Pilot Testing CogSMART: A Novel, Compensatory Program of Cognitive Remediation for Psychosis developed by Elizabeth W. Twamley, PhD

by

Sofia Rae Zaidman
Class of 2016

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, 2016
# Table of Contents

Acknowledgements ........................................................................................................... 3  
1. Abstract ........................................................................................................................ 4  
2. Introduction .................................................................................................................... 5  
   A. Definition of Schizophrenia ....................................................................................... 5  
   B. Etiology ...................................................................................................................... 10  
   C. Neurochemical Theories of Schizophrenia ............................................................... 12  
   D. Typical and Atypical Antipsychotics ....................................................................... 14  
   E. Cognitive Features .................................................................................................... 14  
   F. Cognitive Remediation ............................................................................................. 19  
   G. CogSMART ............................................................................................................... 25  
   H. The Present Study .................................................................................................... 26  
3. Methods .......................................................................................................................... 27  
   A. Recruitment ............................................................................................................... 27  
   B. Cognitive, Social Cognitive, and Symptom Assessments ....................................... 27  
   C. CogSMART Sessions ............................................................................................... 31  
   D. Participants ............................................................................................................... 32  
   F. Statistics ................................................................................................................... 33  
4: Results ............................................................................................................................ 33  
   A. Attrition ..................................................................................................................... 33  
   B. Results of Cognitive Assessments Pre and Post CogSMART .................................. 34  
5. Discussion ....................................................................................................................... 35  
   A. Our Results in Context ............................................................................................. 35  
   B. Evaluating the Hypothesis: Was CogSMART successful at Gilead? ....................... 40  
   C. Limitations and Future Directions ......................................................................... 44  
   D. Conclusions .............................................................................................................. 47  
References ....................................................................................................................... 48
Acknowledgements

This thesis would not have been possible without the mentorship, encouragement and optimism of my advisor, Dr. Matthew Kurtz. Working in your lab has inspired me to grow in ways I never could have imagined or expected.

I would like to thank Dr. Elizabeth Twamley, and everyone at Gilead and the Schizophrenia Cognition Lab (especially Patty, Gail, Samantha and Alejandra) for going above and beyond to support this project. I also extend my deepest thanks to the residents of 37 Home for their moral support, and particularly Steph, whose calming presence made these last few weeks bearable.

Above all, I thank my family. Thank you mom and dad, for providing me with the opportunity to study 3,000 miles from home and always supporting my love of “brains.” Thank you Carina – your mere existence is inspirational. And thank you Gabe. I owe this thesis to you.
1. Abstract

Cognitive and social cognitive deficits affect nearly all individuals diagnosed with schizophrenia and have been shown to be a valid predictor of functional outcome. Great effort has been made in recent years to develop both pharmacological and non-pharmacological methods of mitigating these impairments. Cognitive remediation therapy (CR) has proven to be a reliable means of treating cognitive deficits in schizophrenia. Small to moderate effect sizes for improvements in various domains of cognition are consistently observed after treatment with CR. In strategic CR programs, clients are encouraged to become aware of cognitive deficits, set goals for improvement, and use strategies to compensate for impairments. In this pilot study, we aimed to assess the effectiveness of CogSMART, a strategic cognitive remediation program developed by Dr. Elizabeth Twamley at UCSD, in improving cognitive deficits for clients at the Gilead Community Services Social Rehabilitation Center in Middletown, CT. Five participants were initially enrolled in the study; however, two dropped out of the protocol at different time points and were excluded from our analysis. Changes in cognition, social cognition, and symptoms were assessed using a standardized battery of measures before and after completion of the program. We saw overall trends toward improvement and large effect sizes in the domains of verbal learning/memory, verbal fluency, attention/concentration, processing speed, working memory, social cognition and executive functions after completion of the CogSMART program. These results are encouraging and support continuation of the CogSMART program at Gilead and potentially beyond.
2. Introduction

A. Definition of Schizophrenia

Schizophrenia is considered to be a largely chronic, debilitating psychiatric disorder, with worldwide prevalence estimated at about .5% of the population (Simeone, 2015). It is a syndromic disease, with symptoms often varying greatly between individuals diagnosed. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM 5, APA, 2013), a diagnosis of schizophrenia can be made when at least two of the following five symptoms are observed for a significant portion of a one-month period, with at least one of symptoms 1-3 present:

