A Pilot fMRI Study of the Effects of Cognitive Remediation on Brain Activation Associated with Working Memory in Patients with Schizophrenia

by

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Class of 2012

A thesis submitted to the faculty of Wesleyan University in partial fulfillment of the requirements for the Degree of Bachelor of Arts with Departmental Honors in Neuroscience & Behavior

Middletown, Connecticut April, 2012
Table of Contents

Acknowledgements ............................................................................................................................ 2
Abstract .................................................................................................................................................. 3
Introduction ........................................................................................................................................... 4
  Definition of Illness .............................................................................................................................. 4
  Symptomatology ................................................................................................................................. 5
  Onset and Prevalence .......................................................................................................................... 8
  Cause .................................................................................................................................................. 8
  Prognosis ............................................................................................................................................ 9
Working Memory ..................................................................................................................................... 10
fMRI ...................................................................................................................................................... 11
Cognitive Remediation .......................................................................................................................... 12
Methods .................................................................................................................................................. 16
  Participants ......................................................................................................................................... 16
  Serial Position Task .............................................................................................................................. 17
  Procedure .......................................................................................................................................... 20
  Imaging Parameters ............................................................................................................................. 21
Results .................................................................................................................................................... 23
Discussion ............................................................................................................................................... 24
Future Directions ................................................................................................................................. 30
References ............................................................................................................................................. 31
Figure 1: SPT Schematic ......................................................................................................................... 36
Table 1: Regions of Interest ................................................................................................................... 37
Figures 2, 3, and 4: Activation Maps ...................................................................................................... 38
  Encode Phase (2a) ............................................................................................................................... 38
  Rehearse Phase (3a-d) .......................................................................................................................... 39
  Response Phase (4a-f) ......................................................................................................................... 43
Acknowledgements

The following thesis was made possible by a host of people who have guided and supported me throughout the previous months. I would like to thank my advisor, Professor Matthew Kurtz, for his guidance, knowledge, support, encouragement, and upbeat personality. From our first encounter in my freshman year he has inspired me with his love of neuroscience and the study of schizophrenia. In addition, I would like to acknowledge the aid provided by Krishna Pancholi at the Institute of Living for the hours she has devoted to teaching me the skills necessary to analyze my data. I would also like to thank my family for their continuous support in my studies and every other facet of my life. A special thanks is necessary for my mother who has devoted many hours to enthusiastically reading my work and supporting all of my endeavors.
Objective: To determine changes in functional brain activation during a working memory task in patients with schizophrenia after undergoing cognitive remediation (CR).

Methods: A total of 5 participants with schizophrenia received a 12-month course of cognitive remediation. Participants underwent fMRI imaging during an administered working memory task, the serial position task (SPT), before and after CR treatment. The encoding, rehearsal, and response phases of the SPT were analyzed separately using whole brain analysis.

Results: Cognitive remediation treatment was associated with an increase in activation in the left middle frontal gyrus during the encoding phase, and in the right cuneus of the occipital lobe, right lingual gyrus (Broca’s Area 18), left cingulate gyrus, and the right fusiform gyrus during the rehearse phase. There was found to be a decrease in activation in the left sub-gyral region of the temporal lobe, left middle temporal gyrus (Broca’s Area 21), right precuneus (Broca’s Area 39), right middle frontal gyrus (Broca’s Area 6), left cuneus, and left parahippocampal gyrus (Broca’s Area 35) during the response phase.

Conclusion: In agreement with previous findings, cognitive remediation does indeed have an affect on brain activity over time. Through cognitive training, patients with schizophrenia displayed both increased and decreased activation in brain regions associated with the three phases of working memory in order to select the correct response during a working memory task.
**Introduction**

**Definition of Illness:**

The neuropsychiatric disorder known as schizophrenia is a widespread phenomenon that affects millions of people around the globe, approximately 24 million in the latest estimate provided by the World Health Organization (2012). To place schizophrenia in a more familiar perspective, estimates have been made that “about 1 person in 100 may experience this disorder at some time in their lives,” which is a risk comparable to that of developing rheumatoid arthritis (Frith & Johnstone, 2003). Historically the disorder itself was characterized by abnormalities in the perception of reality and was first medically classified as early onset dementia (dementia praecox) by Benedict Morel in 1860. Moving beyond this general categorization, Emil Kraepelin, a German psychiatrist, classified schizophrenia based on outcome under Morel’s term of dementia praecox, recognizing the chronic nature of the disorder. As such, schizophrenia was viewed as having a separate neuropathology compared to other forms of psychosis. The modern term of schizophrenia (Greek root “split” “mind”) that is used today was coined around the same time by the Swiss psychiatrist Eugen Bleuler. Not to be confused with a description of a split personality, Bleuler meant to convey a “loosening of the associations between the different functions of the mind so that thoughts became disconnected and coordination between emotional, cognitive, and volitional processes became weaker” (Frith & Johnstone, 2003). Today, schizophrenia has been subject to more stringent forms of classification and diagnosis, which is mostly compiled in the
fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The DSM-IV defines schizophrenia as the following:

A disturbance that lasts for at least 6 months and includes at least 1 month of active-phase symptoms (i.e., two or more] of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms) (1994).

