = Wechsler Test of Adult Reading Intelligence Quotient, Total CPZ = Total Chlorpromazine Equivalence, BPRS = Brief Psychotic Rating Scale.

Chapter 4: Neuro-plastic Changes in Schizophrenia Patients Undergoing Cognitive Remediation in a Triple-Blind Trial: A Replication Study

Foreword: This chapter was written in collaboration with Angus W. MacDonald and Tasha M. Nienow who provided edits and revisions to earlier drafts. The methods in this chapter are largely redundant with those outlined in Chapter 3. Methods specific to this chapter can be found under "Planned Analyses."

Abstract

Background: Patients with schizophrenia have shown cognitive improvements following computerized cognitive remediation training (CRT), but the neuroplastic changes that support these processes are not fully understood. The current triple-blind placebo-controlled trial examined neural activation before and after a CRT intervention or a computer skills training (CST) placebo.

Method: Twenty-seven participants underwent fMRI before and after being randomized to either the CRT or CST condition. Participants completed two variants of the n-back during scanning, and were assessed on measures of cognition, psychosocial functioning, and symptoms.

Results: We observed a group-by-time interaction in the left prefrontal cortex, wherein the CRT group showed increased activation. These changes correlated with improved task accuracy, and modestly correlated with improvements in functioning. Effects were not observed in other hypothesized areas.

Conclusions: We partially replicate previous findings, showing that CRT for schizophrenia increased prefrontal activation during a working memory task, and relate to improvements in untrained skills.

Introduction

Cognitive remediation training (CRT) is becoming an increasingly promising class of interventions to alleviate the cognitive deficits associated with schizophrenia and related illnesses. Though emerging evidence suggests that therapist-guided computerized training can improve both cognition and functional outcome in schizophrenia (McGurk et al., 2007; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011), we are only just beginning to identify the neural substrates that support this change. In a meta-analysis of studies examining changes in brain activity following CRT for schizophrenia, areas of both the prefrontal and sub-cortex showed increases following treatment (Ramsay & MacDonald, 2015). For example, previous work in our own laboratory found evidence of neuroplasticity in response to cognitive training. Patients with schizophrenia randomized to undergo up to 25 hours of working memory-focused cognitive training (compared to a cognitive behavioral social skills training control condition) showed prefrontal activation increases and associated improvements in performance on n-back tasks (Haut et al., 2010). To our knowledge, no examination of neuroplasticity from CRT in schizophrenia has been systematically replicated. Therefore, to expand on these promising preliminary findings, the current study aimed to replicate the findings of Haut and colleagues (2010), by examining a subgroup of participants from a triple-blind, placebo-controlled study

examining CRT for schizophrenia. In addition, we sought to extend this inquiry to examine relationships between neural changes and cognitive, psychosocial functioning, and symptom outcomes associated with training. Last, we also examined whether patients' baseline cognition, functioning, or symptom profile was predictive of neural response to training. We hypothesized that changes in functional activation from CRT would coincide with changes in cognition and functioning, and that higher baseline functioning and cognition, as well as lower symptom severity, would predict a greater neuro-plastic response to training.

Methods

Participants

Patients with schizophrenia or schizoaffective disorder who had previously elected to participate in a clinical trial of a cognitive remediation intervention (Clinical Trial # NCT00995553) were recruited for the current study. Diagnosis was established using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1997). Master's and doctoral level clinicians conducted the interviews, and the principal investigator (TMN) assigned a study diagnosis after review of available medical records, patient reports, and interviewer observations. All participants were between the ages of 18 and 60 years old, were clinically stable with no antipsychotic medication changes or hospitalizations in the previous four weeks, had a Weschsler Test of Adult Reading (WTAR) score of 70 or above, had no substance/alcohol dependence within the past six months and no substance/alcohol abuse in the past month, had no history of head injury

with loss of consciousness for greater than 20 minutes, and no known history of neurological conditions that could comprise cognitive functioning. All participants demonstrated capacity to give consent.

Fifty-three of the 80 participants enrolled in the clinical trial were screened for MRI compatibility. Forty consented to the imaging study. Three participants were withdrawn by the principal investigator prior to scanning after additional review of their medical history found them to be ineligible. Two additional participants were withdrawn due to inability to complete the scans. Five participants chose to withdraw because lack of interest (N=3) or anxiety in the scanner (N=2). Thirty participants completed scanning but data was lost from three due to experimenter error. Twenty-seven participants completed all study procedures. No participants were removed after employing a 2mm mean displacement movement cutoff within each scan. There were no differences in sex, age, race, education, parental education, or chlorpromazine (CPZ)-equivalent medication dosage between those in the final sample and those who were removed for any of the above reasons (all p's>.13). Additionally, participants included in the present study did not differ between treatment groups on factors related to age, education, parental education, WTAR IQ score, duration of illness, or total CPZ equivalence (see Table 4.1). Groups also did not differ based on sex (χ^2=.02, p=.88) or diagnosis (χ^2=1.94, p=.16). The protocol and consent process were approved by the Institutional Review Board at both the University of Minnesota and the Minneapolis VA Health Care System (VAHCS).

Study Design and Blinds

Participants were randomized to undergo either a working memory focused CRT (N=15) or a computer skills training (CST; N=12) active placebo condition (though 15 participants underwent CRT, one did not complete the picture n-back at both time points, leaving N=14 in the CRT group for that task). Data collection and analysis were conducted 'triple-blind,' wherein the participants, providers and technicians, as well as statisticians were unaware of group membership. All fMRI analyses were conducted blind to group status, and the blind was not broken until whole-ROI confirmatory analyses were completed as described below.

Training Procedure

All training took place at the Minneapolis VAHCS as part of a larger trial examining cognitive and behavioral outcomes associated with a working memory-focused CRT. Patients completed 48 hours of training over the course of 16 weeks (Three 1-hour sessions weekly) in either the CRT or CST condition. Groups did not statistically differ with regard to average number of training hours (CRT=48 (SD=0), CST=48 (SD=.28)), or number of training days needed to complete the protocol (CRT=40 (SD=4.09), CST=36 (SD=10.43)).

Participants randomized into the CRT group completed a computer-based training program that consisted of 21 adaptive computer exercises, which placed demands on working memory functions through verbal, visual, and spatial stimulus modalities. The tasks were selected from three sources: Psychological Software Services CogReHab program developed by Bracy (Indianapolis: Psychological Software Services; 1995),

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Participants randomized into the active placebo control group engaged in a computer skills training (CST) course, focusing on keyboarding skills and learning to use Microsoft Office 2007 for word processing, spreadsheet management, and presentation creation. The CST condition was designed to have the same level of training time, exposure to computers, and attention from treatment providers as the CRT condition, but did not rely on errorless-learning principles like that of the CRT condition.

CRT and CST interventions were both facilitated by Master's or Bachelor's level interventionists, who provided instruction, monitored progress, acknowledged effort, and intervened as necessary to minimize frustration. In addition, a doctoral level clinician (TMN) led weekly half hour bridging sessions where group members discussed the skills they were learning and how they could be applied in other real-life situations. Participants' reactions to the trainings were also processed in these meetings.

Assessment Procedure

Enrolled participants underwent clinical, cognitive, and functional assessment at baseline and after 4 months of training. Cognitive assessment included two variants of the n-back task: a word version featuring English language words, and a picture version featuring still-frame images of animals, both switching between blocks of 2-back and 0-back trials (Figure 4.1A). Five variants of the word n-back task, including the version used at the pre and post-intervention assessment, were practiced throughout the training procedure in the CRT group, and were included as a manipulation check. A picture n-back task with novel stimuli was included to measure skill transfer and generalization (i.e. improving performance in untrained domains) to an untrained version of the working memory task. N-back task performance was assessed using the sensitivity measure D-prime (D'), which compared the number of 'hits' to 'false alarms' in the 2-back condition.

Other cognitive measures included the MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008), which was specifically developed to assess cognitive functioning in schizophrenia, and measures domains of attention/vigilance, speed of processing, working memory, verbal learning, visual learning, problem solving/reasoning, and social cognition. For this study, we specifically examined the working memory and overall cognitive functioning domains as dependent variables to measure near (generalization to related, though untrained task demands) and far transfer (generalization to unrelated skills with distinct task demands) in the context of our working memory-focused CRT intervention.

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Imaging Procedure

In the scanner, participants completed the two previously described variants of the n-back task. Both versions of the task switched between 0-back trials and 2-back trials to measure baseline encoding and working memory or executive functioning respectively. Items were displayed on the screen for 500 ms with an inter-stimulus interval of 2,000 ms. Each task switched between blocks of 0-back trials and blocks of 2-back trials. All participants practiced the n-back tasks outside of the scanner before each imaging session. The whole scanning procedure including consenting, training, scanning, and debriefing procedures took approximately 1.5 hours.

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with a high pass frequency cutoff of 100 seconds. Field maps were collected to carry out B0-unwarping. Mean average displacement (movement) across all scan sessions was .24mm (*SD*=.30).

Planned Analyses

Behavioral analyses of the two n-back tasks to measure training generalization were conducted using the sensitivity measure D-prime (D') comparing the hit-rate (correct responses) to the false-alarm rate (incorrect response) during the 2-back condition (Nuechterlein, 1991). Results were entered in a repeated-measures ANOVA, as well as examined in paired-samples t-tests.

Functional imaging analyses were conducted in FSL using a general linear model (GLM) procedure, wherein subjects' fMRI time series were modeled in a block design comparing 2-back blocks to 0-back blocks (2Bv0B) for each task. Confirmatory imaging analyses to replicate the findings of Haut and colleagues (2010) relied on five regions of interest (ROIs) previously shown to improve with CRT training, four of which showed greater increases in activity among patients with greater performance improvements on a N-back task. These spherical ROIs were generated by dilating the peak voxels to approximate a volume close to that observed in the previous study (See Supplementary Figure 4.1). We first performed a confirmatory voxel-wise ROI analysis constrained to the same five ROIs previously described in a small-volume correction. Group images were cluster-thresholded within the ROI at $Z>2.3$ and a brainwise significance threshold of $p=0.05$. Next, individual subjects' beta values (% signal change) were extracted for

each of the five ROIs individually and entered in a repeated-measures ANOVA to examine group by time interactions in the statistical program R.

After confirmatory analyses were completed, the blinding of the statistical analysis was broken. We then performed exploratory voxel-wise imaging analyses to determine if either group showed activation changes in unhypothesized brain areas or other contrasts of interest (i.e. the 2-back condition alone). Group images were again cluster-thresholded at $Z>2.3$ and a brainwise significance threshold of $p=0.05$.

Last we performed correlations between change in activation observed in the voxel-wise analyses in the CRT group (individual subject betas were extracted and averaged across the voxels surviving correction), with the previously described outcome measures of cognition, functioning, and symptoms. All tests were calculated one-tailed in the hypothesized direction. We also examined whether baseline measures of cognition, functioning, and symptoms correlated with activation change observed in the voxels previously described.

Results

Behavioral Treatment Effects Measured by the N-Back

D' values were entered in a repeated measures ANOVA. D' values on the picture n-back task showed a trend for a group by time interaction ($F(1,24)=3.63$, $p=.07$, $\eta^2=.13$), wherein subjects in the CRT condition improved performance from pre ($M=2.62$, $SD=.60$) to post-training ($M=3.15$, $SD=.82$; $t=2.25(12)$, $p<.05$, $d=.74$), while the CST

condition showed no significant change over time (Figure 4.1B). The word n-back task did not show a group by time interaction, but did show a significant effect of time across groups ($F(1,25)=10.57$ $p<.005$, $\eta^2=.30$), with increases in D' from pre to post-training for both the CRT ($t=2.25(14)$, $p<.05$, $d=.41$) and CST ($t=2.40(11)$, $p<.05$, $d=.59$) conditions (Supplemental Figure 4.1B). Because these behavioral results highlighted changes in the picture n-back to measure cognitive transfer and generalization, imaging analyses focused on that task.

Voxel-wise and Individual ROI Confirmatory Imaging Results

Confirmatory analyses to replicate the findings of Haut and colleagues (2010) examined the average 2-back versus 0-back (2Bv0B) contrast activations in five ROIs identified from a previous examination of CRT in schizophrenia (See Supplemental Figure 4.1A) (Haut et al., 2010). First, to examine voxel-wise activation changes in these areas, we conducted a small volume analysis using the previously defined ROIs as a mask. We observed a group by time interaction in the left DLPFC, wherein activation in the CRT group increased from pre to post-training, but not in the CST group (See Figure 4.2A; Table 4.2a). Observed activation changes in the left DLPFC (post>pre) positively correlated with change in D' score on the picture n-back task ($r=.51$, *p-one-tailed*$<.05$). No activation changes were observed in other ROI areas.

Next we conducted confirmatory analyses of each ROI individually by extracting their beta values and entering them in a repeated measures ANOVA. No whole individual ROI showed a significant group by time interaction. However, the left DLPFC ROI

showed a trending interaction favoring the CRT group ($F(1,24)=3.16$ $p=.09$, $\eta^2=.11$), supported by a hypothesized increase in activation in the CRT group from pre to post-training ($t=2.46(13)$, *p one-tailed*$<.05$, $d=.53$). Additionally, the left frontal pole ROI showed a significant effect of time ($F(1,24)=10.17$, $p<.005$, $\eta^2=.28$), and a significant unexpected decrease in activation from pre to post-training in the CST group ($t=2.93(11)$, $p<.05$, $d=1.31$). Hypothesized changes in ROI activation for the CRT group did not significantly correlate with changes in n-back performance.

Voxel-wise Exploratory Imaging Results

Next we conducted exploratory whole-brain imaging analyses to determine whether activation was changing in any other unhypothesized brain areas during 2Bv0B. We observed no group by time interactions in any brain region; however, we did observe reduced activation in the CST group from pre to post-training in the left frontal polar area and the left ventrolateral PFC.

To better understand the activations observed in the 2Bv0B contrast, we examined the 2-Back condition within the same voxel-wise analysis constrained to the previously defined ROIs. We observed the same group by time interaction as in the 2Bv0B contrast, wherein a subset of voxels in the left DLPFC ROI showed increased activation on the 2-Back for the CRT group (Table 4.2b).

We also examined the 2-Back condition in a whole-brain voxel-wise exploratory analysis. We observed no group by time interactions, but did observe an increase in activation from pre to post-training in the CRT group in the left DLPFC, left frontal pole,

and left superior frontal gyrus (See Figure 4.3a; Table 4.2c). Changes in these regions did not correlate with behavioral changes in D' as measured by the n-back task (Figure 4.3c).

Change in DLPFC on 2Bv0B Predicting Change in Clinical Outcomes Results

We examined whether change in activation observed in the CRT group during 2Bv0B was related to changes in cognition. Though changes in left DLPFC activation correlated with changes in D' on the n-back task, this pattern was not observed in hypothesized near transfer working memory tasks from the MCCB, including the Letter Number Sequencing Task or the Spatial Span Task. Change in left DLPFC activation also did not relate to changes in overall cognition score on the MCCB.

Additionally, we examined whether activation change in the CRT group related to measures of psychosocial functioning and symptoms. Change in left DLPFC activation did not correlate with changes in social competence and community functioning measured by the SSPA or SFS. While change in functional capacity measured by the UPSA was not significantly related to change in left DLPFC activation, we did observe a non-significant trend in the hypothesized direction (r=.42, *p-one-tailed*=.07). Change in symptoms, as measured by the BPRS total score, was not related to change in functional activation.

Change in 2-Back Activation Predicting Change in Clinical Outcomes Results

Next we examined whether change in 2-back activation observed within the CRT group was related to any hypothesized changes in measures of cognition. Increased

activation from pre to post-training in the left DLPFC during the 2-back condition did not significantly correlate with changes in near transfer measures of working memory from the MCCB, or overall cognition score.

We also examined whether left DLPFC changes on the 2-back related to psychosocial functioning measures and symptoms. We observed a positive correlation between increased activation and score on the SFS (r=.48, *p-hypothesized*<.05), but only a trend level correlation with the SSPA (r=.42, *p-hypothesized*=.06), and not with the UPSA. We observed no correlations with symptoms measured by the BPRS. Increased activation during 2-back for the CRT group in the left frontal pole and superior frontal gyrus did not correlate with any of the hypothesized cognition, functioning, or symptom measures.

Baseline Cognition and Behavior Predicting Functional Activation Change

Finally, we were interested to determine whether baseline measures of cognition, psychosocial functioning, or symptoms were predictive of plasticity in the left DLPFC for the CRT group. No measure of interest, including baseline n-back performance, MCCB working memory performance, SSPA, SFS, UPSA, symptoms measured by the BPRS, or readiness for change were predictive of activation increases in the left DLPFC during the 2Bv0B contrast. Similarly, no change in the left DLPFC, left frontal pole, or superior frontal gyrus during the 2-back condition was related to baseline measures of cognition, functioning, or symptoms.

Discussion

The current study examined the neural response to a working memory focused CRT intervention in schizophrenia and explored the clinical significance of observed brain changes. In doing so, we sought to replicate and expand on previous findings that showed functional activation changes in prefrontal areas supporting improvements on a working memory task (Haut et al., 2010). Consistent with hypotheses, we observed a group by time interaction in a subgroup of voxels in the left DLPFC, wherein the CRT group increased in activation following training. Change in activation over time in these voxels correlated with improvements on the picture n-back task in the CRT group, but did not show transfer effects to other measures of working memory, general cognition, or psychosocial functioning. However, we did observe a trend in the hypothesized direction showing that change in DLPFC activation was related to change in functional skill performance measured by the UPSA.

Contrary to expectations, we did not observe confirmatory functional activation change in any other of the four hypothesized ROIs during the 2Bv0B contrast, indicating that we only partially replicated previous findings. We also conducted exploratory analyses to examine 2-back activation alone, and observed increased activation in the CRT group in the left DLPFC, left frontal pole, and superior frontal gyrus. Change in 2-Back activation in these areas did not correlate with improvements in N-back performance or other measures of working memory, general cognition, or symptoms. However, we did observe a correlation between activation change on the 2-Back in the

left DLPFC and psychosocial functioning improvements measured by the SFS, and evidence for a statistical trend with the SSPA.