1. Hallucinations
2. Delusions
3. Disorganized speech
4. Grossly disorganized or catatonic behavior
5. Negative symptoms

Hallucinations (false sensory experiences) and delusions (firmly held beliefs that are at odds with reality) are known more generally as positive symptoms, while disorganized speech and grossly disorganized or catatonic behavior are grouped together as disorganized symptoms. Negative symptoms refer to reductions in normal function, most notably in the areas of motivation and affect. Therefore, schizophrenia as we know it today is primarily characterized by the presence of symptoms in three domains: positive, negative and disorganized.

Along with the presence of two or more of the above symptoms, social/occupational dysfunction must be present to some degree, and some symptoms must have lasted for a period of at least 6 months. There are also exclusion criteria for
major manic or depressive episodes, and qualifiers if autism or developmental delay is present (APA, 2013).

**Dementia Praecox and Schizophrenia.**

The modern definition and understanding of schizophrenia can in large part be traced back to Emil Kraepelin, a German psychiatrist of the late 19th and early 20th century. He originally defined the disease “dementia praecox,” meaning premature dementia, in his textbook *Psychiatrie* in 1899. Kraepelin’s first definition characterized a disease with an onset in early adulthood and a chronic and degenerative course with no hope for recovery. Since 1899, the definition and name of dementia praecox have grown to represent our current understanding of the disease known as schizophrenia.

The term schizophrenia (meaning “split mind”) was first suggested as a more accurate name for dementia praecox in Berlin by Swiss psychiatrist Eugen Bleuler at the 1908 German Psychiatric Association meeting (Yeragani, 2012). Bleuler argued that dementia praecox was an inappropriate name for a disease that did not always arise in youth, and was not necessarily degenerative. In his 1919 textbook *Dementia Praecox and Paraphrenia*, Kraepelin himself agreed that dementia praecox might not be the best name for the disorder. He concedes, “the assumptions upon which the name chosen rested are at least doubtful” (p.4).

**Kraepelin’s Definition.**

The definition Kraepelin puts forth in his 1919 volume is well aligned with Bleuler’s concept of schizophrenia. Kraepelin defines dementia praecox as consisting
of “a series of states, the common characteristic of which is a peculiar destruction of the internal connections of the psychic personality” (p.3).

Kraepelin’s characterizations of the symptoms of dementia praecox, written just about a century ago, continue to shape our modern concept of the symptoms of schizophrenia and are quite valuable in helping us understand the nature of the disease, which is so often misunderstood due to improper representation in the media and colloquial misuse.

The first symptom that Kraepelin identified in his 1919 textbook is deficits in attention. He notes, “It is quite common for [patients] to lose both inclination and ability on their own initiative to keep their attention fixed for any length of time” (p.6). He also identifies a “loss of mental activity and therewith a certain poverty of thought,” (p.19) which would go along with deficits in attention to make up what we now classify as the cognitive deficits observed in schizophrenia.

Related to deficits in attention is “disorganized thinking,” which has been conserved in the DSM-5 definition of schizophrenia within the disorganized symptoms category. Kraepelin observed, “The patients digress, do not stick to the point, let their thoughts wander without voluntary control in the most varied directions. On the other hand the attention is often rigidly fixed for a long time” (p.6). Stereotyped thinking is another common and related feature of the disease. Kraepelin explains, “If the patient continues talking, the same ideas and expressions usually turn up again from time to time” (p.21).

After outlining the cognitive deficits of schizophrenia, Kraepelin provided a detailed description of what are now known as positive symptoms: hallucinations and
delusions. He specified the importance and prevalence of auditory hallucinations in dementia praecox, stating, “By far the most frequent [hallucinations] are hallucinations of hearing,” and he identifies what has continued to be one of the most defining features of the disease, “the hearing of voices.” Kraepelin notes, “what the voices say is, as a rule, unpleasant and disturbing” (p.9).