Additionally, the DSM-IV also recognizes five schizophrenia subtypes, which includes paranoid, disorganized, catatonic, undifferentiated (prominent active phase symptoms not included in the previous three subtypes), and residual (continued disturbance, but with a lack of active phase symptoms). These subtypes are time based, where the patient’s diagnosis relies on what is observed as the most prominent feature at that time. Of those suffering from schizophrenia, typical symptoms include a spectrum of cognitive and psychiatric complaints that affect “perception, inferential thinking, language and communication, behavioral motorizing, affect, fluency and productivity of thought and speech, hedonic capacity, volition and drive, and attention” (DSM-IV, 1994). However, it is critical to understand that schizophrenia is not defined by a single symptom, but is instead diagnosed based on an array of symptoms along with impairments in social functioning.

Symptomatology:

Persons affected by schizophrenia display a distinct set of symptoms that can be subdivided into the three categories of positive, negative, and cognitive symptoms. Positive symptoms are classified as a marked increase in or distortion of normal
functioning and are not typically expressed in the healthy population. Positive symptoms can be further subdivided into those with psychotic or disorganized dimensions. Psychotic symptoms include delusions and hallucination, while disorganized symptoms include disorganized speech and behavior (DSM-IV, 1994). Schizophrenia involves hallucinations in any of the five sensory systems (auditory, visual, olfactory, gustatory, and tactile); various auditory hallucinations are the most common, followed by tactile and visual. Delusions, a false belief stemming from a misinterpretation of perceptions or experiences, may take on any number of themes in schizophrenia with the most common being persecutory in nature; other common delusions involve religious and grandiose themes, or are referential and somatic in nature. Disorganized thought is generally assessed through disorganized speech and what has been labeled as a ‘loosening of associations.’ Finally, disorganized behavior is defined by gross disruptions in normal functioning, which can manifest as catatonic motor behaviors where patients may sit or stand immobile for significant durations of time.

Negative symptoms are a decreased deviation from normal behaviors and typically include flattened affect, social withdrawal, blunted speech (alogia), blunted emotion, anhedonia, and apathy/avolition (DSM-IV, 1994). Care providers and researches have adopted the PANSS (positive and negative symptom scale) as a means of standardizing patient symptom assessment and “as an operationalized, drug-sensitive instrument that provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology” (Kay et al., 1987). The PANSS hold widespread use and support in
the clinical and research community and has been augmented over the years to better assess patient symptoms (Fredrikson et al., 1997).

The scientific community’s understanding of schizophrenia is constantly under reform. What was once thought of as a disorder dominated by only positive and negative symptomatology has been amended to recognize deficits in cognition as an independent symptom and included as an integral element of the disorder. It has been well documented that deficits in cognition are a “core feature” of schizophrenia and as such demands further inquiry as to how cognition can be utilized to better understand and treat this mental illness. In today’s clinical setting many patients have greatly benefited from the introduction of antipsychotics and other medications. However, these medications only go so far as to mostly alleviate the patient’s positive symptoms (Harvey & Keefe, 2001). Thus, cognitive decline persists along with negative symptoms and is of concern considering that cognitive deficits are linked to the functional future outcome of the patient (Green et al., 2004; Kraus and Keefe, 2007). In addition, the underlying issues of cognition can be seen years before a patient’s first psychotic episode and many studies have been conducted finding correlations to cognitive deficits in patient’s family members (Horan et al., 2008). Cognition has been shown to be impaired in patients with consistently lower performance compared to healthy controls in working memory, attention, problem solving, verbal and non-verbal memory, language, and processing speed (Mesholam-Gately et al., 2009).
Onset and Prevalence:

The onset of schizophrenia has been typically recorded as occurring “between the late teens and the mid-30’s, with onset prior to adolescence rare” (DSM-IV, 1994). Late-onset schizophrenia is also rare, and includes a higher ratio of women, more prominent mood symptoms, and a better prognosis (DSM-IV, 1994). It is important to note that findings differ in the incidence of schizophrenia between the sexes due to discrepancies in data collection and definition; often hospital based studies point to a higher rate of male patients, while equal sex ratios are seen in community based studies (DSM-IV, 1994). The age of onset also generally differs between sexes, whereas “the median age at onset of the first psychotic episode” occurs about five years later in females (DSM-IV, 1994). Apart from the first expression of positive symptoms, negative and cognitive symptoms are generally displayed earlier at various levels of disturbance. Depending on the mode of data collection and criteria, lifetime prevalence rates have been estimated at 0.5-1%; however, due to the chronic nature of the disorder “incidence rates are considerably lower than prevalence rates and are estimated to be approximately 1 per 10,000 per year” (DSM-IV, 1994).