Though we observed a group by time interaction in voxels in the left DLPFC ROI, by and large, our findings only modestly replicated those of Haut and colleagues (2010). In the picture n-back we demonstrated a behavioral effect, but were unable to replicate group by time interaction effects in the left or right frontal pole, the anterior cingulate cortex, or a left prefrontal area. This indicates that the current CRT intervention either did not sufficiently invoke plasticity in these regions, or that we were underpowered to demonstrate such interactions. We also did not observe significant behavioral or neural interactions in the word n-back, which was surprising given the relationships observed in the picture n-back task. Though this in some ways weakens the significance of the current findings, it potentially underscores the importance of the relationship between observed behavioral changes in relation to neural plasticity. That is, since behavioral changes were observed across both groups in the word n-back, it is perhaps not surprising that interactions in the imaging data were also not observed. It is unclear why similar n-back tasks would have yielded different patterns of results, but it may be due in part to the computer skills control condition, which was balanced for time spent on a computer as well as non-specific cognitive challenge. Notably, a previous study with a related intervention and control condition showed similar across group improvement in working memory (Kurtz et al., 2007), potentially indicating that the CST condition was also influencing cognition and subsequent plasticity. However, we did not observe significant relationships between functional activation changes and behavioral

performance, cognition, functional, or symptoms status during the word n-back, so the clinical significance of this change remains unclear, and may be purely due to practice or placebo effects.

Aspects of the current findings stand in contrast to other studies of CRT in schizophrenia, which have found evidence of neural change in response to cognitive training, and the magnitude of change being related to behavioral task performance. One trial examined a letter n-back task before and after undergoing 16 weeks of an auditory training intervention for schizophrenia, showing increased ROI activation in the left middle and inferior frontal gyrus, as well as bilateral insula (Subramaniam et al., 2014). Additionally, changes in the right middle frontal gyrus activation were positively correlated with changes in working memory performance on the 2-back task. Another trial used a CRT intervention that targeted attention, working memory, logical thinking, and problem solving over a 7-week training period. They demonstrated that CRT increased activation on a spatial n-back task in the left inferior and middle frontal gyrus, cingulate gyrus, and precuneus (Bor et al., 2011). The results of these trials converge with findings by Haut and colleagues (2010), as well as the voxel-wise confirmatory analysis in the current study that demonstrated increased DLPFC activity following working memory focused CRT. Taken together, observations from these studies suggest that CRT interventions have the capacity to increase prefrontal activation in brain areas previously shown to be disrupted in patients with schizophrenia (Minzenberg et al., 2009).

In line with predictions and consistent with previous studies, change in activation in the DLPFC during 2Bv0B on the picture n-back correlated with change in task

performance. While this relationship did not transfer to changes in measures of cognition, social capacity, or symptomology, it did show a trend level relationship with improvements in functional capacity as measured by the UPSA. Though to be interpreted cautiously, this finding may indicate that working memory training for schizophrenia engages and enhances brain areas that also support functional capacity to carry out skills associated with daily living. Previous studies have indicated that neuropsychological measures strongly predict functional capacity in schizophrenia (Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006; McClure et al., 2007), and the current findings suggest that working memory training may influence this relationship.

We also examined the clinical significance of 2-back activation change in the DLPFC, and demonstrated a positive relationship between neural changes and improved social functioning measured by the SFS, and a trend level relationship with improved social capacity measured by the SSPA. Again, to be interpreted cautiously, this may suggest that working memory training influences frontal brain regions that also support improvements in community functioning, independent living, and social competency. Neuropsychological measures have been previously shown to have both direct and indirect influences on both community functioning and social competency in schizophrenia, with functional capacity potentially mediating this effect (Bowie et al., 2006). There is also evidence that cognition more generally may be predictive of community functioning status in schizophrenia (Dickinson & Coursey, 2002; Green et al., 2000; Velligan, Bow-Thomas, Mahurin, Miller, & Halgunseth, 2000). The current results support the notion that training working memory may hold promise for influencing

relationships with psychosocial functioning, potentially by way of neural plasticity in brain areas that support cognitive functioning more broadly. By and large, the currently observed relationships would not survive correction for multiple comparisons in this limited sample, but offers an important demonstration that CRT-influenced neural changes support clinical improvements outside the domain of cognition alone.

Last, we did not observe relationships between baseline cognitive, psychosocial, or symptom measures predictive of neuroplastic changes associated with CRT. Other studies have demonstrated that baseline working memory and other neuropsychological measures may be predictive of the course of treatment and response to CRT (Kurtz et al., 2009; Twamley, Burton, & Vella, 2011). We sought to extend this question to examine whether individual differences before treatment may predict neural changes, but no such relationships were observed.

A clear limitation of this and many other studies examining neuroplasticity related to CRT in schizophrenia is the issue of limited sample size and consequently limited power. This affected our ability to observe hypothesized effects given this constraint, as we were quite limited in our ability to demonstrate group by time interactions, and were only able to show modest effects of skill transfer. As such, this field of inquiry will require further study to more clearly understand the specific effects of CRT and the neural processes that support brain plasticity. Additionally, it will necessitate further meta-analytic investigation, as the current study will contribute to ongoing activation likelihood findings that suggest these types of interventions influence both cortical and subcortical brain areas in schizophrenia (Ramsay & MacDonald, 2015).

There are also methodological limitations to the current investigation, as neural plasticity measured by a GLM is only sensitive to increases and decreases in functional BOLD activity. While the current demonstration of increased functional activity in response to CRT is useful, emerging evidence indicates that aberrant neural connections may also characterize the pathophysiology of schizophrenia (Pettersson-Yeo et al., 2011). As such, the underlying neural mechanisms supporting CRT may also work by either restoring or reorganizing the brain's connections to improve cognition and psychosocial functioning. To date, one study has demonstrated that both structural and functional connections are influenced by CRT in schizophrenia (Penadés et al., 2013b). Future investigations of neural plasticity following CRT in schizophrenia should investigate functional connectivity in addition to activation, as these metrics may elucidate different aspects of neuronal functioning predictive of outcome and response.

Conclusion

The current triple-blind placebo-controlled study demonstrates that working memory-focused training has a modest influence on prefrontal plasticity in patients with schizophrenia. We observed a group by time interaction in favor of the CRT group in the left DLPFC, but were unable to replicate previously observed findings in other prefrontal regions of interest. While change in DLPFC activation correlated with improvement on the n-back task, it did not correlate with improvements in external measures of working memory or cognition. However, it did modestly correlate with improvements in measures of daily living skills and social competence, and community functioning, suggesting that

these types of interventions have the capacity to influence domains outside of their direct training goals. Further examination of working memory focused CRT interventions such as this one will be required to definitively understand how they might influence neural activity supporting cognition and functioning more broadly.

Table 4.1 Demographics

	CRT (SD)	CST (SD)	t-value	p-value
Age	42.93 (10.6)	45.75 (7.7)	0.8	0.4322
Education	13.47 (1.5)	12.42 (1.04)	1.2	0.2424
Parental Education	12.83 (4.3)	13.21 (1.79)	0.3	0.7628
WTAR IQ	104 (10.76)	101.42 (11.56)	0.6	0.5576
Duration of Illness	20.93 (12.73)	18.5 (11.11)	0.53	0.601
Total CPZ	551.8 (466.24)	320.75 (280.81)	1.6	0.1248
BPRS Total Time 1	42.53 (9.74)	45 (11.17)	0.6	0.5525

Table 4.1 Note: Pre-Treatment Group Demographics. CRT = Cognitive Remediation Training (N=15), CST = Computer Skills Training (N=12), WTAR IQ = Wechsler Test of Adult Reading Intelligence Quotient, Total CPZ = Total Chlorpromazine Equivalence, BPRS = Brief Psychotic Rating Scale.

Table 4.2 Observed functional activation changes

Region	N Voxels	Z-Max	X	Y	Z
A) Confirmatory Voxel-wise DLPFC ROI 2Bv0B CRT>CST Pre<Post					
Left Middle Frontal Gyrus	19	3.52	-56	12	38
Left Precentral Gyrus		2.69	-56	12	32
B) Voxel-wise DLPFC ROI 2-Back CRT>CST Pre<Post					
Left Middle Frontal Gyrus	11	3.49	-56	12	38
C) Exploratory Whole-Brain 2-Back CRT>CST Pre<Post					
Left Middle Frontal Gyrus	1,086	3.77	-48	10	50
Left Frontal Pole, Superior Frontal Gyrus		3.58	-12	44	50
Left Frontal Pole		3.53	-16	50	44
Left Frontal Pole		3.38	-12	54	44
Left Frontal Pole		3.33	-8	58	42
Left Precentral Gyrus		3.28	-56	12	36

Table 4.2 Note: Observed functional activation changes.

Figure 4.1 Picture N-Back Task and Behavioral Findings

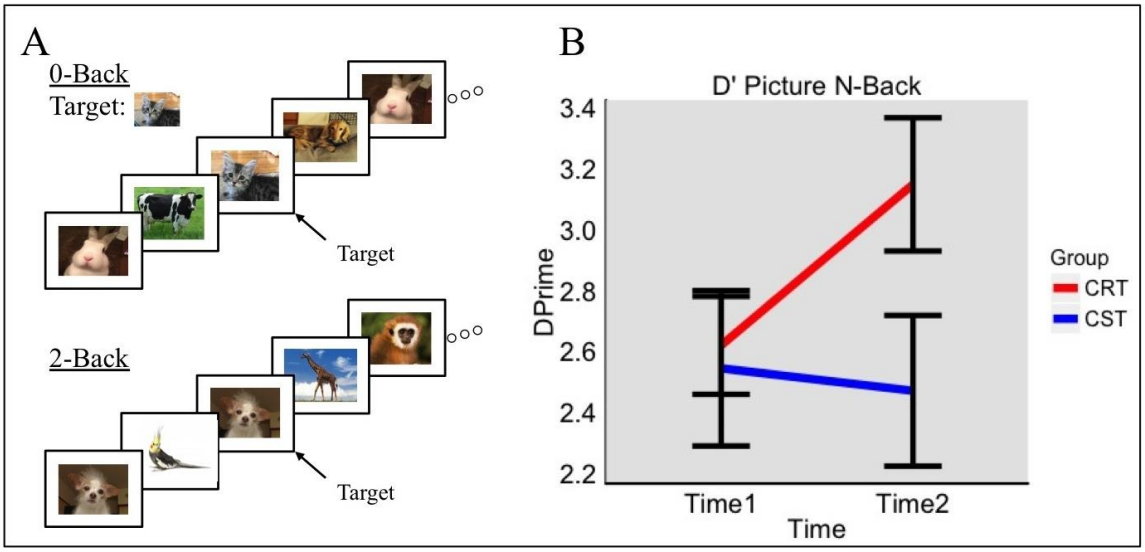


Figure 4.1 Note: Picture N-Back Task and Behavioral Findings. (A) Picture N-Back task design. (B) Patients in the CRT group showed an increase in D' from time 1 (*M*=2.62, *SD*=.60) to time 2 (*M*=3.15, *SD*=.82) on the 2-back trials of the picture n-back task, while those in the CST group showed no change from time 1 (*M*=2.54, *SD*=.88) to time 2 (*M*=2.47, *SD*=.86).

Figure 4.2 Group by Time Interaction in the DLPFC ROI for 2Bv0B

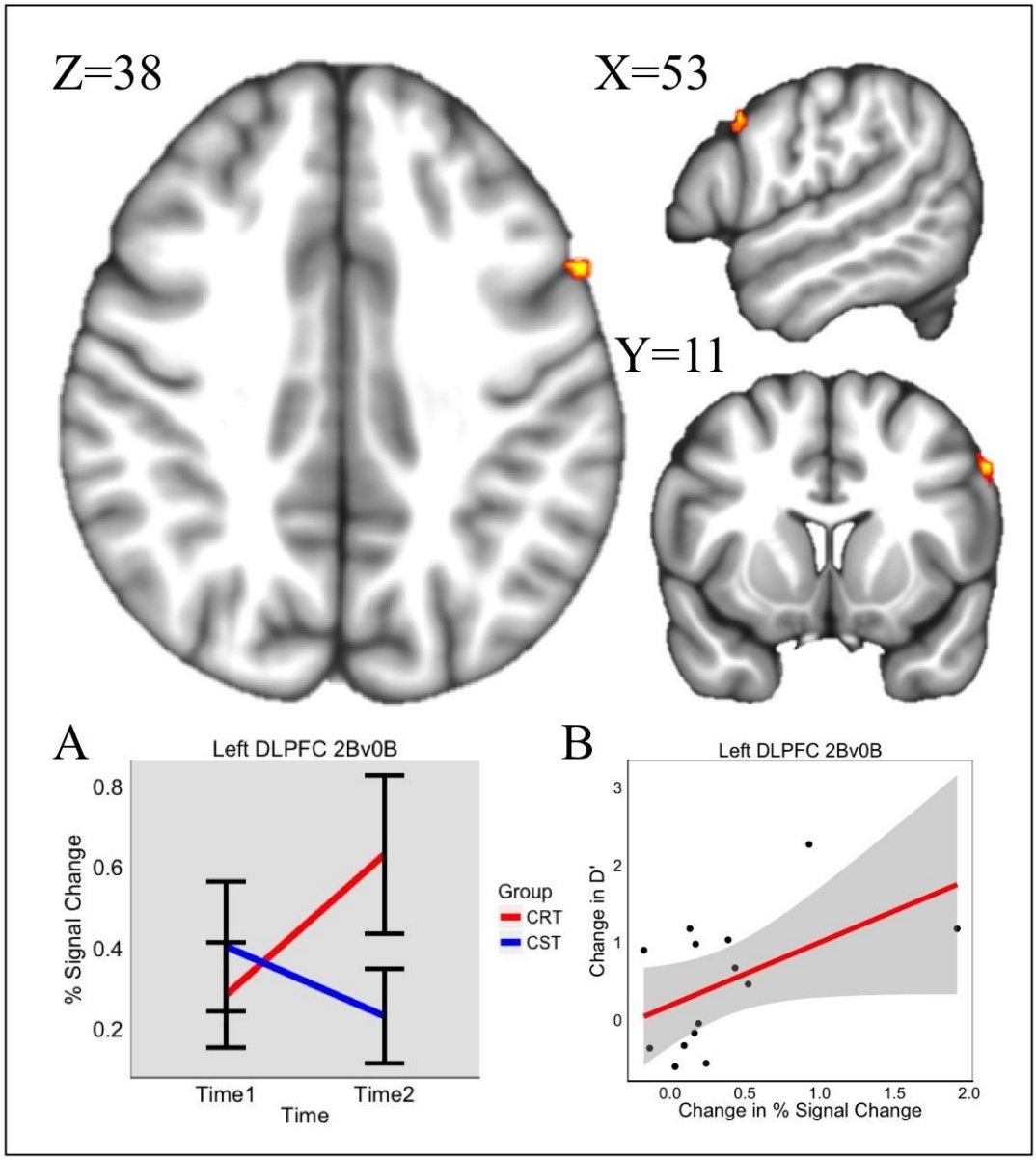


Figure 4.2 Note: Group by Time Interaction in the DLPFC ROI for 2Bv0B. A) We observed a voxel-wise group by time interaction in the left DLPFC ROI during the 2Bv0B condition driven by increases from time 1 to time 2 in the CRT group. B) Change in percent signal change extracted from the significant voxels in the left DLPFC were positively correlated with changes in D' on the picture n-back task (r=.51, *p-hypothesized*<.05). This relationship held when using a robust linear estimator to control for the effects of outliers (r=.56, *p-hypothesized*<.05).

Figure 4.3 Activation Increases in the CRT Group During 2-Back Condition

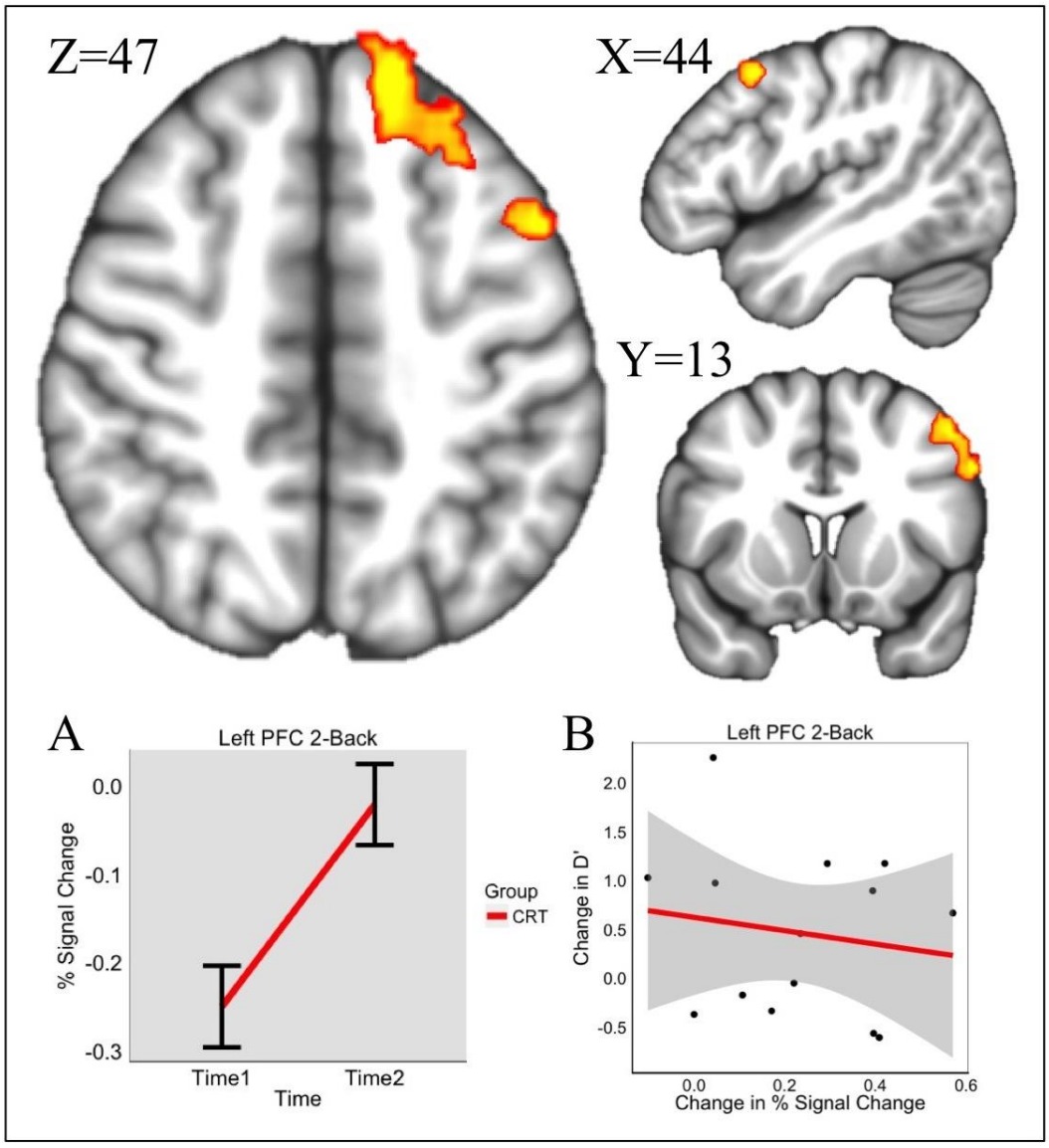
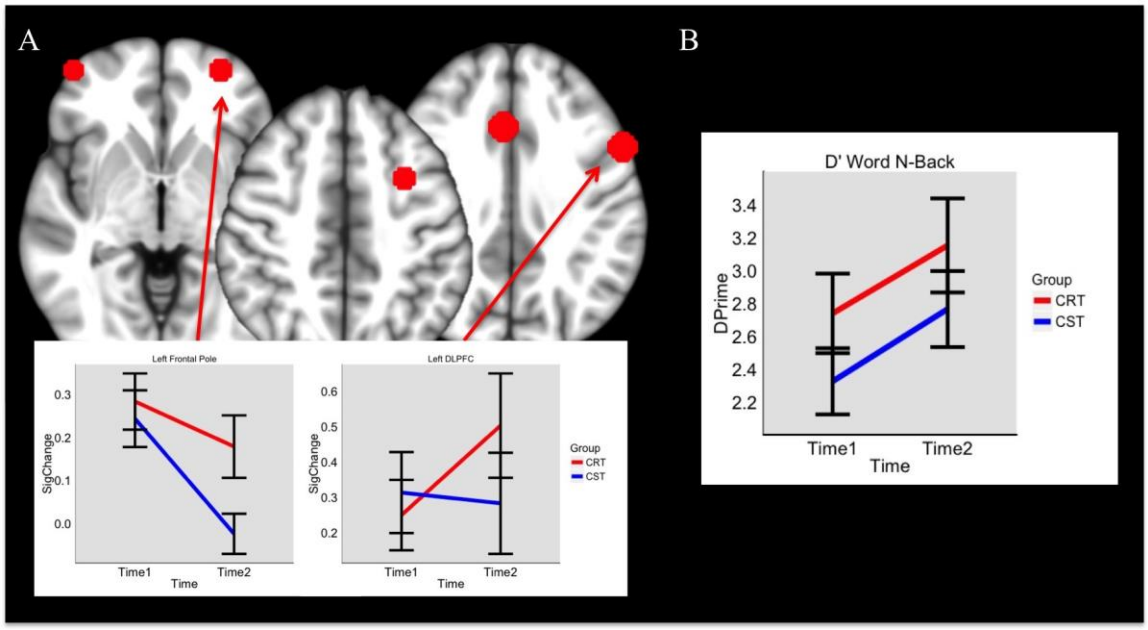