Kraepelin also emphasized the presence of delusions as a defining feature of the disorder: “Delusions, either transitory or permanent, are developed with extraordinary frequency on the foundation of the morbid change which is created by dementia praecox” (p.26). Some of the most common delusions observed in schizophrenia are persecutory delusions (believing that one is being persecuted or harmed), delusions of control (believing that one is being controlled by some force outside themselves) grandiose delusions (believing that one is superior or special), “thought broadcasting” (believing that others can hear ones thoughts) religious delusions (believing that one is God, the son of God, etc.), delusions of guilt (irrational belief that one has done something wrong, needs punishment), and somatic (irrational belief having to do with one’s body or health) (Appelbaum, 1999).

Hallucinations and delusions often go hand in hand. For instance, as Kreapelin observes, “there are also frequently ‘good voices,’ ‘good wishes,’ ‘praise,’[...] God makes known to the patient that he will proclaim him, send him into the world as his son” (p.10). Kraepelin’s description exemplifies the ease with which hallucinations and delusions frequently interact. In this particular case, auditory hallucinations lead to a common religious delusion of being God’s messenger.
After defining what we now know as the cognitive deficits and positive symptoms of schizophrenia, Kraepelin described the emotional and motivational disturbances of dementia praecox at length. Many of these symptoms are now classified as the negative symptoms of schizophrenia, which include blunted affect, decreased motivation (avolition), reduced speech (aloria), inability to feel pleasure (anhedonia), reductions in arousal, and social withdrawal. Kraepelin’s account of the negative symptoms of schizophrenia seen in patients a century ago is applicable to what is currently observed:

“The patients have lost every independent inclination for work and action; they sit about idle, trouble themselves about nothing, do not go to their work, neglect their most pressing obligations, although they are perhaps still capable of employing themselves in a reasonable way if stimulated from outside” (p.37).

**Diseases Within the Disease.**

While certainly our understanding of the neural correlates, treatments, and etiology has grown exponentially in the past century, the actual symptoms and presentation of schizophrenia (dementia praecox), as evidenced by Kraepelin’s extensive clinical observations, have stayed quiet consistent. However, this consistency does not necessarily support Kraepelin’s claim that “dementia praecox on the whole represents a well characterized form of disease.” Kraepelin himself identified nine “clinical pictures” of dementia praecox based on his own observations, though he emphasized that the delineation between these was weak at best, and that they should not be considered to have “special clinical value” (p.89).
In his 1920 textbook, *Lehrbuch der Psychiatrie*, Bleuler argued that schizophrenia could be divided into a series of distinct diseases within the disease (Bleuler, 1920). Based largely on observations made by Kraepelin, Bleuler identified four clinical subtypes of schizophrenia (paranoid, catatonic, hebephrenic, and “schizophrenia simplex”) in his chapter titled “Die Schizophrenien (dementia praecox),” or “the schizophrenias.” Subtypes closely resembling those identified by Bleuler were used in the diagnosis of schizophrenia up until 2013, when they were eliminated in the DSM 5 (APA, 2013). This decision was made primarily due to their “poor description of the heterogeneity of schizophrenia” and practical insignificance (Tandon et al., 2013).

In recent years, researchers have been able to distinguish subtypes based on measures of cognition (Kurtz & Wexler, 2006; Rangel et al., 2015), which appear to be linked to distinct patterns of structural neuropathology (Geisler et al., 2015). Additionally, subtypes have been classified based on immunohistochemistry (Schwartz et al., 2014). These more empirical approaches to classifying potential “diseases within the disease” have yielded promising results, but are still in their infancy. As it stands, the current DSM includes no subgroups for schizophrenia.

**B. Etiology**

As might be expected for an illness with such high prevalence, identifying the causes of schizophrenia has been difficult. However, great progress has been made towards uncovering the risk factors and mechanisms that underlie the disease since Kraepelin’s time.
Genetics.

Schizophrenia has an estimated heritability of 80% (Singh et al., 2014), meaning that approximately 80% of the variation of the schizophrenic phenotype (schizophrenia vs. non-schizophrenia) observed in the general population can be attributed to genetics. This number comes from sibling and family data collected for several heritability studies in multiple countries spanning the globe (Tsuang, 2000). More recently, with advances in gene sequencing technology, researchers have been able to identify certain alleles of genes that may contribute to the schizophrenia phenotype. Several genome-wide association studies of schizophrenia have been published since 2006, which have together identified various statistically significant risk loci for schizophrenia and psychotic illnesses (Bergen & Petryshen, 2012).