Cause:

The cause of schizophrenia remains unknown. Schizophrenia is an extremely complex disorder that is comprised of multiple features. Recent advancements in genetic and neurobiological research have lead to the understanding that schizophrenia has a significant genetic link (Bray et al., 2010). The literature has
largely agreed that schizophrenia is a polygenic disorder, in which “variants in multiple genes that are individually insufficient to cause the illness […] act in combination and with environmental factors to increase the risk of its development” (Bray et al., 2010). Patterns of familial inheritance have been well documented, displaying the increased risk of developing schizophrenia especially between first-degree relatives and twins (Keshavan et al., 2009). However, such findings as those found in monozygotic twins also point to the importance of environmental factors (Sullivan, Kendler & Neale, 2003). Multiple studies exist on the topic of environmental induction/exacerbation, including risk due to prenatal environment and recreational drug exposure later in life (Brown et al., 2004; Susser et al., 1996; Hambrecht & Häfner, 1995).

**Prognosis:**

While the exact course of the disorder varies for every individual, it remains clear that schizophrenia is a life-long illness. Remission in terms of a complete return to premorbid functioning is extremely unlikely if not nonexistent; however some patients can be stabilized to a degree with current medical treatments, while many patients experience a worsening and disabling decline of functional abilities. Currently various antipsychotic medications have been a key tool in treating schizophrenia; unfortunately, while these medications often display a significant reduction in positive symptoms, negative and cognitive deficits have proven to be less responsive to treatments (Evans et al., 2004). As such researchers have turned to non-medicine based treatments, such as CR, in order to address such shortcomings. A
better prognosis is sometimes associated with “good premorbid adjustment, acute onset, later age at onset, being female, precipitating events, associated mood disturbance, brief duration of active-phase symptoms, good inter-episode functioning, minimal residual symptoms, absence of structural brain abnormalities, normal neurological functioning, a family history of mood disorder, and no family history of schizophrenia” (DSM-IV, 1994). In general, the average lifespan of persons diagnosed with schizophrenia is about 15 years lower than that of the general population, a statistic that is accompanied by a higher than average suicide rate and a high prevalence of smoking and obesity related pathologies and the effects of long term use of antipsychotics (DSM-IV, 1994).

Working Memory:

Working memory itself is defined as the ability to hold and manipulate information for short periods of time (Baddeley, 1992). Mirroring the phases of the SPT, working memory is commonly divided into three epochs: encoding, maintenance, and response (Meda et al., 2008). Working memory has been further defined through two main subsystems used for the maintenance of information: the visuospatial sketchpad, which maintains visuospatial images, and the phonological loop, which “is specialized for processing verbal material and is composed of two subsystems: a phonological store and an articulatory rehearsal process” (Salmon et al., 1996). The final response phase can be described as an episodic memory retrieval, which is defined as the cognitive operations needed for conscious retrieval of
“information about recently experienced events and the spatial and temporal contexts in which they occurred” (Rugg & Henson, 2003).

**fMRI:**

The use of functional magnetic resonance imaging (fMRI) in the study of schizophrenia is a relatively new advancement in the search for answers to one of the most enigmatic disorders. Past imaging techniques solely examined structural abnormalities in patients with schizophrenia and have generally concluded the presence of enlarged ventricles, increased basal ganglia size, and decreased temporal lobe, hippocampus, and cerebral size (DSM-IV, 1994). The introduction of fMRI as a tool in schizophrenia research is of importance as it allows for multiple scanning sessions unlike PET and SPECT, which expose the subject to ionizing radiation (Frith & Johnstone, 2003). Furthermore, the utilization of fMRI comes with many other advantages, namely, higher spatial resolution, noninvasive procedure, direct correlation with anatomical imaging, greater repeatability, feasibility in children, and affordability (Gur and Gur, 2010). However, it is also important to note that the use of fMRI does hold some disadvantages, such as a loud noise production during scanning, need to adapt stimulus presentation and recording of performance to the magnet bore setting, low signal-to-noise ratio, lack of quantitation in physiologic units for the most abundant methods, and the exclusion of individuals that have metal in their bodies or are claustrophobic (Gur and Gur, 2010). In addition, fMRI is a technique that provides a time relative representation of brain activation in a subject and can be paired with an array of tasks; the temporal resolution of fMRI is measured
in relation to the time frame of the hemodynamic response (2-16 seconds), versus minutes in other imaging methods (Gur and Gur, 2010).}

The activation data collected is a reflection of detected changes in blood oxygenation levels. These levels in turn are mirrors of changes in blood flow to a region when it is in use by the subject. The machine itself utilizes strong magnets, due to the susceptibility of deoxyhemoglobin to magnetic fields, and sensors that are sensitive to regional signal changes; the produced BOLD (blood oxygenation level-dependent) signal is thus able to be viewed as a direct representation of task related increases in regional oxygenated blood flow that exceeds regional oxygen consumption (Gur and Gur, 2010). An essential goal of fMRI based schizophrenia studies has been to demonstrate how failure to activate (or in some cases deactivate) a given neural system leads to behavioral deficits in patients. This particular study aims to determine regions of activation or deactivation that reflect working memory deficits common to patients with schizophrenia.