Figure 4.3 Note: Activation Increases in the CRT Group During 2-Back Condition. A) Whole-brain activation changes were observed from time 1 to time 2 in the CRT group in areas of the left DLPFC, left frontal pole, and superior frontal gyrus. B) Increased activation in these regions did not correlate with change in D' on the n-back task.

Supplemental Figure 4.1



Supplemental Figure 4.1 Note: (A) The five confirmatory ROIs included the ACC (N Voxels=147, MNI=6,20,36), LDLPFC (N Voxels=147, MNI=-54,10,36), LPFC (N Voxels=81, MNI=-28,8,46), Right Frontal Pole (N Voxels=81, MNI=46,56,0), and Left Frontal Pole (N Voxels=81, MNI=-28,56,-6). The left frontal pole showed a group by time interaction wherein activation decreased in the CST

Chapter 5: Examining Changes in Functional Coherence and Connectivity in Response to Cognitive Remediation for Schizophrenia

Foreword: Methods outlined in this chapter are again redundant with those in chapter 3. Chapter specific analyses are described in the "Planned Analyses and ICA Procedure" section.

Abstract

Cognitive remediation for schizophrenia has been previously demonstrated to influence functional activation changes in the brain, but little is known about whether these types of interventions may also affect functional connections. The current study used an independent component analysis approach to examine functional coherence and inter-connectivity during both a working memory task and during rest, before and after undergoing a cognitive remediation intervention or a computer skills training placebo. By and large, no significant changes in functional coherence were observed during either task or rest after accounting for subject movement during the scan. However, we did observe a significant group by time interaction during rest when examining inter-connectivity between the default mode network and a frontal executive network. Reductions in connectivity between these networks following cognitive remediation coincided with reduced symptomology, suggesting that this intervention may improve psychiatric outcomes by influencing the connections between key neural networks.

Introduction

Background

Cognitive remediation training (CRT) has been shown to hold modest promise for alleviating the cognitive and psychosocial difficulties experienced by patients with schizophrenia (Mcgurk, Ph, Twamley, et al., 2007; Wykes et al., 2011). However, the neural mechanisms by which this functional recovery can be possible are only just beginning to be understood. Investigations of functional activation changes associated with CRT have shown that this type of training may increase activation in both frontal (Haut et al., 2010; Subramaniam et al., 2014) and subcortical areas (Hooker et al., 2012, 2013). This is consistent with meta-analytic findings demonstrating that CRT initiates target engagement by increasing functional brain activation in areas of the prefrontal cortex and thalamus, in addition to increasing activation in other areas supporting cognition, social, and motor functioning (Ramsay & MacDonald, 2015). These functional activation increases in response to training support hypotheses that schizophrenia is characterized by hypoactivation in various brain areas (Weinberger & Berman, 1996), and that normalized activation patterns may reflect improvements in cognition and other areas of functioning (Wexler, Anderson, Fulbright, & Gore, 2000). However, it is becoming increasingly understood that the pathophysiology of schizophrenia is characterized by both hypo- and hyper-activation (Glahn et al., 2005; Minzenberg et al., 2009), as well as widespread dysconnectivity (Cole et al., 2011; Lynall et al., 2010). This may suggest that increased functional brain activation in response to CRT may not be the only neural marker associated with cognitive or functional recovery.

Disrupted connectivity has been found to relate to both cognitive and psychotic symptomology in schizophrenia (Pettersson-Yeo et al., 2011), with various methods measuring these structural and functional relationships in the brain. While both diffusion tensor imaging (DTI) and seed-based connectivity approaches have been previously employed to examine questions about connections in the brain, independent components analysis (ICA) is an emerging model-free, blind-source separation procedure that can characterize connectivity within neural networks in functional imaging data. The functional integration or "coherence" of these networks is becoming an increasingly common and useful method for examining functional connectivity, and patients with schizophrenia have been observed to have widespread differences in these functional components observed both during task (Dae et al., 2009; Garrity et al., 2007; Meda et al., 2009) and at rest (Mingoia et al., 2012; Rotarska-Jagiela et al., 2010).

Particular focus has been on the default mode network (DMN) and fronto-parietal executive networks (EN), which are independent component networks found to be negatively and positively related to cognitive engagement respectively. The DMN is well known to be composed of the posterior cingulate cortex, ventral anterior cingulate cortex, and bilateral lateral occipital areas, and has been historically associated with the brain's baseline or "default" state (Raichle et al., 2001; Raichle & Snyder, 2007). It is also understood to be important for "self-referential" processing and related "mentalizing" tasks (Gusnard, Akbudak, Shulman, & Raichle, 2001). The DMN has been shown to have an inverse relationship with lateral prefrontal executive networks, and is thought to attenuate during cognitive processing (Greicius, Krasnow, Reiss, & Menon, 2003a), with

some evidence suggesting that the DMN exerts a modulatory effect over task-positive ENs (Uddin, Kelly, Biswal, Castellanos, & Milham, 2009). The importance of these networks in cognitive processing makes them critical targets for CRT, especially as they have been previously shown to be malleable in response to neural stimulation (Venkatakrishnan et al., 2011).

To date, one study has examined both structural and functional connectivity in patients with schizophrenia undergoing CRT, using both DTI and ICA (Penadés et al., 2013a). Results from this study demonstrated that participants in the CRT group (N=17) had increased structural connectivity (fractional anisotropy; FA) in areas of the corpus callosum and thalamus associated with improvements in both executive and overall cognitive functioning. They also used a tensor ICA method on data from a spatial *N*-back task to show that the CRT group selectively decreased engagement of the central EN and the DMN following CRT. Observed reductions in the central EN component were also shown to correlate with improvements in overall cognition score. Though promising, these functional connectivity results can only speak to changes measured during a working memory task, offering insights about how CRT influences the brain when cognitively engaged, but not how it might influence intrinsic functioning.

To understand more clearly the capacity for generalization from cognitive training, we propose to measure both task-based functional brain activity, as well as intrinsic changes in the brain observed during rest. Resting state functional connectivity as measured by fMRI is becoming an increasingly popular and powerful tool to understand neural fluctuations outside the constraints of a cognitively demanding task or

circumstance (van den Heuvel & Pol, 2010). In addition to replicating and expanding on the task-based findings of Penadés and colleagues (2013), we seek to understand whether cognitive training influences endogenous brain activity at rest, and if so, whether changes in functional connectivity during task and rest reflect improvements in cognition, psychosocial outcome, or symptomology in schizophrenia.

Hypothesis

In the current study, we sought to determine whether functional connectivity (in this case a measure of functional network coherence) measured using temporal concatenation ICA is influenced by a working memory focused cognitive training for schizophrenia. Specifically, we examined functional connectivity in both the DMN and fronto-parietal EN derived both during a working memory task and rest. To replicate previous findings we hypothesized that participants in the CRT group would show reduced network coherence in both the DMN and the EN during an *N*-back task. Next we sought to extend this investigation to observe reduced functional coherence during rest. We also examined inter-connectivity (strength of connections between networks) between the DMN and EN, and predicted that CRT would reduce inter-connectivity between these opponent networks during both task and rest. Last, we conducted exploratory analyses to determine whether individual differences in connectivity following CRT were predictive of improvements in task performance, cognition, psychosocial outcome, and symptom profile. We also examined whether baseline task

performance, cognition, or psychosocial functioning, was predictive of connectivity changes in response to the CRT intervention.

Methods

Participants

Patients with schizophrenia or schizoaffective disorder who had previously elected to participate in a clinical trial of a cognitive remediation intervention (Clinical Trial # NCT00995553) were recruited for the current study. Diagnosis was established using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1997). Master's and doctoral level clinicians conducted the interviews, and the principal investigator (TMN) assigned a study diagnosis after review of available medical records, patient reports, and interviewer observations. All participants were between the ages of 18 and 60 years old, were clinically stable with no antipsychotic medication changes or hospitalizations in the previous four weeks, had a Weschsler Test of Adult Reading (WTAR) score of 70 or above, had no substance/alcohol dependence within the past six months and no substance/alcohol abuse in the past month, had no history of head injury with loss of consciousness for greater than 20 minutes, and no known history of neurological conditions that could comprise cognitive functioning. All participants demonstrated capacity to give consent.

Fifty-three of the 80 participants enrolled in the clinical trial were screened for MRI compatibility. Forty consented to the imaging study. Three participants were withdrawn by the principal investigator prior to scanning after additional review of their

medical history found them to be ineligible. Two additional participants were withdrawn due to inability to complete the scans. Five participants chose to withdraw because lack of interest (n = 3) or anxiety in the scanner (n = 2). Thirty participants completed scanning but data was lost from three due to experimenter error. Twenty-seven participants completed all study procedures. No participants were removed after employing a 2mm mean displacement movement cutoff within each scan. There were no differences in sex, age, race, education, parental education, or chlorpromazine (CPZ)-equivalent medication dosage between those in the final sample and those who were removed for any of the above reasons (all *p*'s>.13). Participants included in the present study did not differ between groups on factors related to age, education, parental education, WTAR IQ score, duration of illness, or total CPZ equivalence (see Table 1). Groups also did not differ based on sex (χ^2=.02, *p*=.88) or diagnosis (χ^2=1.94, *p*=.16). The protocol and consent process were approved by the Institutional Review Board at both the University of Minnesota and the Minneapolis VA Health Care System (VAHCS).

Study Design and Blinds

Participants were randomized to undergo either a working memory focused CRT (N=15) or a computer skills training (CST; N=12) active placebo condition (though 15 participants underwent CRT, one did not complete the picture n-back or resting scan at both time points, leaving N=14 in the CRT group for picture n-back task and rest). Participants, providers, and technicians were blind to group status.

Training Procedure

All training took place at the Minneapolis VAHCS as part of a larger trial examining cognitive and behavioral outcomes associated with a working memory-focused CRT. Patients completed 48 hours of training over the course of 16 weeks (Three 1-hour sessions weekly) in either the CRT or CST condition. Groups did not statistically differ with regard to average number of training hours (CRT=48.00, CST=47.92), or the average number of training days needed to complete the protocol (CRT=40.20, CST=35.83).

Participants randomized into the CRT group completed a computer-based training program that consisted of 21 adaptive computer exercises, which placed demands on working memory functions through verbal, visual, and spatial stimulus modalities. The tasks were selected from three sources: Psychological Software Services CogReHab program developed by Bracy (Indianapolis: Psychological Software Services; 1995), Captain's Log educational software (Brain Train) developed by Sandford and colleagues (Sandford, Browne, & Turner, 1996), and variants of English word and picture n-back tasks used in experimental psychopathology research in patients with schizophrenia (Gevins & Cutillo, 1993). Approximately 1/3 of training time focused specifically on training with a version of the N-back task (0-2 back, 2-back, 3-back, or 4-back). Participants were advanced to a higher training level after demonstrating mastery performance (85% accuracy) at the previous level across three consecutive trial runs.

Participants randomized into the active placebo control group engaged in a computer skills training (CST) course, focusing on keyboarding skills and learning to use

Microsoft Office 2007 for word processing, spreadsheet management, and presentation creation. The CST condition was designed to have the same level of training time, exposure to computers, and attention from treatment providers as the CRT condition, but did not rely on errorless-learning principles like that of the CRT condition.

CRT and CST interventions were both facilitated by Master's or Bachelor's level interventionists, who provided instruction, monitored progress, acknowledged effort, and intervened as necessary to minimize frustration. In addition, a doctoral level clinician (TMN) led weekly half hour bridging sessions where group members discussed the skills they were learning and how they could be applied in other real-life situations. Participants' reactions to the trainings were also processed in these meetings.

Assessment Procedure

Enrolled participants underwent clinical, cognitive, and functional assessment at baseline and after 4 months of training. Cognitive assessment included two variants of the n-back task: a word version featuring English language words, and a picture version featuring still-frame images of animals, both switching between blocks of 2-back and 0-back trials (Figure 1A). Five variants of the word n-back task, including the version used at the pre and post-intervention assessment, were practiced throughout the training procedure in the CRT group, and were included as a manipulation check. A picture n-back task with novel stimuli was included to measure skill transfer and generalization (i.e. improving performance in untrained domains) to an untrained version of the working memory task. N-back task performance was assessed using the sensitivity measure D-

prime (D'), which compared the number of 'hits' to 'false alarms' in the 2-back condition.

Other cognitive measures included the MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008), which was specifically developed to assess cognitive functioning in schizophrenia, and measures domains of attention/vigilance, speed of processing, working memory, verbal learning, visual learning, problem solving/reasoning, and social cognition. For this study, we specifically examined the working memory and overall cognitive functioning domains as dependent variables to measure near (generalization to related, though untrained task demands) and far transfer (generalization to unrelated skills with distinct task demands) in the context of our working memory-focused CRT intervention.

Functional capacity was measured using the University of California, San Diego Performance-Based Skills Assessment (UPSA) overall score which is a measure assessing skillfulness on activities of daily living (Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001). Capacity for social competence was measured with the Social Skills Performance Assessment (SSPA) overall score, which rates domains including social competence and appropriateness, clarity, fluency, affect, interest/disinterest, grooming, and overall conversation skills based on role-plays of social interactions with a confederate (Patterson, Moscona, et al., 2001). This scale is significantly related to other social performance-based measures and self-report measures of quality of wellbeing. Inter-class correlation coefficients (ICC) amongst the clinical raters for the SSPA ranged from .82 to .95, with mean ICC for scaled scores ranging from .70 to .80 across raters.

The composite score from the self-report Social Functioning Scale (SFS; six subscales that assess the frequency of engagement in social and recreational activities, independent living skills, and employment) was used to examine level of functioning in the community (Birchwood et al., 1990). ICCs for the SFS were .88 or higher for both the total scores and scaled scores.

Clinical symptoms were assessed using the expanded Brief Psychiatric Rating Scale (BPRS; Leukoff, Neuchterlein, & Ventura, 1986), which examines symptoms related to positive symptoms, negative symptoms, depression, mania, and disorientation. For the current study we relied on a total composite score to examine psychiatric symptomology. Mean ICCs from the BPRS ranged from .80 to .87, with the median ICC across items ranging from .84 to .89.

Imaging Procedure

In the scanner, participants completed the two previously described variants of the n-back task. Both versions of the task switched between 0-back trials and 2-back trials to measure baseline encoding and working memory or executive functioning respectively. Items were displayed on the screen for 500 ms with an inter-stimulus interval of 2,000 ms. Each task switched between blocks of 0-back trials and blocks of 2-back trials. All participants practiced the n-back tasks outside of the scanner before each imaging session. The whole scanning procedure including consenting, training, scanning, and debriefing procedures took approximately 1.5 hours.

FMRI scans were conducted at the University of Minnesota Center for Magnetic Resonance Research (CMRR). Participants were counterbalanced to receive either the word or picture n-back task first. Each n-back task was performed over two scanning blocks, each containing 212 functional scans, for a total of 424 functional scans per task. Images were collected using a 3 Tesla Siemens Trio MRI scanner, and a 32-channel head coil (repeat time (TR) = 1.5 seconds, echo time (TE) = 40, flip angle = 90 degrees, voxel size = 3.5 x 3.5 x 2 mm thickness, FOV= 22 cm, 35 axial slices). 240 resting scans used these same parameters. T1 reference images were also collected (voxel size = .86 x .86 x 1.5 mm thickness, 256 x 256 x 124 dimensions). Data were preprocessed using FSL (see: http://www.fmrib.ox.ac.uk/fsl/). Images were motion corrected using rigid body transformations (FLIRT) and a motion regression procedure. Scans were spatially smoothed at FWHM = 7 mm, normalized using the mean volume intensity, and filtered with a high pass frequency cutoff of 100 seconds. Field maps were collected to carry out B0-unwarping. Mean average displacement (movement) across all scan sessions was .24mm (*SD*=.30).

Planned Analyses and ICA Procedure

Behavioral analyses of the two n-back tasks to measure training generalization were conducted using the sensitivity measure D-prime (D') comparing the hit-rate (correct responses) to the false-alarm rate (incorrect response) during the 2-back condition (Nuechterlein, 1991). Results were entered in a repeated-measures ANOVA, as well as examined in paired-samples t-tests.