**Cognitive Remediation (CR):**

As previously described, the presence of cognitive deficits is a core feature of schizophrenia and has numerous detrimental effects on a patient’s ability to function in everyday life. While these cognitive deficits have been resistant to medical interventions, a set of cognitive exercises has been used in an attempt to improve cognitive functioning in affected areas. Specifically, CR consists of repeated drill-and-practice computerized training in attention, memory (both verbal and non-verbal), language, and problem solving in order to recover neurocognitive functions,
ameliorate symptoms, and increase life functioning (Kurtz et al., 2007; Kurtz et al., 2009).

Literature findings using imaging techniques to identify the neural effects of cognitive remediation (CR) on patients with schizophrenia have emerged over the last decade. In a study by Wexler et al. (2000) a ten-week CR training period was utilized, after which it was found that three of the eight patients in this study displayed marked improvement in verbal, but not non-verbal memory. A significant increase in task-related activation in the left inferior frontal cortex (p<0.04) was found in relation to the implemented word based serial position task.

Following these findings Wykes et al. (2002) built upon the procedure and tested three groups of participants (patients receiving CR, patients receiving a control therapy, and a healthy control group) using an n-back task. In accordance with their hypothesis, healthy controls decreased activation, while the two patient groups showed an increase in activation, especially in regions associated with working memory (and particularly the frontocortical areas) after CR intervention. Importantly, these increases in activation correlated with successful performance were hypothesized to be linked to increases in concentration and attention due to the implemented cognitive training and were observed in conjunction with increases in activation in the visual cortex (Wykes et al., 2002). This study was particularly important as it was the first study to show that “brain activation changes can be associated with psychological rather than pharmacological therapy” (Wykes et al., 2002). Compared to healthy controls and baseline there was a significant increases in FPQ (fundamental power quotient, which is the power of the response divided by its
standard error) in the right inferior frontal gyrus (BA=47), right occipital cortex (lingual gyrus) (BA=18), and left occipital cortex (lingual gyrus) (BA=18). The control therapy group showed an increase in the left orbitofrontal cortex (BA=10) and right frontal cortex (BA=11). The healthy controls showed significant decrease in activation in the left inferior/middle gyrus (BA=46), right frontal cortex (BA=11), right inferior frontal gyrus (BA=47), and right insula/inferior frontal (BA=47).

Furthermore, of the patients that improved on tests of neuropsychological memory measures there were changes in the right prefrontal cortex (BA=47), left anterior temporal pole (BA=38), hippocampus (BA=30/19), right post-cingulate gyrus (BA=31), and right primary visual cortex (18).

In a recently published study by Subramaniam et al., (2012) the focus turned toward impaired reality monitoring—ability to distinguish internal from external experiences—seen in patients with schizophrenia. Such dysfunction of reality monitoring is linked to abnormal decreases in activation in the medial prefrontal cortex and was ameliorated with computer-based training. These findings were compared to a control group of patients, which saw no behavioral or neural improvements. Thus, cognitive training was shown to induce “normalization” of patients’ brain-behavior associations, specifically with an increase in activation in the medial prefrontal cortex (FEW p<0.05) in parallel with better performance on self-generated vs. presented word identification tasks. It is also important to note that of those patients showing an increase in medial prefrontal activation displayed improved real world social functioning in a six-month follow-up test.
Apart from activation based fMRI studies, structural findings have contributed to the cognitive remediation discussion as deficits in memory and executive function in patients with schizophrenia correlate with “frontotemporal dysfunction and gray matter loss in the prefrontal cortex, anterior cingulate, hippocampus, and superior temporal gyrus” (Eack et al., 2010). Moreover, dysregulation in perspective taking, emotion perception, and foresight have been linked to abnormalities in medial temporal and medial frontal brain networks including the amygdala, fusiform gyrus, and orbitofrontal cortex (Eack et al., 2010). Changes in brain morphology following cognitive remediation included gray matter differences (decelerated loss and/or increase in gray matter volume) in the left medial temporal lobe, specifically the amygdala, parahippocampal gyrus, hippocampus, and fusiform gyrus. Furthermore, decelerated loss of volume in the left parahippocampal and fusiform gyrus, and increases in volume in the left amygdala were related to improved cognition over a 2-year period.
**Methods**

**Participants:**

The study included five (3 males) clinically-stable outpatients with schizophrenia or schizoaffective disorder. Diagnosis was confirmed by the patient form of the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon,, & Williams, 1995). All participants included in this study were recruited from the Institute of Living in Hartford, Connecticut. Patients were admitted for testing and evaluation regardless of sex, race, or age. Exclusion criteria for all potential participants were: (a) known neurological disease, (b) developmental disability, (c) current substance abuse, (d) mental retardation as evidenced by a history of services, (e) lack of fluency in English, or (f) history of serious neurological or endocrine disorder, including head trauma or epilepsy. All patients provided written informed consent and all procedures met institutional ethical review. Participants were screened for MRI compatibility before entering the scanning room. All participants were paid in compensation for their time and cooperation in the study. Data for this study was collected at entry to an ongoing study of the effects of cognitive remediation on cognitive and social dysfunction in people with schizophrenia (Kurtz et al., 2007). In addition, all five of these patients were on atypical antipsychotics during the time of the study. Patient age pre- and post-training ranged from 19 to 47 (Mean=31.8, SD=13.61) and from 20 to 48 (M=32.6, SD=13.67) respectively. Age of onset of illness ranged from 14 to 26 (M=21, SD=5.85). Also, illness duration spanned 1 to 21 years (M=4, SD=7.5). Note that data on one patient was not included for age of onset and illness duration as this information was missing.
Serial Position Task:

The serial position task (SPT) was selected as an appropriate measure of working memory. Through this task it was possible to examine and compare activation in various stages of the task, such as encoding of the stimuli, rehearsal during a brief delay, and response to a probe stimulus. During the task the subjects were shown a set of three words in succession over a six second interval, which comprised the encoding phase; after which the subject was allowed rehearse for a total of nine seconds. In the final phase of the task the subject was presented a chosen target word from the previously shown set. The chosen target word from the three-word set held an equal probability of being from each of the possible positions. During a three second period the subject was tasked with identifying the position of that target word. (See Figure 1 for a diagram of the task.) This response was entered on a keypad by the subject’s right index finger, with the first/second/third key corresponding to the word position. The SPT was chosen to be employed in this study due to its greater demand on temporal ordering compared to other tasks in the literature such as the n-back task and Sternberg task.

Patients were trained over a twelve-month period with a target of 100 hours of training, and with increasingly difficult goals in response to improvements in performance (starting goals were set at a level of total patient success). The components of the standardized cognitive remediation included the following tasks as described in Kurtz 2007:

Simple Visual Reaction Time (Bracy, 1995) The participant was asked to respond as quickly as possible by single-clicking a computer mouse whenever a
yellow-square was presented on the computer screen. The task was made more difficult by varying the size of the square (large or small) and its location (fixed or random). This exercise was targeted at sustained attention and response time.

Simple Auditory Reaction Time (Bracy, 1995) The participant was asked to single-click on the computer mouse as quickly as possible whenever a tone was presented. This exercise was targeted at sustained attention and response time as well.

Simple Choice Reaction Time Visual (Bracy, 1995) The participant was asked to respond as quickly as possible by single-clicking a computer mouse whenever a yellow- square was presented. The participant had to inhibit responding whenever a blue square was presented. This exercise was targeted at sustained attention, response time and response inhibition.

Simple Choice Reaction Time Auditory (Bracy, 1995) The participant was asked to respond as quickly as possible by single-clicking a computer mouse whenever a high- pitched tone was administered. The participant must inhibit responding whenever a low- pitched tone was played. This exercise was targeted at sustained attention, response time and response inhibition.

Progressive Attention Training-Respond to a Selected Color (Loong, 1988) The participant was presented a series of playing cards and asked to press the space bar whenever a red card was shown. The level of difficulty was modified by varying the duration of stimulus exposure. This exercise targeted sustained visual attention and response inhibition.

Progressive Attention Training-Alternate Black and Red by a Signal (Loong, 1988) The participant was presented with a series of playing cards and asked to
respond whenever the color of the card was black. Every 10–15 cards the word “change” was presented at the top of the screen and the participant was asked to shift the response rule from black cards to red cards. Level of difficulty was modified by varying stimulus-exposure time. This exercise targeted sustained visual attention, response inhibition and set-shifting.

**Sequenced Recall Digits Auditory (Bracy, 1995)** The participant was orally presented with a series of 2 to 10 digits. The participant was then asked to select the numbers, in the order they were presented, from a list of numbers located at the bottom of the computer screen. This exercise was targeted at auditory attention and memory.

**Sequenced Recall Digits Visual (Bracy, 1995)** The participant was presented with a series of 2 to 10 digits displayed serially on the computer screen. The participant was then asked to select the numbers in the order that they were presented from a list of numbers at the bottom of the computer screen. This exercise was targeted at sustained visual attention and memory.

**Sequenced Recall Words Visual (Bracy, 1995)** The participant was presented with 2 to 10 words on a computer screen. After a study period the participant was asked to select the studied words from a list of 16 words in the same order that the studied words were presented. This exercise was targeted at memory for verbal material and serial position.

**Verbal Memory Categorizing (Bracy, 1995)** The participant was asked to sort a series of 20 words into four semantic categories. After sorting, the words were removed from the screen and the participant was asked to select the 20 studied words
out of a list containing both the 20 target words and distractor items. Task difficulty was manipulated by increasing the delay period between study and recall. This exercise was targeted at semantic processing and verbal memory.

**Speed Reader** The participant was asked to read and remember a narrative presented on the computer monitor, typically several paragraphs in length. Reading comprehension questions were then administered immediately after presentation of the passage. Task difficulty was modified by the speed of presentation of the passages (in words-per-minute). This exercise trained language processing speed.