Task-based and resting state ICA procedures were carried out in FSL. After preprocessing and converting all subject scans to a common standard space, word and picture n-back scans were merged across their two respective task runs at each time point collected for each subject. One subject did not complete the picture n-back task prior to training and another only completed one picture n-back run prior to training. These two subjects were therefore eliminated from the picture n-back analyses, but remained in the word n-back analyses. Additionally, one subject did not complete their resting scan at pre-treatment. Each of the word and picture n-back scans, as well as the resting scan, were run and analyzed individually.

Next, to separately estimate the group's baseline independent components, we carried out a temporal concatenation ICA using FSL's MELODIC tool on the baseline data collected prior to training. To maximize component reliability and stability, we used a meta-MELODIC procedure (Poppe et al., 2013; Wisner, Atluri, Lim, & Macdonald, 2013) wherein the scans were entered in 25 random subject orders. Group ICA was then carried out on each random order at a dimensionality set to obtain 60 independent components (ICs). After completing the 25 randomly ordered ICAs, we entered the resulting components (25 x 60) in a meta-level group ICA set to obtain 60 new ICs. For the purposes of this study, the resulting baseline group ICs were thresholded by normalizing them at their maximum value, and then thresholded at $Z>0.3$, which was found to maximize reproducibility of these components in our laboratory's previous work (Poppe et al., 2013).

At this step we visually identified our components of interest from each of the three group ICAs. Our primary ICs of interest included the default mode network (DMN) known to subsume areas of the posterior cingulate cortex, ventral anterior cingulate cortex (ACC), and bilateral inferior parietal cortices (Greicius, Krasnow, Reiss, & Menon, 2003b), and fronto-parietal executive networks (ENs) known to be composed of the dorsolateral PFC, ACC, and inferior parietal cortex (Naghavi & Nyberg, 2005).

Next we used a dual-regression procedure to generate individual subject spatial maps and time courses for both pre- and post-training for each of the 60 baseline meta-level components. Average coherence for each subject in each component was estimated by calculating the mean of all voxels within the norm-thresholded masks. Larger coherence values reflect more integrated network dynamics, while lower values reflect less integrated dynamics, and therefore lower coherence. Individual subject coherence scores for the identified components of interest were then entered in a repeated measures ANOVA in the statistical program R to identify whether functional connections changed across groups between time points. Mean displacement for each subject in each scan was included as a covariate in this model to account for subject motion.

To identify the spatial changes associated with training in a mapwise analysis, we again relied upon spatial components derived for individual subjects in the dual regression. To contrast Time 1 to Time 2 images, we subtracted the obtained *Z*-image (image in Z-space) at Time 2 from Time 1, leaving us with a single difference image for each subject. We then used the permutation-testing tool “randomise” (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) to conduct t-tests to compare the difference images

between groups. Parameters included using 5,000 permutations, threshold-free cluster enhancement (Smith & Nichols, 2009), and a family-wise error correction of $p<.05$. Resulting images were masked to contain only the voxels within the pre-training component, then thresholded within this mask at a level of $p<.05$ to identify voxels that significantly differed across time points and groups. To assess the directionality of these results, we extracted coherence values from the voxels surviving correction and plotted them in R.

Last, we conducted inter-connectivity analyses by performing Pearson correlations between individual subject time courses derived from the dual-regression for each component pair of interest at both time points. A Fisher's Z-transformation was applied to all correlation values before entering each component pair Z-value into a repeated measures ANOVA including mean displacement as a covariate. We also examined correlations between significant changes in inter-connectivity with measures of cognition, psychosocial functioning, and symptoms.

Results

Behavioral Treatment Effects Measured by the N-back Task

D' values were entered in a repeated measures ANOVA. D' values on the picture n-back task showed a trend for a group by time interaction ($F(1,24)=3.63$, $p=.07$, $\eta^2=.13$), wherein subjects in the CRT condition improved performance from pre ($M=2.62$, $SD=.60$) to post-training ($M=3.15$, $SD=.82$; $t=2.25(12)$, $p<.05$, $d=.74$), while the CST

condition showed no significant change over time (Figure 5.1A). The word n-back task did not show a group by time interaction, but did show a significant effect of time across groups ($F(1,25)=10.57$ $p<.005$, $\eta^2=.30$), with increases in D' from pre to post-training for both the CRT ($t=2.25(14)$, $p<.05$, $d=.41$) and CST ($t=2.40(11)$, $p<.05$, $d=.59$) conditions (Figure 5.1B).

Mapwise ICA

ICA results from the picture n-back yielded three relevant components, including the DMN and two EN components. The DMN component subsumed the precuneous, posterior cingulate cortex, paracingulate gyrus, and bilateral lateral occipital cortex (Figure 5.2a). The first EN consisted of fronto-parietal areas including the right middle frontal gyrus (MFG), the anterior cingulate cortex (ACC), and bilateral lateral occipital cortex (Figure 5.2b). A second EN was also identified, and was composed of bilateral MFG, left inferior frontal gyrus (IFG), and ACC (Figure 2c).

Four components were derived from the word n-back task, with the DMN splitting into separate anterior and posterior components, as well as two EN components. The anterior DMN component subsumed the paracingulate gyrus (Figure 5.2d), while the posterior component was observed in the posterior cingulate, precuneous, and bilateral lateral occipital cortex (Figure 5.2e). The first EN consisted primarily of bilateral MFG, as well as right IFG (Figure 5.2f). The second EN was a fronto-parietal network including the right MFG, ACC, and bilateral lateral occipital cortex (Figure 5.2g).

Three relevant components were identified for the resting state fMRI analysis, including one DMN component and two EN components. The DMN component subsumed the precuneous, posterior cingulate cortex, and bilateral lateral occipital cortex (Figure 5.2h). The first EN component consisted of fronto-parietal areas including the left middle frontal gyrus (MFG), bilateral angular gyrus, and bilateral lateral occipital cortex (Figure 5.2i). The second EN component was primarily frontal, and contained bilateral frontal pole, bilateral MFG, and anterior cingulate cortex (ACC; Figure 5.2j).

Mapwise Change in Functional Coherence

Mapwise changes in functional coherence of these components was measured using the permutation tool randomise. Using a stringent family-wise error correction, functional coherence changes were observed in the picture n-back condition in the DMN in the posterior cingulate cortex (Figure 5.3a). However, this may be driven by differences between CRT and CST at baseline, with the CRT group showing a marginal increase in coherence from pre to post-training (t=1.67; p=.12). Changes in coherence were also observed in a right occipital region of the fronto-parietal EN (Figure 5.3b), reflected by increased pre- to post-treatment coherence in this area in the CRT group (t=3.21; p=.008), and a decrease in coherence in the CST group (t=-2.60; p=.02). No changes in mapwise coherence were observed in the word n-back task.

We also examined whether there were mapwise changes in intrinsic coherence from the resting state scans. Only the fronto-parietal EN demonstrated change in a voxel-wise group by time interaction. This was observed in a cluster of 139 voxels wherein the

CRT group showed decreased functional coherence after training, while the CST group showed increased coherence at time 2 (Figure 5.4).

Whole Component Functional Coherence Analysis

Next we examined whether training influenced the whole component functional coherence values of each IC of interest. Mean coherence value for individual subjects with each component of interest were entered in repeated measures ANOVAs, along with mean relative movement as a covariate of non-interest. No DMN or EN component across either of the two n-back tasks or the resting scan showed a significant group by time interaction in a model accounting for individual subject motion.

Interconnectivity Analysis

In addition to examining whether training influenced coherence within components, we also sought to examine connections *between* the DMN and EN components during the task and resting scans. No group by time interactions were observed between the DMN and EN components in either of the picture or word n-back task scans. Additionally, no group by time interaction was observed for the interconnectivity between the DMN and the fronto-parietal EN in the resting scan. However, we did observe a significant group by time interaction when examining interconnectivity between the DMN and the frontal EN during rest (Figure 5.5a; $F(1,23)=4.70$, $p<.05$). This relationship was characterized by a non-significant decrease

in connectivity in the CRT group (t=1.41, p=.18), and an increase in connectivity in the CST group (t=-2.84, p<.05).

Next we aimed to determine whether the observed resting state changes in interconnectivity were related changes in performance related measures of working memory, overall cognition, psychosocial functioning, or symptom profile. Change in interconnectivity was not related to proximal changes in measures of working memory (2-Back Task, Spatial Span, and Letter-Number Sequencing) or more distal measures of changes in overall cognition measured by the MATRICS Battery. Interconnectivity was also unrelated to changes in community or social functioning measured by the SFS and SSPA respectively. However, we did observe a trend-level correlation between reduced in interconnectivity in the CRT group and improved functional capacity measured by the UPSA (r=-.43, *p-hypothesized*=.06), and a significant relationship between a reduction in symptoms measured on the BPRS and reduced interconnectivity (Figure 5.5b; r=.55, *p-hypothesized*<.05). Significant increases in interconnectivity for the CST group were not related to any changes in measures of cognition, functioning or symptoms. Also, baseline measures of cognition, psychosocial functioning, or symptoms were not predictive of changes in interconnectivity for either group.

Discussion

The current study used ICA to identify whether CRT for schizophrenia influences functional coherence in the DMN or EN. Behavioral findings demonstrated that the CRT group selectively improved on the picture n-back task, but this relationship was not

observed in the word n-back task. We identified three components of interest from the picture n-back task, four components of interest from the word n-back task, and three components of interest from the resting state scan. We observed mapwise changes in functional coherence during the picture n-back task in both the DMN and EN and in the fronto-parietal EN during rest, but it is unclear whether these changes were due to noise. Models examining coherence in a group by time interaction were found not to be significant when accounting for individual subject motion. We also did not observe changes in inter-connectivity between the DMN and EN during the task, but these changes were observed during rest in a group by time interaction. Adding to this finding, decreased resting state inter-connectivity in patients in the CRT group coincided with reductions in symptoms measured by the BPRS.

The current findings failed to replicate task-based ICA findings of Penades and colleagues (2013) that showed that CRT reduced task-related connectivity in both the DMN and a fronto-parietal EN. While we observed reductions in both of these networks following CRT during both the task and rest, these changes were not significant after accounting for subject motion. We therefore could not conclude that CRT influenced task-related functional coherence in this current sample. We also examined functional inter-connectivity between the DMN and EN during both n-back tasks, and again differences in observed inter-connectivity were not significant after accounting for subject movement during the scan. This also contextualizes the mapwise findings we observed in the EN and DMN from picture n-back task, and may indicate that these observed changes are better accounted for by noise as well. We could not directly test this

because of current limitations for accounting for covariates of non-interest within the 'randomise' toolbox supported by FSL.

However, these null findings may not be completely surprising, as the current constraints of our methodology required us to measure coherence averaged across both 2-back and 0-back trials. Therefore, these results could be blurred by the fact that coherence was averaged across variable levels of working memory demand. Future investigations may better examine these questions by analyzing related CRT data sets that did not switch back and forth between n-back trial-types within scan.

Coherence results in the resting task were largely subject to the same movement-related noise as that of the n-back task data, again making it difficult to interpret changes in either the CRT or CST group from pre- to post-training. However, we did observe a group by time interaction in resting state inter-connectivity changes between the DMN and the frontal EN while controlling for movement. Additionally, the observed reductions in inter-connectivity in the CRT group corresponded with reductions in psychiatric symptoms, suggesting that improved dissociation between the DMN and EN following CRT reflects psychiatric recovery. This coincides with previous findings that show that aberrant intrinsic connectivity within these networks correlates with worsened positive and disorganized symptoms in schizophrenia (Rotarska-Jagiela et al., 2010), and that intrinsic hyper-connections both within and between these networks reflect psychopathology and working memory disruptions in this population (Whitfield-Gabrieli et al., 2009). Therefore, working memory-focused CRT may serve to not only exercise

cognitive functioning, but also influence brain areas that support improved overall mental health in schizophrenia.

While resting state interconnectivity between the DMN and EN showed a group by time interaction, this relationship was in part driven by significant increases in connectivity in the CST group. These increases did not relate to any outcome measure of interest, making it unclear whether increased connectivity between these areas reflects behavioral change in the CST group, or if this was instead related to practice or experience effects of being in the scanner following training. Though the CST condition was not hypothesized to have any specific influence on cognition or neural functioning, the observed changes in this group warrant attention, and ultimately detract from conclusions that might otherwise establish that interconnectivity differences are the result of CRT specifically.

The current study presented numerous methodological challenges and limitations, which in large part limited the types of conclusions that could be drawn. Behavioral findings related to the CRT trial were observed in the picture task, but not the word n-back task, which raises questions about whether practice or placebo effects were present. Not surprisingly, we did not observe neural significant group by time interactions in the word condition, but it detracts from the other findings, as it is unclear whether participants did indeed benefit from the training. In the fMRI data, the procedure used here was thought to be maximally reliable for the meta-ICA approach (Poppe et al., 2013); though it did present challenges for adequately accounting for noise, which in our case may have been related to motion or other factors. We were also constrained by the

small sample size in each group, which would have required medium effect sizes to offer interpretable results. There is considerable variability in methodology for comparing groups using an ICA approach (Calhoun, Liu, & Adali, 2009; Erhardt et al., 2010), and it is possible that the one we chose as best suited for our dataset and hypotheses also constrained our findings. Future examinations with this and other datasets will be called upon to examine ICA using various approaches to adequately determine whether CRT influences functional coherence and connectivity.

The current results indicate that there were no changes in functional coherence during either task or rest following CRT for schizophrenia. Though we did observe a group by time interaction in intrinsic interconnections between the DMN and EN, with reduced connectivity in the CRT group coinciding with a reduction in psychiatric symptoms, this interaction was in part driven by unpredicted increases in interconnectivity in the CST group. This clearly detracts from this finding, and may suggest that unmeasured factors related to practice or scanner experience could have contributed to this finding. Moving forward, alternative approaches will be required to better understand how CRT influences functional connectivity and coherence in schizophrenia.

Figure 5.1. Behavioral Results

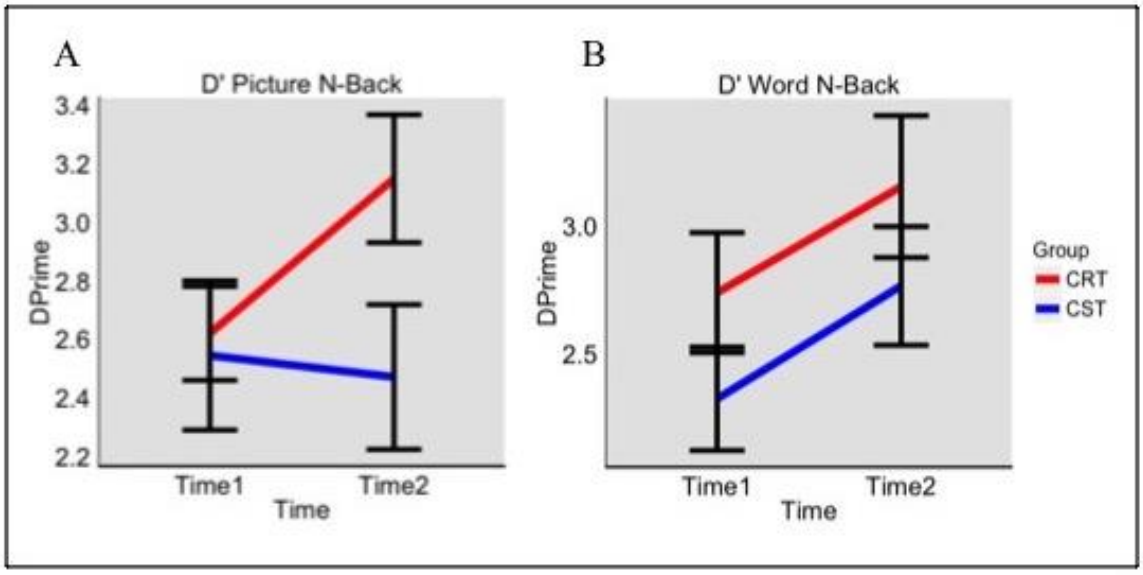


Figure 5.1. Behavioral Results. (A) The CRT group showed a significant increase in performance (D') on the picture n-back task, while the CST group showed no change. (B) Performance improved for both the CRT and CST groups on the word n-back task.

Figure 5.2. Components for the picture n-back, word n-back, and rest scans

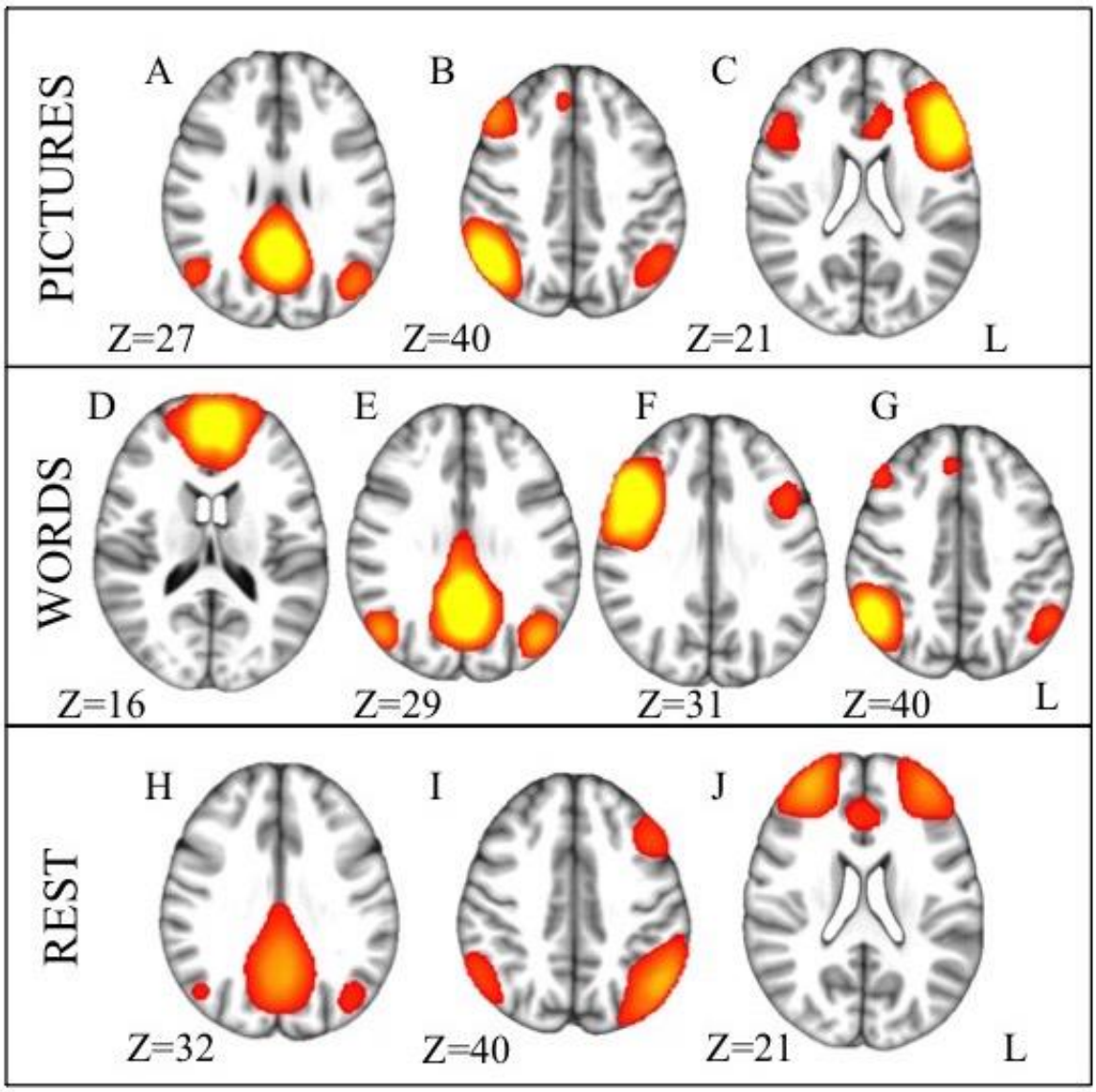


Figure 5.2. Identified components for the picture n-back, word n-back, and rest scans.

Figure 5.3. Mapwise changes in the picture n-back task

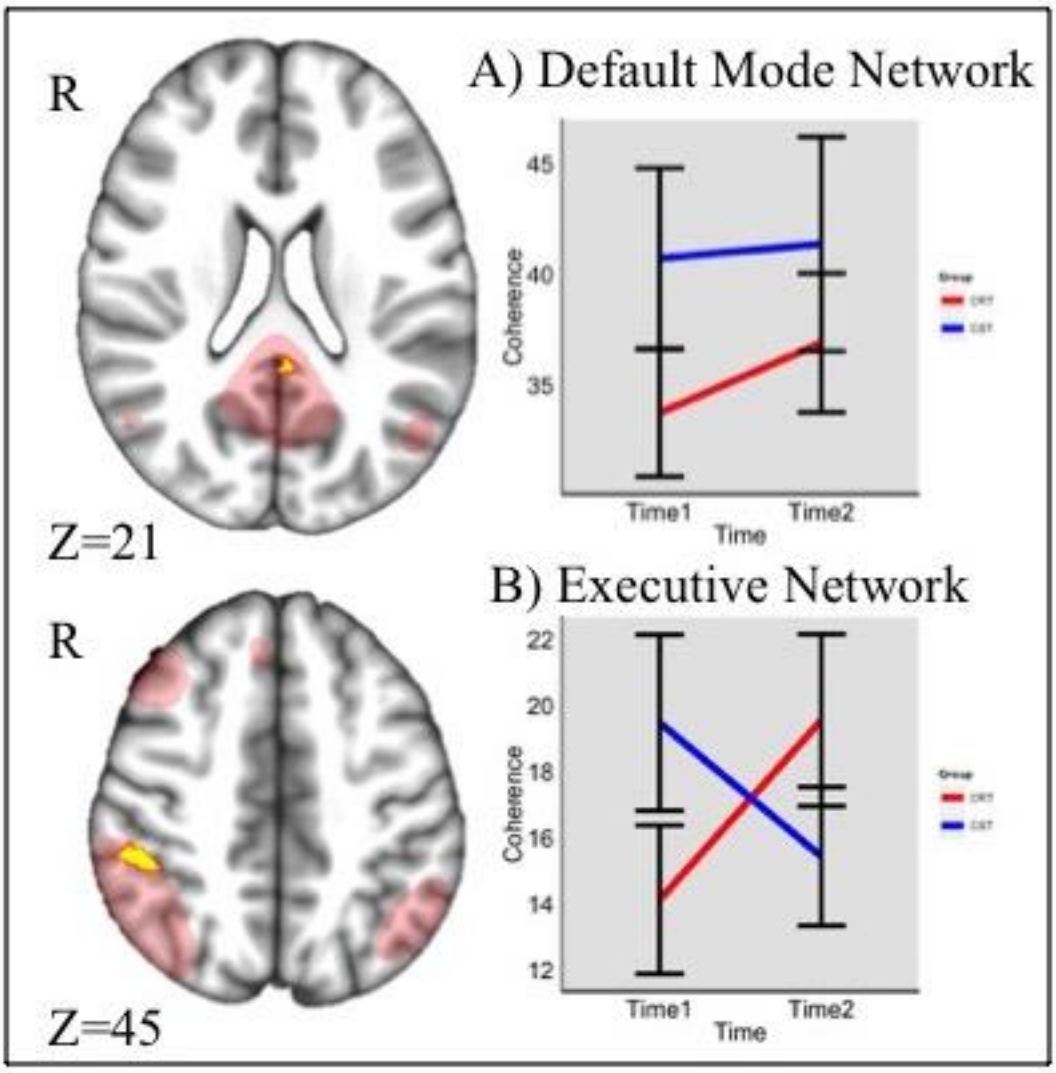


Figure 5.3. Mapwise changes in the picture n-back task. (A) A group by time interaction was observed in a posterior cingulate region of the DMN, though changes were not reflected by extracted coherence values in the line plot. (B) A group by time interaction was observed in the right posterior parietal region of the fronto-parietal EN. However, this interaction may be driven by group differences prior to training.

Figure 5.4. Mapwise changes in the EN during rest

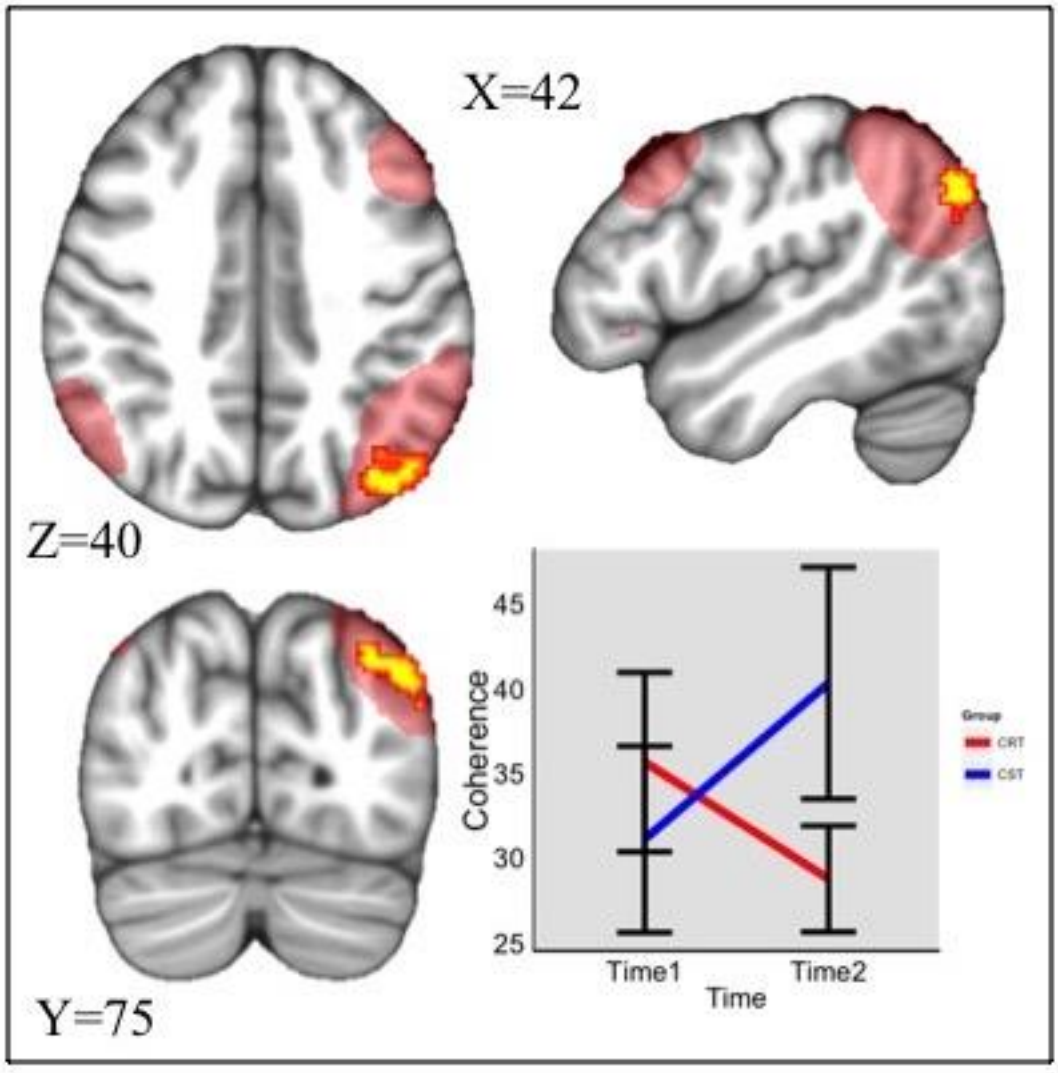


Figure 5.4. Mapwise changes in the EN during rest. Voxels in a left posterior parietal region showed a group by time interaction during rest. This relationship was driven by reduced coherence in the CRT group and increases in the CST group.

Figure 5.5. Interconnectivity at rest between the DMN and frontal EN

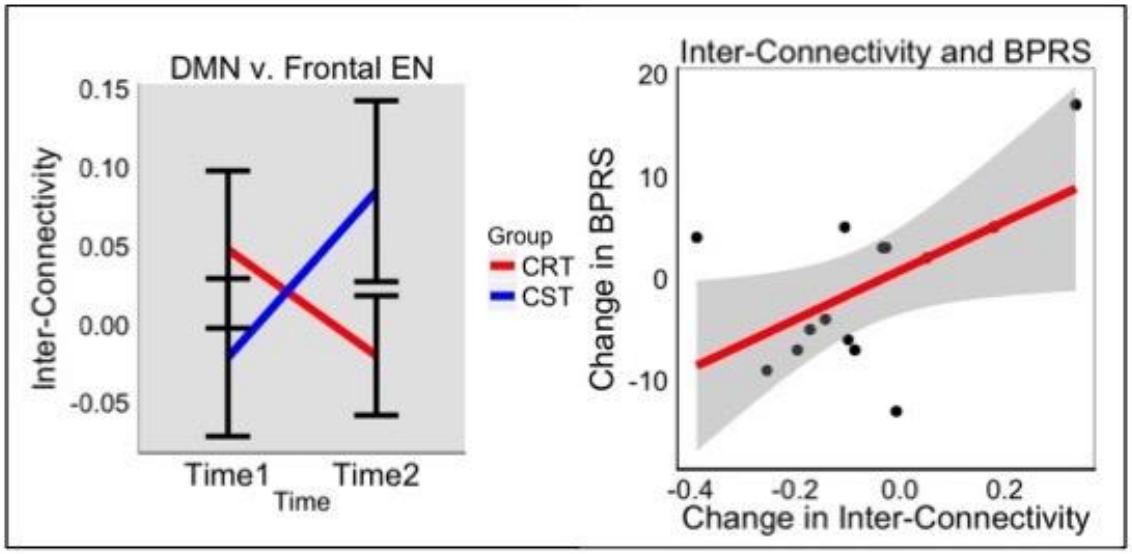


Figure 5.5. Interconnectivity at rest between the DMN and frontal EN showed a group by time interaction driven by reduced inter-connectivity in the CRT group, and increased interconnectivity in the CST group. Reduced inter-connectivity in the CRT group correlated with reduced symptomology measured by the BPRS.

Chapter 6: Increases in Intrinsic Thalamocortical Connectivity and Overall Cognition following Cognitive Remediation in Schizophrenia

Foreword: Methods outlined in this chapter are again redundant with those in chapter 3. Chapter specific analyses are described in the "Planned Analyses" section.

Abstract

Thalamic projections to the prefrontal cortex are found to be critical for cognition, and disruptions in these circuits are thought to underlie the pathophysiology observed in schizophrenia. Cognitive remediation training (CRT) is an emerging class of behavioral interventions that holds modest promise for improving cognition and functioning in schizophrenia. Previous findings indicate that these types of trainings influence functional activation to support cognitive improvements, but it is unknown whether they may influence thalamocortical connections. The current study examined whether CRT influences intrinsic functional connectivity between the thalamus and prefrontal cortex (PFC) in schizophrenia patients undergoing CRT or a placebo control. We observed changes in intrinsic connectivity in the right MFG and ACC for the CRT group but not the placebo group. The increases in connectivity between the thalamus and right MFG significantly correlated with improvements on a measure of overall cognition. Additionally, lower baseline cognition scores correlated with greater increases in connectivity between the thalamus and both the right MFG and ACC. Our results demonstrate that CRT for schizophrenia generalizes to influence intrinsic neural

connectivity in thalamocortical circuits critical for cognition. Additionally, lower baseline cognition was associated with greater neuroplastic response to CRT, indicating that lower functioning patients may show explicit benefit from a working memory-focused CRT intervention.

Introduction

Thalamic projections to the prefrontal cortex (PFC) show distinct patterns of connectivity in both animals and humans (Klein et al., 2010). These thalamocortical connections are thought to underlie critical aspects of cognition and consciousness (Laureys et al., 2000; Tu et al., 2011), and disruptions in these neural pathways have been shown to be associated with cognitive dysfunction (Zhang et al., 2009). Animal models have demonstrated that perturbations to the medial dorsal thalamic nuclei within this network have a direct influence on connectivity with prefrontal cortex, and have subsequent influence working memory function (Duan et al., 2015; Parnaudeau et al., 2013). These observations demonstrate that insults to this thalamus-prefrontal network can alter cognitive functioning, which may have important implications for understanding the pathophysiology of serious mental illnesses such as schizophrenia.

Schizophrenia is a chronic, debilitating mental illness characterized by a concert of psychotic, disorganized, and cognitive symptoms. Developments in treating this and related psychiatric disorders has come a long way in the last half century, but a limited understanding of the pathophysiology associated with this disorder has constrained further advances (Miyamoto, Miyake, Jarskog, Fleischhacker, & Lieberman, 2012).

Emerging hypotheses have proposed that schizophrenia is characterized by a series of neural "dysconnections", with disorganized over and under-connections throughout the brain (Andreasen et al., 1998; Friston & Frith, 1995; Pettersson-Yeo et al., 2011). This disrupted neural connectivity has been observed to be widespread (Lynall et al., 2010), and may underlie heterogeneous symptom presentation within schizophrenia (Cole et al., 2011).

Both prefrontal (Glahn et al., 2005; Minzenberg et al., 2009) and thalamic disruptions (Pergola et al., 2015) have been associated with schizophrenia, but more recently connections between these regions have emerged as potential markers associated with the pathophysiology of this illness (Lewis, 2000). Consistent with the animal literature, numerous resting state fMRI (rsfMRI) studies have identified aberrant thalamocortical connections in schizophrenia, with implications for cognitive functioning. Patients have been shown to have both reduced prefrontal-thalamic connectivity, as well as hyper-connectivity between the thalamus and temporal, parietal, somatosensory/motor, and visual cortices (Anticevic et al., 2013; Atluri et al., 2014; Klingner et al., 2014; Welsh et al., 2010; Woodward et al., 2012). Emerging evidence also demonstrates that the structural and functional abnormalities within cortico-striatal-thalamal circuits are linked to overall cognitive impairments (Sui et al., 2015). These findings indicate that disrupted connections from thalamus to the prefrontal cortex may be involved in the widely observed cognitive deficits associated with schizophrenia. However, while these widespread intrinsic dysconnections may characterize the cognitive

disturbances of patients in a disease state, it is unclear whether they are malleable in response to psychiatric recovery.

Basic research in behavioral neuroscience has established that the brain undergoes changes in organization and function in response to rehabilitative training (Taub, 2004), and these principles have begun to be applied to treatments for cognitive dysfunction. Cognitive remediation training (CRT) is an emerging class of behavioral treatments that aims to rehabilitate cognitive and psychosocial disruptions to facilitate psychiatric recovery in illnesses like schizophrenia. CRT interventions typically consist of computerized cognitive training tasks that exercise a range of cognitive abilities, with the ultimate goal of generalizing improvements to untrained skills. CRT for schizophrenia has demonstrated reliably modest improvements in cognition and psychosocial functioning (Mcgurk, Ph, Twamley, et al., 2007; Wykes et al., 2011), and recent meta-analytic findings have established both prefrontal and subcortical areas to be associated with neural plasticity following CRT in schizophrenia (Ramsay & MacDonald, 2015). Notably, increased activation in areas of the thalamus and prefrontal cortex overlapped with areas previously shown to be associated with working memory(Minzenberg et al., 2009) and affective processing disruptions(Delvecchio et al., 2013). However, while this further establishes the thalamus and prefrontal cortex as potential neural targets for treatment in schizophrenia, it is unclear whether CRT can influence connections between them.

To build on previous findings establishing under-connectivity between the thalamus and prefrontal cortex (Andreasen et al., 1998; Anticevic et al., 2013; Lewis,

2000; Welsh et al., 2010) along with disrupted cognition as a result of dysfunction in these thalamocortical networks (Sui et al., 2015), this investigation sought to determine whether CRT could potentially influence these intrinsic connections. We focused our investigation on the bilateral middle frontal gyrus (MFG) and the anterior cingulate cortex (ACC), as these regions are well known to be associated with cognitive disruptions in schizophrenia (Barch & Ceaser, 2011; Perlstein, Carter, Noll, & Cohen, 2001; Sanders, Gallup, Heinsen, Hof, & Schmitz, 2002), and also showed consistent under connectivity with the thalamus in a previous study (Anticevic et al., 2013). We hoped to learn whether changes in these specific circuits could be linked to patients' cognitive improvements on domains beyond those for which they were trained. The current study used a seed-based method to examine whether thalamocortical connectivity measured during rsfMRI is influenced by a working memory-focused CRT intervention in schizophrenia. We hypothesized that functional connections between the thalamus and MFG, and thalamus and ACC would show increased connectivity following training. Furthermore, we sought to demonstrate that these treatment-mediated changes in connectivity generalize to improvements in overall cognition. Last, we examined whether these thalamocortical relationships were also observed in response to a working memory task.