**Procedure:**

Two runs of stimuli were presented to the participant with a custom visual and auditory presentation package (VAPP; [http://www.psychiatry.ubc.ca/sz/nilab/software/vapp](http://www.psychiatry.ubc.ca/sz/nilab/software/vapp)) that precisely controls stimuli presentation and synchronization with the MR scanner. Participants were told that they would be shown a series of three words followed by a period in which they were to rehearse the presented words. In the last phase of each trial participants were told that they would be shown one of the three words, which will be references as the target word. Participants were instructed to respond as quickly and as accurately as possible with their right index finger on the first key if the first word was presented, the second key if the second word was presented, etc. The probability a probe item was presented first, second, or third in the word list on each trial was equal. Prior to beginning the task, each participant performed a practice block of 2 trials to ensure understanding of the instructions. Word items for the task were monosyllabic and
were selected only if they were within 1 SD of ratings of pleasantness and concreteness from the norms of Toglia and Battig (1978). A commercially available MRI compatible fiber-optic response device co-designed by one of the co-authors (KAK; Lightwave Medical, Vancouver, BC) was used to acquire behavioral responses. Stimuli events and behavioral responses were time-locked to scanner data acquisition timings using software run on a separate PC. Reaction times were computed on trials for which the participant responded correctly within 3,000 ms post-stimulus. Thus, omission errors included without any response or with latencies greater than 3,000 ms following the onset of the recognition stimulus. A schematic diagram of the task is presented in Figure 1.

**Imaging Parameters:**

**fMRI Data Acquisition:**

Data was acquired at the Olin Neuropsychiatry Research Center on a Siemens Allegra 3T scanner (Siemens, Erlangen, Germany) using a gradient-echo-planar sequence with repetition time (TR)=1500msec, echo time (TE)=27msec, field of view (FOV)=22cm, flip angle=60 degrees, acquisition matrix=64x64, voxel size=3.44mmx3.44mm, slice thickness=4mm, spacing between slices =5mm, and number of slices=29.

**fMRI Image Analysis:**

**Data Preparation:** FMRI images were preprocessed using Statistical Parametric Mapping (SPM8 [www.fil.ion.ucl.ac.uk/spm/software/spm8/]), running in MATLAB 7.1 (MathWorks, Natick, Massachusetts) on a Linux platform. The first six
images of each time series were removed to compensate for saturation effects. Images were realigned using INRIAlign and normalized to standard echo-planar-image (EPI) template in Montreal-Neurological-Institute (MNI) space available in SPM8. A gaussian kernel of 8mm full-width half-maximum (FWHM) was used to smooth images after normalization. Data were re-sampled at 3x3x3mm.

**fMRI Statistical Comparisons: Serial Position Task:** The two stimulus runs lasted 582 seconds during which 194 volumes of the brain were collected. Each run was prefaced by a 12-second rest period that was collected to allow for $T_1$ effects to stabilize. These initial four volumes were not included in any subsequent analyses. Contrasts were specified that evaluated changes in activation longitudinally for the five participants in the cognitive remediation group; contrasts were generated for the three main phases (1) encoding phase, (2) rehearsal interval, and (3) response phase across the two time points. For the response phases only scan data during correct responses were used. In order to reduce the impact of spatially varying hemodynamic delays and delays due to slice timing differences, the true amplitude of the hemodynamic response, which is a function of both the non-derivative and derivative terms, was calculated (Calhoun et al., 2004). The images containing these amplitudes were then entered into the second level analysis (i.e., random effects analysis). The uncorrected threshold $p<.001$ was utilized for all analysis in light of the preliminary nature of the work and the goal of identifying key regions of remediation for future studies with larger sample sizes. Additionally, the analysis was conducted without the use of covariates for sex and age, as the sample size did not allow for it.
Results

Longitudinal Findings:

Analysis of activation during the three phases of the working memory task comparatively in patients pre- and post-training with cognitive remediation tasks yielded several findings (Table 1). During the encoding phase there was a significant increase in activation in the left middle frontal gyrus following training (Figure 2). Furthermore, there was found to be an increase in rehearse phase activation post-cognitive training in the right cuneus of the occipital lobe, right lingual gyrus (Broca’s Area 18), left cingulate gyrus, and the right fusiform gyrus (Figures 3a-d). During the response phase (in which a correct response was given) there was found to be a deactivation in the left sub-gyral region of the temporal lobe, left middle temporal gyrus (Broca’s Area 21), right precuneus (Broca’s Area 39), right middle frontal gyrus (Broca’s Area 6), left cuneus, and left parahippocampal gyrus (Broca’s Area 35) following cognitive remediation (Figures 4a-f).
Discussion

The literature on cognitive deficits and a corresponding reduction in activation in key neural regions during cognitive tasks administered in fMRI paradigms in schizophrenia has been well documented. However, to date there have been few fMRI-based studies investigating the effects of cognitive training on brain activation during working memory tasks. As such this study augments existing knowledge and results in the field. In addition, few studies have divided working memory into the three subcomponents of encode, rehearse, and response, and thus this study will be valuable in its ability to provide insight into activation changes during the distinct phases. Furthermore, the field of cognitive remediation to date has provided limited literature, especially in conjunction with fMRI data, and this study’s results will serve to increase a growing body of evidence in the debate on the effects of cognitive training.