Methods

Participants in the current study were recruited from a larger clinical trial examining cognitive remediation (Clinical Trial # NCT00995553). All participants were required to have a DSM-IV diagnosis of schizophrenia or schizoaffective disorder (First

et al., 1997), be between 18 and 60 years old, be clinically stable with no medication changes or hospitalizations in the previous four weeks, a Wechsler Test of Adult Reading IQ score greater than 70, no substance dependence or abuse in the past month, no history of serious head injury or neurological disorder that could compromise cognition, and showed capacity to give consent.

Forty participants (out of 80 total randomized in the full clinical trial) consented to participate in the imaging study, which was approved by both the Minneapolis VAHCS and University of Minnesota IRBs. Three participants were ineligible, three subsequently refused, three were too anxious to complete the protocol, two missed their scanning sessions, three were lost due to experimenter error, and no additional subjects were excluded for in-scanner movement (mean displacement threshold > 2mm). This left 26 total participants in the current study, who were randomized to undergo either 16 weeks of a working memory-focused CRT (N=14) or a computer skills training (CST) placebo condition (N=12). Participants in the two groups did not differ on sex, age, education, parental education, WTAR IQ score, duration of illness, total antipsychotic chlorpromazine (CPZ) equivalence, or DSM-IV diagnosis (all *p*'s > .12) (Table 6.1). Additionally there were no differences on these variables between those included in the imaging study and those who only participated in the clinical trial (all *p*'s>.13)

Training Procedure

Training took place at the Minneapolis VAHCS. Participants completed up to 48 hours of training over the course of 16 weeks (three 1-hour sessions weekly). The CRT

and CST groups did not statistically differ with regards to the number of training hours (CRT=48 (SD=0), CST=48 (SD=.28)), or number of training days needed to complete the protocol (CRT=40 (SD=4.09), CST=36 (SD=10.43)).

Participants randomized into the CRT condition completed a computer-based training program that consisted of 21 adaptive computer exercises, which used errorless-learning principles to place demands on working memory in verbal, visual, and spatial modalities. The tasks were selected from the Psychological Software Services CogReHab program developed by Bracy (Indianapolis: Psychological Software Services; 1995), and the Captain's Log educational software (Brain Train) developed by Sandford and colleagues (Sandford, Browne, & Turner, 1996). Additionally, 1/3 of training time focused specifically on training with a version of the N-back task (0, 2, 3, or 4-back). Participants were advanced to a higher N-back level after demonstrating mastery performance (85% accuracy) at the previous level across three consecutive task runs.

Participants in the CST condition participated in a course focusing on keyboarding skills and learning to use Microsoft Office 2007 for word processing, spreadsheet management, and presentation creation. The CST condition was designed to have the same level of training time, exposure to computers, and attention from treatment providers as the CRT condition, but did not rely on errorless-learning principles.

Both conditions were facilitated by master's or bacherlor's level interventionists who provided instruction, monitored progress, offered encouragement, and intervened to minimize frustration when necessary and were unaware of the hypotheses being tested. Additionally, a doctoral level clinician led weekly half-hour bridging sessions for both

conditions. In these sessions, participants discussed their reactions to the training, skills they were learning, and how they might apply them in real-world situations.

Assessment Procedure

As part of the full clinical trial, enrolled participants underwent clinical, cognitive, and functional assessment at baseline and after the 16 weeks of training. For the purposes of the current study, patients were assessed on the MATRICS Cognitive Consensus Battery (MCCB), which measures functioning in domains of attention, processing speed, working memory, verbal learning, visual learning, reasoning, and social cognition(Keith H. Nuechterlein et al., 2008). The dependent measure in the current investigation relied on the MCCB overall age-normed T-score.

Imaging Procedure and Pre-processing

Patients underwent a six-minute rsfMRI scan (240 scans) immediately after completing a word and picture n-back task (424 scans per task). The N-back tasks switched between 0-back trials and 2-back trials, and were counterbalanced for whether the word or picture condition was given first. All images were collected at the University of Minnesota Center for Magnetic Resonance Research using a 3 Tesla Siemens Trio MRI scanner, and a 32-channel head coil (repeat time (TR) = 1.5 seconds, echo time (TE) = 40, flip angle = 90 degrees, voxel size = 3.5 x 3.5 x 2 mm thickness, FOV= 22 cm, 35 axial slices). T1 reference images were also collected (voxel size = .86 x .86 x 1.5 mm thickness, 256 x 256 x 124 dimensions). Data were preprocessed using FSL (see:

http://www.fmrib.ox.ac.uk/fsl/). Images were motion corrected using rigid body transformations (FLIRT) and a six parameter motion regression procedure. Scans were spatially smoothed at FWHM = 7 mm, normalized using the mean volume intensity, and filtered with a high pass frequency cutoff of 120 seconds. Field maps were collected to carry out B0-unwarping. Mean average displacement (movement) across pre and post-training resting scans was .31mm (*SD*=.40) and .30mm (*SD*=.33) in CRT and CST

Planned Analyses

A bilateral thalamus region of interest (ROI) was established using the Harvard-Oxford Subcortical Atlas and setting the probabilistic mask's threshold to 50% likelihood. The ROI was then transformed into each subject's space using FSL's linear transformation tool. Individual subject time courses were then extracted from the preprocessed data for each subject's thalamus ROI for both pre- and post-training rest scans. The time course was then entered into individual subject GLMs as a single regressor in FSL, and then contrasted within subjects to compare pre and post-training rest scans.

Following GLM analyses, we performed voxel-wise small volume ROI analyses constrained to a ROI containing the left middle frontal gyrus (LMFG), right middle frontal gyrus (RMFG), and anterior cingulate cortex (ACC). All ROIs were established with the Harvard-Oxford Cortical Atlas, and thresholded at 20% likelihood. Participants' duration of illness and WTAR IQ scores was included as covariates of non-interest in the model. Group images were cluster-thresholded at $Z>2.3$ and a within-mask significance

threshold of p=0.05. After within-mask analysis, individual subject beta values were extracted and Fisher's z-transformed before being entered into a repeated-measures ANOVA to examine the magnitude and directionality of group by time interactions. We then correlated these z-transformed values with change in overall cognition scores from the MATRICS. We also assessed whether baseline MATRICS score correlated with change in connectivity.

Last, we sought to replicate the above analysis in the picture N-back task. We chose to focus our analysis on the picture task as opposed to the word N-back because the picture condition showed the clearest behavioral effect of training, wherein patients in the CRT group showed improved accuracy, and those in the CST group did not. Using the same bilateral thalamus ROI, we again extracted the time course from pre- and post-training N-back scans. Time courses were then entered into a GLM as a psychophysiological interaction (PPI) with the 2-back and 0-back conditions. At the group level, we again performed a voxel-wise small volume ROI analysis constrained to the same LMFG, RMFG, and ACC regions. Group images were again cluster-thresholded at Z>2.3 and a within-mask significance threshold of p=0.05. Last, we also extracted and Fisher's Z-transformed beta values from significant voxels to examine the directionality of interactions and to examine correlations with MATRICS scores.

Results

Voxel-wise small-volume ROI analyses revealed differences between groups in the RMFG and ACC (Figure 6.1; Table 6.2). To clarify these observed relationships, we

extracted and plotted the beta values from the significant voxels. Connectivity differences in the RMFG reflected a group by time interaction ($F(1,24)=13.07$) driven by a significant increase in the CRT group ($t=-3.10$, $p=.009$), and a trending decrease in the CST group ($t=2.14$, $p=.06$). A similar group by time interaction was observed in the ACC ($F(1,24)=9.59$), driven by increased connectivity in the CRT group ($t=-2.37$, $p=.03$), and a trend toward decreased connectivity in the CST group ($t=2.04$, $p=.07$). No significant changes were observed in the LMFG.

Next we examined whether changes in the observed voxels were associated with training-related changes in cognition. Increases in thalamus-RMFG connectivity were positively correlated with changes in overall cognition score on the MATRICS ($r=.55$, $p=.043$; Figure 6.2a). Additionally, we observed a negative relationship between baseline MATRICS scores and increased thalamus-RMFG connectivity ($r=-.53$, $p=.05$; Figure 6.2c), indicating that lower cognition scores at baseline were related to greater changes in intrinsic connectivity. Change in MATRICS scores did not significantly correlate with changes in connectivity in the ACC ($r=.18$, $p=.54$; Figure 6.2b), though lower baseline MATRICS scores evidenced a trend related to increased connectivity between the thalamus and ACC ($r=-.52$, $p=.05$; Figure 6.2d).

Last, we sought to determine whether the observed changes in intrinsic thalamocortical connectivity during rest were also present during task engagement. We observed task-based connectivity changes between the thalamus and ACC ($F(1,24)=15.89$), driven by increases in connectivity in the CRT group ($t=-3.15$, $p=.008$), and decreases in the CST group ($t=2.52$, $p=.02$) (Figure 6.3). We also observed task-

based connectivity changes with the LMFG ($F(1,24)=12.28$) driven by increases in the CRT group ($t=-3.13$, $p=.008$), and a trending decrease in the CST group ($t=2.04$, $p=.07$) (Figure 6.3). No changes were observed in the RMFG. Notably, these relationships were not modulated by interactions with the 2-back or 0-back conditions, but persisted across the duration of the task, indicating that these differences are characterized by tonic changes in thalamocortical connectivity present during working memory engagement. Also, changes in connectivity with neither the ACC nor LMFG were predictive of changes in MATRICS score or improvements in task N-back task performance, but lower baseline MATRICS score did show a trend level correlation with change in connectivity with the ACC ($r=-.46$, $p=.099$).

Discussion

The current findings establish that the effects of CRT for schizophrenia may generalize not only to untrained abilities, but also influences the intrinsic function of the brain. Patients who underwent 16 weeks of a working memory-focused CRT showed increased functional connections between the thalamus and both the RMFG and ACC. This is notable given previous evidence for reductions in connectivity between these regions (Anticevic et al., 2013; Welsh et al., 2010). Moreover, these findings offer a plausible mechanism by which CRT may influence the brain's intrinsic functional architecture. Focused cognitive training may influence neuroplastic changes in the brain at rest and support improved cognitive functioning.

In particular, increased thalamic-RMFG connectivity correlated with improvements in overall MATRICS score, suggesting that plasticity in this circuit supports the training-related generalization to improve overall cognition. Few studies to date have demonstrated that changes in neural functioning from CRT coincide with improvements on distal measures of overall cognition. This is especially relevant, as previous studies have established that disrupted structural and functional circuitry between the thalamus, PFC, and other subcortical regions may underlie the observed cognitive disruptions measured by the MATRICS in schizophrenia (Sui et al., 2015). Here we show that CRT may directly influence this mechanism to facilitate treatment-related gains in cognition.

We also demonstrated that lower baseline measures of cognition were correlated with increased thalamocortical intrinsic connectivity in both the RMFG and ACC. This indicates that those with poorer cognition at the start of CRT were those that showed the most neural plasticity; potentially making them target candidates for this type of treatment. This is especially encouraging, as previous findings that have identified individuals with higher baseline cognition as more responsive to broad-targeting CRT interventions (Kurtz et al., 2009). In contrast, others have shown that lower functioning patients show more gains in response to functional skill-focused trainings (Twamley et al., 2011), which may coincide with the current findings. In the current intervention, patients trained a single cognitive domain: working memory. This may have allowed lower functioning patients to target their cognitive exercises on disrupted neural pathways, thereby showing greater neuroplastic changes. Therefore, instead of the “rich

getting richer" with regards to cognition, working memory-focused training may be ideal for lower functioning patients with schizophrenia, and could prove critical as providers begin to tailor and personalize cognitive interventions for psychiatric disorders.

The current findings also demonstrate that observed changes in thalamocortical connectivity may also be present in the face of cognitive demands, as the ACC and LMFG showed tonic connectivity changes during a N-back task. This suggests that training initiated changes are not present only during rest, but may also characterize neural connectivity during a task or in an otherwise cognitively challenging state. However, these changes were not found to correlate with task improvement or changes in overall cognition measured by the MATRICS, therefore making it unclear whether this change plays a direct role in task approach or performance. Despite the lack of a behavioral correlation with these functional connectivity changes, it demonstrates that the previously observed intrinsic connectivity changes may persist across cognitive states, and have thereby changed the functional architecture of this thalamocortical circuit.

A limitation of the current study is that we were constrained to an ROI approach, wherein we examined changes in hypothesis driven brain areas of the prefrontal cortex. In line with the findings of Anticevic and colleagues (2013) as well as Atluri and colleagues (2015), we also examined whether CRT influenced previously observed hyperconnections to parietal and temporal areas, though no relationships were observed. However, thalamocortical connections between these areas may be important to investigate in future studies, especially as they may coincide with recovery or alleviation of other types of psychiatric symptoms in schizophrenia. It is also not yet clear whether

CRT may influence other neural circuits, in particular others that may connect through the thalamus, though the current study offers an important starting point for these types of investigations.

We also note that the thalamus is a particularly complex neural region, composed of subnuclei that project to various cortical structures (Sherman & Guillery, 2006). In particular, the dorsomedial nucleus of the thalamus may be especially important in thalamus-prefrontal connectivity, as it is well understood to have direct projections to the prefrontal cortex (Kumar, Mang, & Grodd, 2014). Future studies may investigate connectivity seeding from these subnuclei more specifically to determine whether this offers a more nuanced understanding of the nature of CRT-induced connectivity changes. Another important limitation of the current study is the small sample size, which may have limited our power to detect effects in other brain areas, as well as correlations with cognitive outcome measures. Larger samples and replication in extant datasets may help to clarify the nature of thalamocortical connectivity, and how CRT or other psychiatric treatments may influence the nature of these networks.

The current study demonstrates that a working memory-focused CRT intervention increases thalamocortical connectivity at rest, and corresponds to improvements in overall cognitive functioning. Additionally, these changes were found to persist during task engagement, and were correlated with lower pre-treatment cognition. These findings offer theoretical support for a neural mechanism supporting CRT in schizophrenia, and integrate current findings that characterize thalamocortical dysconnectivity in this population.

Tables:

Table 6.1 Pre-Treatment Group Demographics

	CRT (SD)	CST (SD)	t-value	p-value
Age	42.93 (10.6)	45.75 (7.7)	0.8	0.4322
Education	13.47 (1.5)	12.42 (1.04)	1.2	0.2424
Parental Education	12.83 (4.3)	13.21 (1.79)	0.3	0.7628
WTAR IQ	104 (10.76)	101.42 (11.56)	0.6	0.5576
Duration of Illness	20.93 (12.73)	18.5 (11.11)	0.53	0.601
Total CPZ	551.8 (466.24)	320.75 (280.81)	1.6	0.1248
BPRS Total Time 1	42.53 (9.74)	45 (11.17)	0.6	0.5525

Table 6.1 Note: Pre-Treatment Group Demographics. CRT = Cognitive Remediation Training (N=15), CST = Computer Skills Training (N=12), WTAR IQ = Wechsler Test of Adult Reading Intelligence Quotient, Total CPZ = Total Chlorpromazine Equivalence, BPRS = Brief Psychotic Rating Scale.

Table 6.2. Brain areas showing increased connectivity at rest Pre<Post CRT>CST

Region	N Voxels	Z-Max	x	y	z
ACC	520	3.49	2	-4	32
		3.31	10	0	38
		3.17	0	34	22
		3.11	-10	16	28
		3.1	-8	10	32
		3.1	4	2	36
RMFG	460	4.19	42	4	54
		3.75	38	4	58
		3.24	30	30	46
		3.16	26	28	38
		3.15	40	28	46
		3.1	30	0	64

Table 6.3. Brain areas showing increased connectivity during n-back Pre<Post CRT>CST

Region	N Voxels	Z-Max	x	y	z
ACC	494	4.18	6	4	36
		3.98	2	0	36
		3.41	-2	2	34
		3.38	10	12	42
		3.37	4	14	44
		2.97	4	6	26
Left MFG	314	3.83	-34	32	34
		3.21	-32	10	32
		3.15	-36	4	34
		3.91	-22	30	38
		2.83	-38	34	42

Figure 6.1. Activation Changes at Rest Pre<Post CRT>CST

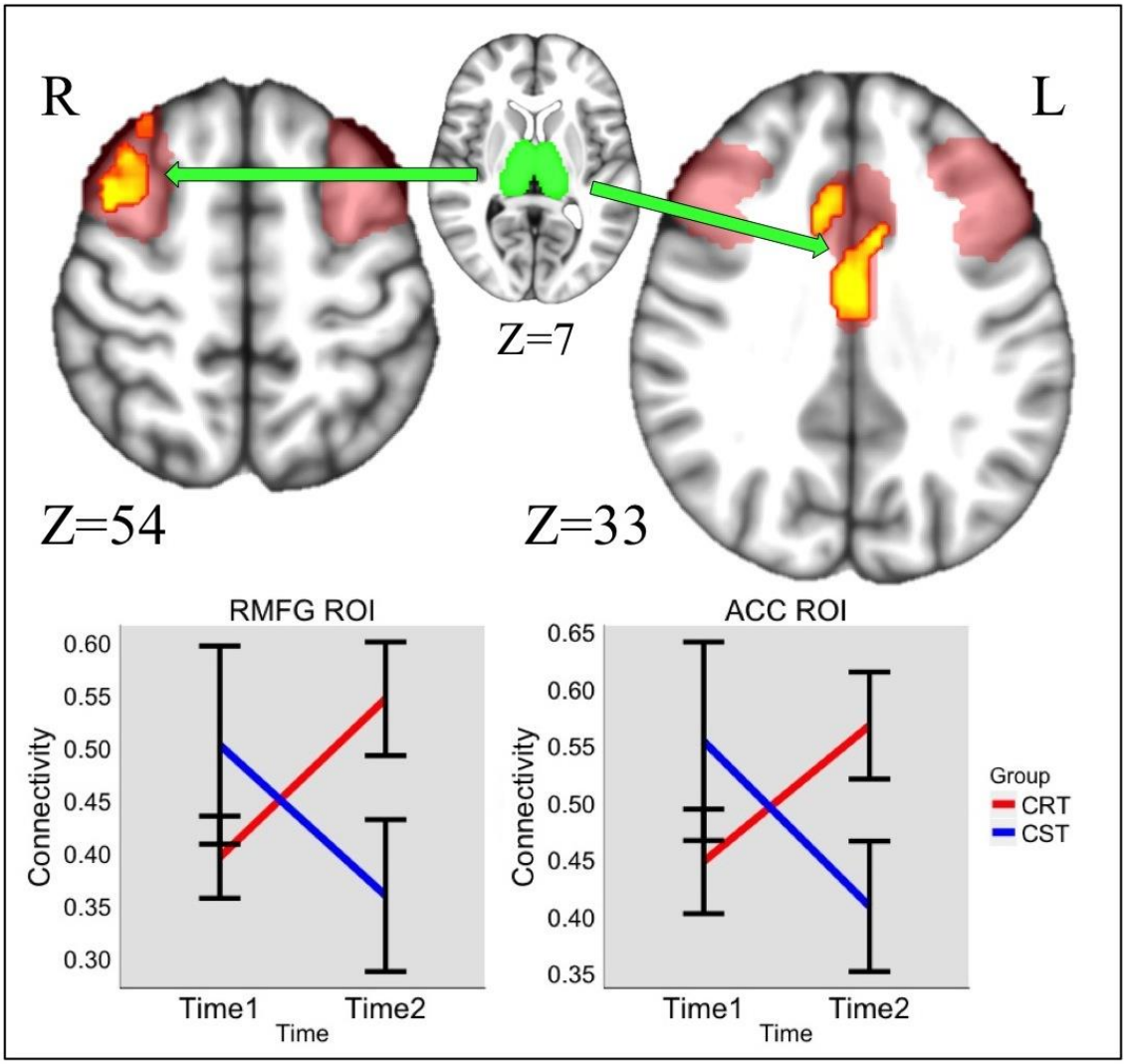


Figure 6.1 Note: Green area denotes the thalamus ROI. Transparent red areas denote the RMFG, LMFG, and ACC ROI. Hot areas denote increased activation from pre (Time 1) to post (Time 2) intervention in CRT > CST. Group by time interactions were observed in the RMFG and ACC, driven by increased thalamocortical connectivity following the CRT intervention.