The longitudinal results for areas of activation and deactivation in the group of five (3 males) patients with schizophrenia were divided into the three previously defined phases of working memory. Note that due to group size constraints and the analysis software used, the longitudinal data was generated without covariance for age and sex. The findings for changes in regional activation for the encoding phase have reflected similar findings in the literature. This study found an increase in activation in the left middle frontal gyrus following cognitive remediation training. Previous studies have specifically identified the frontality of working memory. Activation in the frontal cortex has been associated with “a search for relevant
information strategies that make the task simpler (or less effortful) to complete” (Wykes et al., 2002). Specifically the prefrontal cortex, of which the middle frontal gyrus is a component, has been a common thread in almost all working memory studies (Meda et al., 2008). It has been widely accepted that compared to healthy controls, patients with schizophrenia express marked hypofrontality during tasks of working memory (Wykes et al., 2002; Callicott et al., 1999). Therefore, a possible explanation for the observed increase in activation post cognitive remediation is that the patients are compensating for their deficit through increased activation. In order to complete the task successfully it appears that patients with schizophrenia must employ more resources in the prefrontal (namely middle frontal gyrus) cortex, as replicated in other studies (Wykes et al., 2002). Thus, it is possible to argue that deficits in memory can be improved through cognitive exercise that approaches the pattern of task-related activation seen in the healthy brain—specifically in the left inferior frontal gyrus and left lateral orbital gyrus (Wexler et al., 2000). Furthermore, restoration of function in the medial prefrontal cortex following cognitive training has recently been shown to improve both “self referential cognition” and long term social functioning and quality of life (Subramaniam et al., 2012). Subramaniam has also referenced that by first targeting lower-level processes CR is able to “increase the accuracy, the temporal and spatial resolution, and the signal strength of auditory and visual inputs to working memory and executive functions, ultimately increasing the efficiency of more complex, higher-level cognitive processes in an enduring manner” (2012).
In addition to an increase in activation after undergoing treatment, the cognitive remediation group also displayed an increase in activation in several regions during the rehearsal phase. The regions that were activated post-treatment included the right cuneus of the occipital lobe, right lingual gyrus (Broca’s Area 18), left cingulate gyrus, and the right fusiform gyrus. Cognitive remediation therapies have been documented to improve rehearsal-based strategies, which is of particular importance in working memory tasks; in particular the vision related regions of the brain have been associated with “an improvement in using visual processing strategies in addition to verbal rehearsal” (Wykes et al., 2000). Furthermore, this visual processing has been established in the literature for some time as the visuospatial sketchpad, which can be subdivided into a dorsal stream (occipital-parietal) and ventral stream (occipital-temporal) (Muller and Knight, 2006). The findings of this study follow such logic to a degree; one can suggest that an increase in activation in the cuneus is an attempt to modulate basic vision processes in order to compensate for attention deficits. In addition, Broca’s Area 18 and the fusiform gyrus are both components of the ventral stream. The final area that saw increased use after cognitive remediation during the rehearsal phase was the left cingulate gyrus. This area has been associated with a wide range of functions and has been “implicated in different tasks that require selective attention, significant processing capacity, attention for action, or even preparation and initiation of movement” (Salmon et al., 1996). In reference to the fusiform gyrus, recent morphological findings have specially identified this region as benefiting from cognitive remediation through a
decrease in chronic gray matter loss and hence improved cognition (Eack et al., 2010).

Unlike what was observed in the encode and rehearse phases, the response phase saw deactivation post-cognitive training. The implicated areas included the left sub-gyr al region of the temporal lobe, left middle temporal gyrus (Broca’s Area 21), right precuneus (Broca’s Area 39), right middle frontal gyrus (Broca’s Area 6), left cuneus, and left parahippocampal gyrus (Broca’s Area 35). Currently there have been little studies that focus on the final retrieval phase of a working memory task in patients with schizophrenia. However, general studies on retrieval processes have consistently noted activity in the dorsolateral and anterior prefrontal cortex, medial and lateral parietal cortex, and the medial temporal lobe (Rugg & Henson, 2003).

Before discussing the findings in this study it is necessary to note that the response phase is defined by contributions from multiple processes and types of memory, and as such is often problematic to interpret (Rugg & Henson, 2003). Additionally, it is necessary to note that retrieval can be subdivided into pre- and post-processing; pre-retrieval processing denotes the cognitive functions that “support an attempt to use a cue to retrieve information from memory,” while post-retrieval processing “involves cognitive operations that operate on the products of a retrieval attempt, [such as] the maintenance in working memory of retrieved information and its evaluation with respect to current behavioural goals” (Rugg & Henson, 2003). While it is still being debated whether the role of the prefrontal areas during retrieval is lateralized to the left or right, or both, it has become rather clear that activity in the prefrontal cortex is correlated with episodic retrieval. Moreover, as described by Tulving and Wheeler
(1997), “the functional role of right prefrontal cortex is to support ‘retrieval mode’, a mental state in which environmental events are treated as retrieval cues, and retrieved episodic memories are experienced ‘autonoetically’ (Rugg & Henson, 2003). The findings of this study have identified Broca’s Area 6 (right middle frontal gyrus) as expressing a decrease in activation following cognitive remediation. In light of the described role of this region, one can suggest that due to the cognitive training less effort is needed by this region to produce a correct response. In a similar conclusion, one can describe the findings of deactivation in the right precuneus (Broca’s Area 39) through its function in retrieval. The literature has identified lateral and medial parietal areas—specifically the precuneus and posterior cingulate—as being correlated with a successful retrieval (Rugg & Henson, 2003). Furthermore, it is possible to tie in the found deactivation of the cuneus as these parietal regions are supportive of visual memory; where “activation of [the medial parietal cortex] during successful retrieval reflects the strong demands placed on visual imagery by the representation of episodic information” (Rugg & Henson, 2003). Finally, in accordance with the literature this study found significant correlation with the medial temporal lobe, namely the left middle temporal gyrus (Broca’s Area 21) and left parahippocampal gyrus (Broca’s Area 35), in addition to sub-gyral regions of the temporal lobe. This region as a whole carries importance as the hippocampus and its surrounding regions have long been shown to be crucial to episodic memory as per lesion studies (Zola-Morgan & Squire, 1993). The hippocampus and surrounding tissue, namely the parahippocampal gyrus, have been subject to gray matter loss and
has been shown to resist volume loss and cognitive decline through cognitive remediation techniques (Eack et al., 2010).