Figure 6.2. Change in MATRICS score

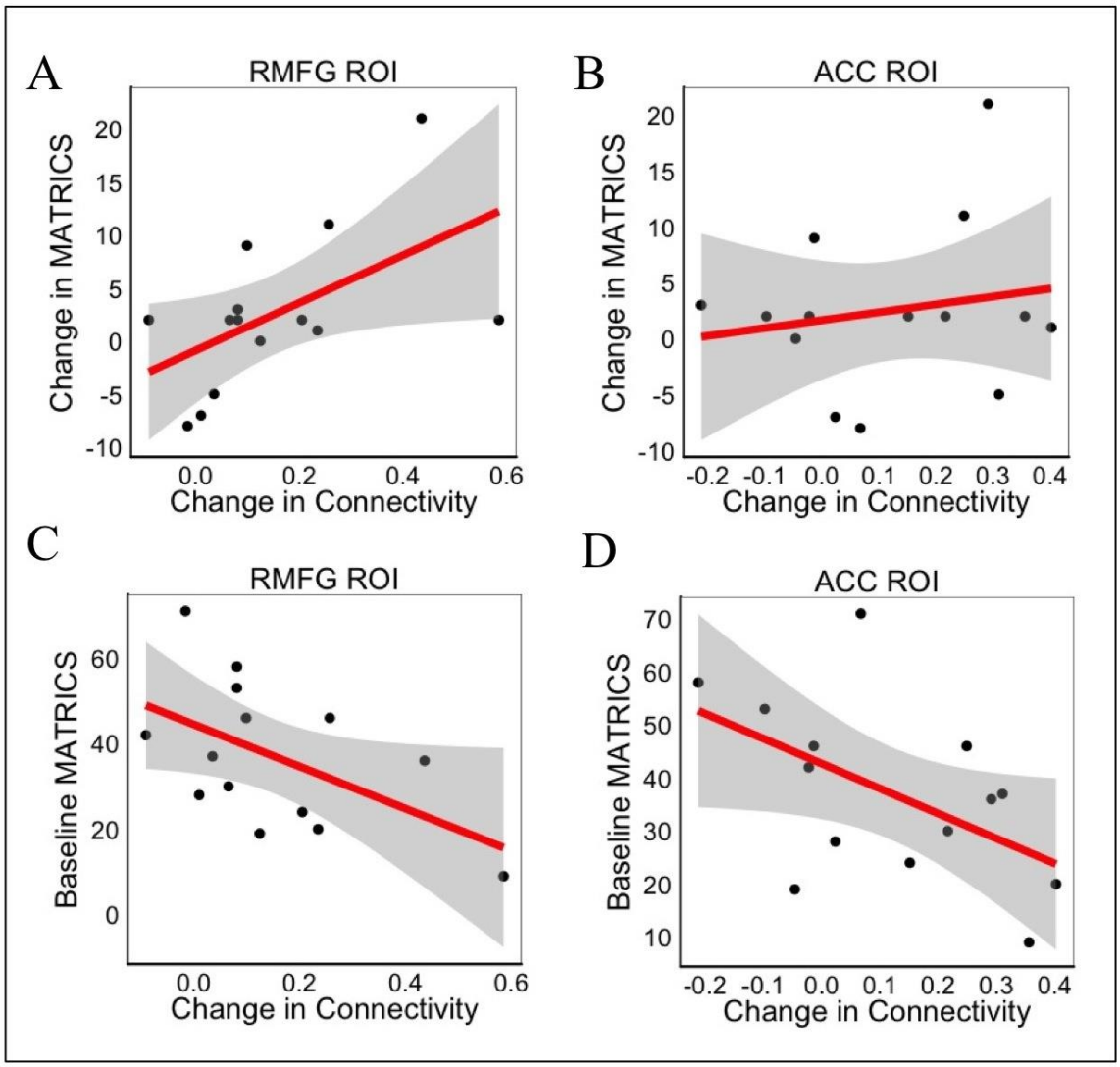


Figure 6.2 Note: (A) Change in MATRICS score significantly correlated with changes in connectivity with the RMFG. (B) Change in MATRICS score did not significantly correlate with changes in connectivity with the ACC. (C) Baseline MATRICS score negatively correlated with changes in connectivity with the RMFG. (D) Baseline MATRICS score negatively correlated with changes in connectivity with the ACC.

Figure 6.3. Activation Changes during N-back Pre<Post CRT>CST

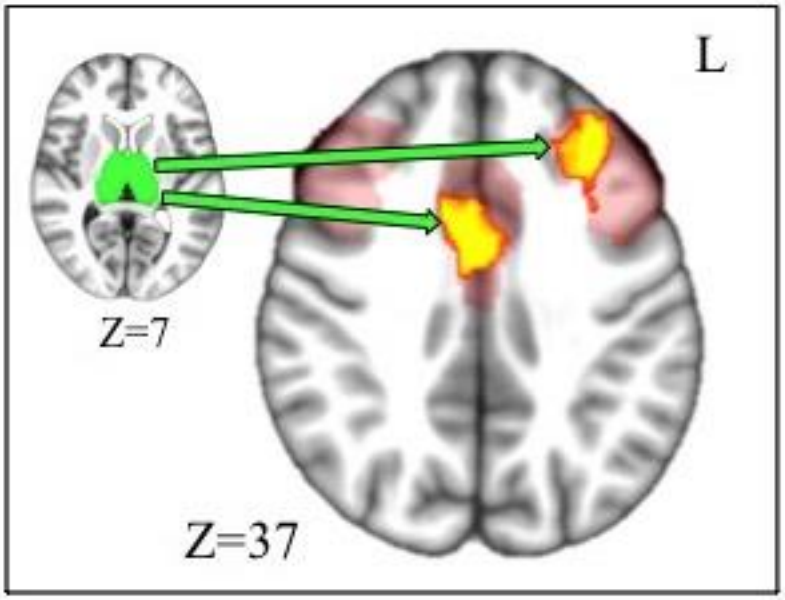


Figure 6.3. Green area denotes the thalamus ROI. Transparent red areas denote the RMFG, LMFG, and ACC ROI. Hot areas denote increased activation from pre (Time 1) to post (Time 2) intervention in CRT > CST in the ACC and LMFG.

Chapter 7: Overall Summary and Conclusions

The current dissertation integrated findings from four related studies to better understand the neural mechanisms that support cognitive remediation for schizophrenia. Specifically, I focused on understanding various measures of neuroplasticity, and how they might relate to changes in cognition and functioning. The first study used an activation likelihood estimate (ALE) approach to identify brain areas consistently influenced by CRT for schizophrenia in nine peer-reviewed studies. Study 2 partially replicated previous findings to show that schizophrenia patients who undergo a working memory-focused CRT show increased activation in the left DLPFC on a picture N-back task. The third study relied on an independent component analysis (ICA) approach to demonstrate the CRT influences intrinsic inter-connectivity between default mode and executive networks in patients with schizophrenia. Last, I showed that CRT strengthens intrinsic connections between the thalamus and prefrontal cortex, and that these changes coincided with improvements in overall cognition.

Study 1 Summary and Conclusions: ALE Meta-Analysis

Results from the ALE meta-analysis offered an important theoretic starting point for the following studies. It was the hope that this study would not only provide justification for continued examination of neural activation changes associated with CRT, but also direct future hypothesis tests. In doing so, we first we determined that though small, the existing corpus of studies examining pre- versus post-training neural activation

in schizophrenia could be reliably meta-analyzed. Our findings demonstrate that there is significant likelihood of activation changes in areas of the prefrontal cortex, as well as subcortical areas including the caudate and thalamus. This study faced a challenge, in that the approaches and methods for measuring and invoking this change varied widely. Therefore it is perhaps not surprising that our results implicated widespread brain areas that support higher order cognition, socio-emotional functioning, motor functioning, as well as basic cognitive processing.

The second goal of the meta-analysis was to determine whether activation likelihood changes associated with CRT coincided or overlapped with previously observed neural disruptions in schizophrenia. We chose to compare our findings to two extant meta-analyses that had previously examined neural dysfunction associated with working memory/executive functioning (Minzenberg et al., 2009) and social affect recognition (Delvecchio et al., 2013). We observed partial overlap in areas of the left PFC and the thalamus, which are two regions that have not only been critically implicated in the pathophysiology of schizophrenia (Glahn et al., 2005; Pergola et al., 2015), but also support findings from the fourth study of this dissertation, which examined connections between these two brain areas.

Our meta-analytic findings are encouraging, and will offer a useful starting point for other studies examining functional activation changes associated with CRT in schizophrenia. It is the hope that the regions we observed can be made publicly available so that future studies can constrain their hypotheses to known neural targets. However, this doesn't preclude the need for continued examination of whole brain activation

changes associated with CRT, as other brain areas may be important sites for neural plasticity. It also highlights a critical limitation of our ALE findings, as we included studies that relied on a region of interest (ROI) approach. Some debate exists about whether ROI studies should be included in such analyses, as ALE is predicated on assumptions of activation likelihood across the whole brain. Because of a very limited corpus of studies, we chose to include studies using an ROI approach, and may therefore be partially biasing our findings. Continued investigation and future updates to this ALE meta-analysis will be required as we continue to refine CRT for schizophrenia, and learn more about how to harness or optimize neural plasticity.

Study 2 Summary and Conclusions: Replicating Change in Functional Activation

The ALE findings led logically to our efforts to understand activation change following CRT in our own sample. The primary goal of the second study was to replicate previous findings from our laboratory by Haut, Lim, and MacDonald (2010), which showed that patients who underwent CRT (versus a cognitive behavioral social skills training) showed increased activation on two variants of the N-back task. These increases in activation were observed in prefrontal areas including the lateral PFC, ACC, and frontal pole, and largely corresponded with improvements in N-back performance. I also sought to expand on these findings, by investigating their relationship with changes in both proximal and distal generalization measures of cognition, psychosocial functioning, and symptoms. In the current study, we used a near identical task procedure in the

scanner, and constrained our primary analyses to these regions for our current study, but only partially replicated the finings of Haut et al. (2010).

Behaviorally, we observed hypothesized changes in performance on the picture N-back task, but not the word N-back task. This was surprising, as the word task served as a manipulation check wherein those in the CRT group trained on the word N-back task while those in the CST group did not. Since both groups showed increased performance on the word N-back, it is possible that improvements were due to practice or placebo effects from pre- to post-training, as opposed to the specific influences of the working memory-focused CRT. Practice effects may be driven by familiarity with the instructions or task demands, while the placebo effect could be present due to expected changes in cognition or improved motivation, and both have been previously shown to drive positive findings in cognition trials for schizophrenia (Goldberg, Keefe, Goldman, Robinson, & Harvey, 2010). Despite the double blind nature of the current study, it is still possible that we were vulnerable to these effects. However, there was an observed group by time interaction in favor of the CRT group in the full behavioral trial on the word N-back, suggesting that this effect may have been unique to the subset of subjects that underwent fMRI. Because of this, it limited the interpretability of neural data associated with these subjects in the word N-back condition, and was the primary reason for choosing to focus on the picture N-back for the ensuing neuroimaging analyses. It is unclear why one condition may have been vulnerable to practice or placebo effects, but perhaps underscores the need for larger sample sizes, as well as including resting state fMRI to further understand neural plasticity outside of a task-based context. Overall, the

behavioral findings limited the conclusions that could be reliably drawn from the task-based data with regards to cognitive training.

As we proceeded to examine the functional imaging data associated with the picture N-back, we observed activation changes in a subset of voxels in the left DLPFC, which correlated with improvements in D' on the picture n-back task. No other pre-defined areas of interest showed this relationship, indicating that we only partially replicated the findings of Haut and colleagues (2010), even despite having a larger sample. Another logical analysis with this data was to examine whether there were neural changes in areas identified in the ALE from study 1 (Ramsay & MacDonald, 2015). No such results were found in this analysis, which may indicate that our findings either do not coincide with previous CRT findings, or that functional activation may not be the most robust indicator of neural change associated with CRT in schizophrenia, which would therefore warrant alternative methods of examining neural plasticity.

Study 3 Summary and Conclusions: ICA During Task and Rest

Study 3 used an independent component analysis (ICA) approach to examine whether functional changes in coherence or inter-connectivity were associated with CRT. This analysis allowed us to not only examine the task data, but also the resting data, as ICA is a model-free approach. We identified the default mode (DMN) and executive network (EN) components in each set of scans, and observed what appeared to be group-by-time interactions wherein functional coherence during both task and rest changed in correspondence with the training. However these changes were nullified when accounting

for subject motion in the model, indicating that these observed changes may have been spurious and unrelated to cognitive training. This has been found to be a problem in other data sets, even when implementing standard pre-processing steps to control for subject motion (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). It may be useful to reanalyze this data in the future using different parameters that could better control for such a problem.

Though CRT did not significantly influence these functional coherence networks, I still examined whether changes in these networks corresponded to changes in cognition, psychosocial functioning, and symptoms. These correlations are summarized in Supplementary Table 7.1, and show that no changes in components of interest significantly correlated with changes in any outcome measure of interest. Specifically, I had hypothesized that changes in functional coherence (a measure of within network connectivity) measured by ICA were better predictors of change in psychosocial outcome compared to measures of functional activation. This was found not to be the case in this sample, as generally, changes in neither neural measure were significantly related to changes in psychosocial functioning. Using Hotelling's t-test to compare correlations, magnitudes of correlation did not differ between functional activation and ICA measures of coherence on their relationships with psychosocial measures (SSPA, SFS, and UPSA) or any measures of interest (all *p's*>.05). Therefore no conclusions could be drawn about whether an ICA or functional activation approach is a psychometrically better predictor of change in outcome. However, future studies may return to this question as techniques using both ICA and functional activation may continue to become more refined.

In an orthogonal analysis using ICA, I examined inter-connectivity between the time courses of the DMN and EN for each of the N-back tasks and the resting scans. Again, no group-by-time interactions were observed when accounting for movement during the task data. However, there was a significant interaction in the resting state data, wherein the CRT group decreased in interconnectivity while the CST group showed increases. Changes in the CRT group corresponded with reductions in psychiatric symptoms, which relates to previous findings showing that dysconnectivity in these networks is related psychiatric status in schizophrenia (Rotarska-Jagiela et al., 2010; Whitfield-Gabrieli et al., 2009). But despite this interesting finding, paired t-tests of the CRT group were not found to be significant, and rather the group by time interaction was being driven by significant un-hypothesized increases in interconnectivity in the CST group. These changes did not correspond with any measured behavioral change, ultimately detracting from the significance and overall interpretability of this finding. Even though these analyses controlled for subject motion, it is possible that they were still subject to spurious changes in correlation, and therefore it is difficult to draw reliable conclusions.

Overall, little could be concluded using the ICA approach, but perhaps warrants the need for using alternative methods. In an unreported analysis, I also examined whether the time course of task-derived components changed in their relationship to the N-back task. No significant results were observed using this method. As our laboratory continues to refine our methods for examining both coherence and interconnectivity

using ICA, I hope to potentially revisit these analyses to more clearly determine whether this method can offer insights into the neuroscience supporting CRT.

Study 4 Summary and Conclusions: Thalamocortical Connectivity

In light of the largely null findings from Study 3, I began looking into other connectivity methods and metrics. The thalamus and its widespread cortical connections has long been implicated in the pathophysiology of schizophrenia (Andreasen et al., 1998; Friston & Frith, 1995; Lewis, 2000; Pergola et al., 2015), and recent human and animal studies specifically identify reduced intrinsic thalamus-prefrontal connectivity as related to disruptions in cognition in schizophrenia (Duan et al., 2015; Parnaudeau et al., 2013; Sui et al., 2015). This offered a very clear target to measure with regards to intrinsic connectivity, and I hypothesized that CRT would selectively increase connectivity in these circuits. Specifically, I conducted a seed-based analysis to determine whether there were changes in connections from the thalamus to the middle frontal gyrus (MFG) and anterior cingulate cortex (ACC) – regions shown previously to have reduced thalamocortical connectivity (Anticevic et al., 2013; Welsh et al., 2010), and important roles in cognition.

Results from these analyses were consistent with my hypothesis, and showed increased connectivity in the CRT group between the thalamus and right MFG, and the thalamus and the ACC. Next I showed that increased connectivity in the thalamus-right MFG circuit correlated with improvements on overall MATRICS score (r=.55, p<.05). This is an exciting finding that warrants attention, as it demonstrates that a working

memory-focused CRT generalizes to influence intrinsic brain circuitry supporting improved cognition. I was interested to know whether improvements on the working memory domain of the MATRICS were driving this relationship, but this turned out not to be the case. In fact, verbal learning (r=.59, p<.05) and visual learning (r=.40, p=.15) appeared to be driving this relationship more so than working memory, which did not show significant improvement related to change in connectivity (r=.26, p=.37). It is unclear why a working memory-focused training would have had more influence on verbal and visual learning domains more than working memory itself, but does make a case for the ability of this domain specific CRT to have more distal generalization to other areas of cognition. It may also underscore the importance of using a working memory-focused CRT approach, as it is well known to have important contributions to cognition more globally (Engle, Kane, & Tuholski, 1999).