The results of this study in combination with past finding presented in the literature have shown that patterns of increased and decreased activation in response to working memory tasks in patients with schizophrenia can be seen following cognitive remediation therapies. These changes in brain activity are specific to and differ across the three phases of working memory, which are defined as encode, rehearse, and response phases. While this study is exploratory, it adds merit to future assessment of the impact of CR on working memory. As deficits in working memory have been found to be resistant to medical treatment, the use of cognitive remediation as a tool to improve the functionality and overall quality of life of patient with schizophrenia cannot be understated.
Future Directions

Due to time constraints the scope of the project was reduced to include the patient population. Future directions in the upcoming months will not only seek to increase the number of patients scanned, but also more importantly include a healthy control group. By including baseline and longitudinal data on healthy participants (who would also be arranged into CR and control groups) it will be possible to identify with a higher degree of certainty the regions of activation and deactivation following cognitive remediation on patients with schizophrenia.
References


the consortium on the genetics of schizophrenia. *Schizophrenia Research, 103*(1-3), 218–228.


Figure 1: Schematic diagram showing the sequence and timing for trial events and data acquisition. Each trial began with the presentation of 3 words followed by a 9-second rehearsal period in which the participant was explicitly told to rehearse. After rehearsal, the participant is shown one of the three words and was asked to indicate whether it was presented first, second, or third on the list and was given 3 seconds to respond with a button press. The final 9 seconds of the trial the participant rested while viewing a fixation cross. A total of 9 scans was collected during each trial. MNI = Montreal Neurological Institute, KE = cluster size (voxels), FEW = family wise error, T = voxel height.
<table>
<thead>
<tr>
<th>Areas of Increased Activation after Cognitive Remediation</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Gyril (Temporal Lobe)</td>
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</tr>
<tr>
<td>Middle Frontal Gyrus (42.12, 11.42)</td>
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</tr>
<tr>
<td>Precuneus</td>
<td>N/A</td>
</tr>
<tr>
<td>Middle Frontal Gyrus (6, 41.42)</td>
<td>Right</td>
</tr>
<tr>
<td>Cuneus</td>
<td>N/A</td>
</tr>
<tr>
<td>Parietal Gyrus (1.8, 72.36)</td>
<td>Right</td>
</tr>
<tr>
<td>Cuneus</td>
<td>N/A</td>
</tr>
<tr>
<td>Fusiform Gyrus (52.12, 42.20)</td>
<td>Right</td>
</tr>
<tr>
<td>Cuneus</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Areas of Decreased Activation after Cognitive Remediation</th>
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</thead>
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<tr>
<td>Middle Frontal Gyrus (42.12, 11.42)</td>
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</tr>
<tr>
<td>Cuneus</td>
<td>N/A</td>
</tr>
<tr>
<td>Parietal Gyrus (1.8, 72.36)</td>
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</tr>
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<td>Cuneus</td>
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</tr>
<tr>
<td>Fusiform Gyrus (52.12, 42.20)</td>
<td>Left</td>
</tr>
<tr>
<td>Cuneus</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Table 1:** Areas of increased and decreased activation following cognitive remediation (p<.001, uncorrected)
Figure 2: Encode phase: Increased activation in the left middle frontal gyrus
Figure 3a: Rehearse phase: Increased activation in the right cuneus
Figure 3b: Rehearse phase: Increased activation in the right lingual gyrus
Figure 3c: Rehearse phase: Increased activation in the left cingulate gyrus
Figure 3d: Rehearse phase: Increased activation in the right fusiform gyrus
Figure 4a: Response phase: Decreased activation in the left sub-gyral temporal lobe
Figure 4b: Response phase: Decreased activation in the left middle temporal gyrus
Figure 4c: Response phase: Decreased activation in the right precuneus
Figure 4d: Response phase: Decreased activation in the right middle frontal gyrus
Figure 4e: Response phase: Decreased activation in the left cuneus
Figure 4f: Response phase: Decreased activation in the left parahippocampal gyrus