The next part of this study examined whether baseline measures of overall cognition corresponded to changes in thalamocortical connectivity. We observed trending negative relationships in both the right MFG and ACC, demonstrating that individuals with lower baseline cognition showed greater thalamocortical increases in response to CRT. This was in some ways surprising, as previous research has indicated that more cognitively intact individuals show a better response to CRT (Fiszdon, Choi, Bryson, & Bell, 2006; Fiszdon, Cardenas, Bryson, & Bell, 2005; Fiszdon et al., 2006; Kurtz, Seltzer, Fujimoto, Shagan, & Wexler, 2009). The current findings suggest that there is either something specific about thalamocortical connectivity that is particularly plastic in lower functioning individuals, or that by training in a single domain such as working memory

lower functioning individuals may show greater neuroplastic gains. Again, these are exciting results that will require replication and further investigation to determine the significance of these thalamus-prefrontal circuits and the role of a working memory-focused CRT to influence them.

Predicting Changes in Behavior and Neural Plasticity

A major thrust of the current dissertation was to determine whether changes in measures of cognition, psychosocial functioning, or symptomology were correlated with changes in neural functioning. We examined this question across a number of domains of neural functioning, but despite our initial hypotheses, results were largely mixed. The individual studies examined whether outcomes of interest coincided with changes on near transfer measures such as task performance, as well as more distal measures within the working memory and cognitive domain, including MATRICS Working Memory score, and MATRICS Overall score. Distal transfer measures were also examined, which included measures of functional capacity assessed with the UPSA, social capacity assessed with the SSPA, social and community functioning measured by the SFS, and overall psychiatric symptoms measured by the BPRS. These were examined in relation to changes on the observed neural outcomes of interest, which included functional activation change in the left DLPFC (Study 2), change in resting state interconnectivity between the DMN and EN (Study 3), and changes in thalamocortical connectivity between the thalamus and RMFG and ACC during rest, and the thalamus and ACC and LMFG during the picture n-back (Study 4).

The results of the correlations between change in neural activation and change in cognitive, psychosocial functioning, or symptoms are summarized in Supplementary Table 7.2a. These results indicate that broadly speaking, very few changes in neural functioning coincided with external measures of change. In two-tailed tests, change in left DLPFC activation showed a trend-level correlation with performance on the n-back alone, possibly indicating that functional activation is generally not a strong predictor of more distal measures cognitive or functional change. Comparatively, reductions in resting state interconnectivity significantly correlated with reductions in psychiatric symptoms (r=.55, p<.05), but also showed an unpredicted trending relationship with reduction in social functioning (r=.50, p=.05). Though these are arguably transfer measures that may speak to CRT's capacity to influence more distal measures of change, the correlation with SFS was in the unhypothesized direction, raising concern about whether measured inter-connectivity is truly coinciding with our construct of interest.

Arguably the most promising finding was from study 4, which showed that increases in connectivity between the thalamus and right MFG correlated with increases on overall MATRICS score. This would indicate that training working memory may generalize to improvements across domains of cognition, and might do so by way increasing thalamocortical connectivity. However, we did not observe a significant relationship between thalamocortical connectivity and the working memory domain score from the MATRICS, which is surprising given that this is the domain on which the CRT participants specifically trained. Again, this raises questions about this neural mechanism,

but maybe indicates that thalamus-PFC relationships more closely relate to overall cognition as opposed to working memory specifically.

The next goal was to determine whether baseline behavioral measures were predictive neural activation changes (Supplementary Table 7.2b). No baseline measure of interest was related to changes in functional activation in the left DLPFC ROI, however we did observe trend-level correlations between baseline MATRICS overall score and changes in thalamocortical connectivity at rest in the right MFG (r=-.52, p=.06) and ACC (r=-.51, p=.06), and in the ACC during the picture N-back task (r=-.49, p=.08). Interestingly, these were negative correlations, implying that lower baseline cognition corresponded to greater changes in connectivity following training. This could indicate that focused training in a single cognitive domain, in this case working memory, may be a particularly useful training strategy for patients who are more impaired prior to training. These individuals showed the largest neuroplastic gains in response to training, which could be valuable knowledge for treatment planning for patients with cognitive disruptions associated with schizophrenia.

Reductions in resting state inter-connectivity between the DMN and EN modestly related to baseline social capacity measured by the SSPA (r=.46, p=.10), and functional capacity measured by the UPSA (r=.50, p=.07). These findings also indicate that lower baseline scores on these laboratory measures corresponded to greater reductions in interconnectivity, and suggest that individuals with poorer psychosocial functioning prior to treatment could be more likely to show intrinsic connectivity changes. Again, this

could be useful for treatment selection, as those with poorer functioning may see greater neural changes in response to working memory-focused CRT.

I also examined whether baseline motivation measured by the Treatment Self-Regulation Questionnaire (TSRQ) was predictive of changes in functional activation. This measure is based on self-determination theory (Ryan & Deci, 2000) and uses self-reports to examine factors related to autonomous motivation, controlled motivation, amotivation, and perceived competence (Levesque et al., 2007). Only baseline amotivation was found to significantly correlate with changes in thalamus-RMFG connectivity during rest (r=.56, p<.05), which again may establish that this type of intervention is particularly useful for lower functioning and less motivated patients. However, no other measures of motivation significantly correlated with any of the other functional activation measures of interest (Supplemental Table 7.3), which may suggest that by and large, motivation is not the best predictor of changes in functional activation.

In Specific Aim 3b, I proposed that baseline modulation of neural activation in prefrontal areas would better correspond to improvements in cognition, psychosocial functioning, and symptomology, and that this measure would provide incremental benefit over and above baseline behavioral measures. These correlation values are summarized in Supplementary Table 8.2c, and only baseline resting state connectivity between the thalamus and right MFG was negatively correlated to change in social skill capacity measured by the SSPA (r=-.59, p<.05). This indicates that individuals with greater intrinsic disconnection between the thalamus and right MFG before training could be more likely to shower changes in social capacity following a working memory-focused

CRT. In comparison, baseline SSPA was also negatively correlated with change on this measure (r=-.55, p<.05), and though correlation with baseline thalamocortical connectivity was slightly stronger, the strength of these correlations did not statistically differ (*Hotelling's* $t(11)$=-.17, p=.58). This was contrary to my prediction that baseline neural measures could hold more predictive power than behavioral measures.

Many of the results summarized did not come out as predicted, but it is worth noting that these analyses were constrained by a very limited sample size, and would have required a robust correlation value (r=.51) to reject a two-tailed null hypothesis test (p<.05) uncorrected for multiple comparisons. This would necessitate that any of the given behavioral measures would need to explain a quarter of the variance in a neural measure, which is more than likely subject to a number of other factors. A more systematic approach might have sought to first identify which, if any of these measures, relate to neural functioning at baseline before determining whether training related changes influence them. This approach would not only cut down on the number of comparisons necessary, but also establish neural targets more specifically associated with behavioral measures. In addition, increased sample sizes in future studies will be important to draw definitive conclusions regarding transfer-related changes from CRT, as the current studies were likely underpowered.

Future Directions

The results outlined in this dissertation show a fair mix of null findings as well as promising new directions for the investigation of the neural underpinnings of CRT for

schizophrenia. As was previously stated, the meta-analytic findings from Study 1 offer a great starting point for future examinations of neural activation in response to CRT, and it is the hope that these results will guide future hypothesis tests. I also hope to continue to expand on these meta-analytic findings, adding new studies as they become available, making this a dynamic and ongoing investigation to understand neuroplasticity in CRT. A weakness of this meta-analysis is that there are not yet enough studies examining different types of CRT to say anything definitively about how different approaches might have different neural impacts. This will be an important question moving forward that could be examined meta-analytically, but also by systematically conducting similar fMRI analyses across datasets.

There are also outstanding questions about the specific aspects of CRT that might initiate neuroplastic changes. In the current studies we examined a working memory-focused training, but it is not known if the results we observed would be similar to that of other computerized CRT interventions, or whether this is special to the case of working memory-focused CRT. Meta-analytic findings seem to indicate that modest improvements are plausible regardless of training approach (Wykes et al., 2011), but there are likely differences in the neural systems being tapped or exercised. By better understanding the "active ingredients" of CRT, future interventions will be better equipped to target the appropriate neural mechanisms. For this reason, some of my future goals are to not only replicate these findings in related types of working memory-focused CRT, but also examine whether these kinds of changes could be observed in other types of training interventions.

The results of Study 2 were in many ways underwhelming, as we only partially replicated the findings of Haut and colleagues (2010), but there is potential significance of the observed changes in the left DLPFC. This could be an important region for continued research on CRT, given its long held prominence in both the pathophysiology of schizophrenia (Weinberger, Berman, & Zec, 1986) and cognitive control more broadly (MacDonald, 2000). It is possible that increased activation in the DLPFC could coincide with training initiated improvements that lead to improvements in top-down cognitive processing. Future studies may continue to examine this question more specifically.

Study 3 also faced a number of statistical and methodological challenges, and it may be important to revisit this data as we begin to refine methods for approaching and understanding ICA. One outstanding challenge with this dataset was due in part to the study design, in which the in-scanner n-back task switched between 2-back and 0-back trials. I have obtained a similar data set that examines 2-back and 0-back runs separately, which may make it amenable to future analyses using the currently outlined task-based ICA methods.

Study 4 sheds light on a thalamocoritcal mechanism that not only underlies the pathophysiology of schizophrenia, but could also be a critical neural target for CRT. Though it will require replication, this study provides a useful starting point for studies that might target specific neural mechanisms to influence cognition in schizophrenia. Methods relying on transcranial direct current stimulation (TDCS) as well as transcranial magnetic stimulation (TMS) may be able to target thalamus-prefrontal circuits to potentially maximize gains made with cognitive training. These non-invasive techniques

may prove to be important adjunct treatments for CRT, and future studies might pair these interventions to determine the feasibility of using these tools in tandem. We also observed that individuals with lower baseline cognition showed larger increases in functional connectivity in response to the working memory-focused CRT. This could have critical implications for treatment selection and implementation in schizophrenia, and future studies should examine more systematically whether this treatment could be especially useful for lower functioning individuals.

A final future goal addresses a long-held question in this field about whether cognitive and psychosocial gains from training are sustainable. CRT may have enduring influences that impact long-term outcomes, but the neural substrates supporting improvements beyond the acute training period remain unclear. It will be important to examine the subjects from the current studies after a year long follow up to determine whether changes in neural functioning after training may also predict long-term recovery. Future analyses with this dataset could examine whether changes in cognition or functioning coincide with changes in functional activation, functional coherence measured by ICA, or thalamocortical connectivity.

Tables:

Supplementary Table 7.1.

	Component	R (N-back)	*p*	R (MATRICS)	*p*	R (MATRICS WM)	*p*	R (SSPA)	*p*	R (SFS)	*p*	R (UPSA)	*p*	R (BPRS)	*p*
Animal	DMN (IC10)	0.19	0.53	0.02	0.95	0.42	0.15	0.35	0.25	0.21	0.48	0.11	0.7	0.005	0.99
	EN (IC16)	-0.02	0.95	0.03	0.91	-0.08	0.79	0.21	0.49	-0.18	0.57	-0.1	0.74	0.33	0.26
	EN (IC27)	0.02	0.94	-0.14	0.64	-0.02	0.94	0.1	0.75	0.35	0.24	0.001	0.99	0.54	0.06
Words	DMN (IC09)	0.31	0.27	0.28	0.33	0.03	0.92	0.4	0.15	-0.3	0.29	0.007	0.98	-0.12	0.69
	DMN (IC12)	0.2	0.48	0.18	0.54	0.02	0.93	0.45	0.1	-0.27	0.35	0.2	0.49	-0.14	0.61
	EN (IC31)	0.25	0.39	0.27	0.35	0.04	0.88	0.4	0.16	-0.19	0.52	0.29	0.32	-0.24	0.42
	EN (IC37)	0.14	0.63	-0.09	0.76	0.45	0.11	-0.39	0.17	0.06	0.83	0.05	0.85	0.04	0.88
Rest	DMN (IC04)	*NA*	*NA*	0.14	0.62	0.28	0.32	-0.09	0.75	0.34	0.22	-0.09	0.75	-0.12	0.68
	EN (IC11)	*NA*	*NA*	0.16	0.59	0.24	0.4	-0.03	0.91	0.44	0.12	-0.21	0.46	-0.23	0.43
	EN (IC39)	*NA*	*NA*	0.23	0.43	0.07	0.82	0.14	0.63	0.31	0.27	-0.08	0.77	-0.14	0.63

Supplementary Table 7.1 Note. Highlighted areas denote statistical trends or significance $p<.10$. Abbreviations: DMN=Default Mode Network, EN=Executive Network, MATRICS=MCCB Overall Score, MATRICS WM= MCCB Working Memory Domain Score, SSPA=Social Skills Performance Assessment, SFS=Social Functioning Scale Overall Score, UPSA=University of California, San Diego Performance-Based Skills Assessment, BPRS=Brief Psychiatric Ratings Scale Overall Score.

Supplementary
Table 7.2.

	Neural Activation Measure	R (N-back)	*p*	R (MATRICS)	*p*	R (MATRICS WM)	*p*	R (SSPA)	*p*	R (SFS)	*p*	R (UPSA)	*p*	R (BPRS)	*p*
7.2A) Change in Neural Activation v. Change in Behavior	Left DLPFC Functional Activation	0.45	0.1	-0.19	0.51	-0.06	0.84	0.05	0.87	-0.33	0.25	0.38	0.18	-0.01	0.97
	DMN v. EN Interconnectivity Rest	*NA*	*NA*	-0.16	0.59	-0.24	0.39	-0.32	0.26	0.5	0.07	-0.42	0.12	0.55	0.04
	Thalamocortical ACC ROI Rest	*NA*	*NA*	0.18	0.55	0.008	0.98	0.24	0.41	-0.21	0.47	0.13	0.65	0.3	0.3
	Thalamocortical RMFG ROI Rest	*NA*	*NA*	0.55	0.04	0.23	0.44	0.27	0.36	0.13	0.66	0.3	0.3	0.01	0.98
	Thalamocortical ACC ROI Animals	-0.31	0.28	0.07	0.81	-0.1	0.72	0.1	0.72	-0.03	0.91	-0.31	0.28	0.13	0.67
	Thalamocortical LMFG ROI Animals	-0.02	0.96	0.05	0.87	0.18	0.53	-0.26	0.36	0.31	0.27	-0.27	0.36	-0.02	0.96

	Neural Activation Measure	R (N-back)	*p*	R (MATRICS)	*p*	R (MATRICS WM)	*p*	R (SSPA)	*p*	R (SFS)	*p*	R (UPSA)	*p*	R (BPRS)	*p*	
7.2B) Pre-Treatment Behavior v. Change in Neural Activation	Left DLPFC Functional Activation	-0.26	0.37	-0.08	0.78	-0.17	0.57	-0.13	0.66	0.1	0.73	-0.45	0.11	-0.4	0.15	
	DMN v. EN Interconnectivity Rest	*NA*	*NA*	-0.004	0.99	-0.04	0.9	0.46	0.1	-0.36	0.21	0.5	0.07	-0.13	0.65	
	Thalamocortical ACC ROI Rest	*NA*	*NA*	-0.52	0.06	-0.38	0.18	-0.46	0.1	0.2	0.49	-0.29	0.31	0.07	0.82	
	Thalamocortical RMFG ROI Rest	*NA*	*NA*	-0.51	0.06	-0.38	0.18	-0.44	0.12	0.19	0.51	-0.39	0.16	-0.16	0.58	
	Thalamocortical ACC ROI Animals	-0.38	0.18	-0.49	0.08	-0.39	0.16	-0.55	0.04	0.15	0.6	-0.19	0.52	0.06	0.83	
	Thalamocortical LMFG ROI Animals	-0.07	0.81	-0.31	0.27	-0.34	0.23	-0.28	0.33	-0.09	0.77	-0.27	0.34	0.1	0.74	

	Neural Activation Measure	R (N-back)	*p*	R (MATRICS)	*p*	R (MATRICS WM)	*p*	R (SSPA)	*p*	R (SFS)	*p*	R (UPSA)	*p*	R (BPRS)	*p*
7.2C) Pre-Treatment Activation v. Change in Behavior	Left DLPFC Functional Activation	0.14	0.64	-0.13	0.67	0.21	0.48	-0.14	0.63	0.31	0.27	0.22	0.45	-0.1	0.71
	DMN v. EN Interconnectivity Rest	*NA*	*NA*	0.15	0.61	0.16	0.59	0.06	0.83	0.02	0.95	0.17	0.55	0.37	0.2
	Thalamocortical ACC ROI Rest	*NA*	*NA*	-0.11	0.72	0.2	0.48	-0.39	0.16	-0.36	0.21	-0.04	0.9	-0.3	0.3
	Thalamocortical RMFG ROI Rest	*NA*	*NA*	-0.14	0.63	0.42	0.14	-0.59	0.03	-0.35	0.21	0.003	0.99	-0.003	0.99
	Thalamocortical ACC ROI Animals	-0.22	0.46	-0.31	0.29	-0.15	0.62	-0.005	0.99	-0.32	0.27	-0.002	0.99	0.03	0.92
	Thalamocortical LMFG ROI Animals	-0.15	0.61	0.04	0.9	0.13	0.67	-0.27	0.36	-0.28	0.33	0.34	0.23	-0.15	0.61

Supplementary Table 7.2 Note. Highlighted areas denote statistical trends or significance $p<.10$. Abbreviations: DMN=Default Mode Network, EN=Executive Network, MATRICS=MCCB Overall Score, MATRICS WM= MCCB Working Memory Domain Score, SSPA=Social Skills Performance Assessment, SFS=Social Functioning Scale Overall Score, UPSA=University of California, San Diego Performance-Based Skills Assessment, BPRS=Brief Psychiatric Ratings Scale Overall Score.

Supplementary Table 7.3

	Autonomous Motivation	Controlled Motviation	Amotivation	Perceived Competence
Left DLPFC Functional Activation	.11(.71)	-.02(.96)	.44(.12)	.25(.39)
DMN v. EN Interconnectivity Rest	.07(.77)	-.09(.75)	.06(.84)	.05(.86)
Thalamocortical ACC ROI Rest	.37(.19)	.17(.56)	.30(.30)	-.20(.50)
Thalamocortical RMFG ROI Rest	.01(.99)	-.02(.93)	.56(.04)	.01(.96)
Thalamocortical ACC ROI Animals	.36(.21)	.18(.54)	.46(.10)	.11(.72)
Thalamocortical LMFG ROI Animals	-.004(.99)	-.02(.96)	.44(.12)	.25(.39)

Supplementary Table 7.3 Note. Highlighted areas denote statistical trends or significance $p<.10$.

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