Other Risk Factors.

Although positive and negative symptoms tend not to become apparent until late adolescence or early adulthood, an overwhelming amount of evidence points to schizophrenia being a neurodevelopmental disorder (Fatemi & Folsom, 2009). Likely, some combination of genetic abnormalities and environmental stressors resulting in prenatal complications lead to disrupted fetal development and result in the brain neuropathologies which later present as schizophrenia (Fatemi & Folsom, 2009; Owen et al., 2016).

However, increased rates of schizophrenia, which cannot be explained by genetics or prenatal insults, have been consistently observed in certain populations. In a 2005 meta-analysis, Cantor-Graae and Selten found that first generation immigrants had a relative risk of 2.7 for developing schizophrenia, while second generation
immigrants had a relative risk of 4.5 (Contor-Graae & Selten, 2005). Carefully controlled analyses have also found that urban populations experience an increased risk of developing schizophrenia as high as 2.37 compared to rural or suburban populations (Vassos et al., 2012). The greatly increased risk observed in these populations has pointed to “social defeat” as a potential risk factor for the development of schizophrenia (Contor-Graae & Selten, 2005). Social defeat resulting from discrimination due to visible ethnic minority status could explain the higher risk observed in second-generation immigrants (Bourque et al., 2011). Additionally, overcrowding, distancing from nature and environmental pollutants could add to the experience of social stress in urban populations, leading to the heightened rates of schizophrenia observed (Lederbogen et al., 2011).

C. Neurochemical Theories of Schizophrenia

The Dopamine Hypothesis.

The first and most prominent modern theory to provide a possible mechanism underlying the symptoms of schizophrenia was the dopamine hypothesis (DH). It can be traced back to the 1950s, when the first antipsychotic drug, chlorpromazine, was developed and found to be effective in treating psychosis (Ban, 2007). The success of chlorpromazine led to the development of other antipsychotic drugs, whose potency was later found to correlate to dopamine receptor binding capacity (Ban, 2007; Seeman et al., 1975; Creese et al., 1976). This led researchers to hypothesize “that certain dopaminergic pathways are overactive in schizophrenia” (Seeman, 1987).

In a 1991 review, Davis et al. proposed a reformulated dopamine hypothesis to account for counter-intuitive findings on dopamine in cortical regions (Kendler &
Schaffner, 2011). Davis et al.’s review takes us to our current understanding of the DH: in schizophrenia, a hyperdopaminergic state is found in the mesolimbic dopamine pathway, leading to the presence of positive symptoms, while a hypodopaminergic state in the mesocortical pathway corresponds to the presence of negative symptoms and cognitive deficits (Davis et al., 1991).

The Glutamate Hypothesis.

The glutamate hypothesis of schizophrenia (GH), which took shape in the late 1990s and has gained in popularity and complexity since, adds a new level to our understanding of the role neurotransmitters play in the etiology of schizophrenia (Kantrowitz & Javitt, 2010).

The GH posits that decreased tonic excitation of NMDA receptors by glutamate in the dorsolateral prefrontal cortex (DLPFC) causes the decrease in dopamine levels observed in frontal cortical regions, which ultimately leads to the presence of negative and cognitive symptoms. The “top-down” regulation of dopamine is continued through GABA inter-neurons, which project from the PFC to the striatum. These inhibitory inter-neurons are under-activated by faulty glutamate signaling in the DLPFC, which in turn decreases the inhibition of dopamine in the striatum, therefore increasing dopamine’s presence, and producing the positive symptoms of schizophrenia. (Aquila & Citrome, 2015)

More recently, NMDA receptors have been shown to contribute to the integrity of synaptic spines. When NMDA receptors are activated by glutamate, a large influx of calcium sets off a pathway leading to the eventual activation of the proteins responsible for growing a neuron’s synaptic spines. This means that when
NMDA receptors are under-excited, synaptic spine growth will be decreased (Bennett, 2009). Inhibition of synaptic spine formation is one possible mechanism by which decreased glutamate and under-activation of NMDA receptors in the DLPFC could result in altered dopaminergic signaling.

D. Typical and Atypical Antipsychotics

Traditionally, positive symptoms have been treated with first-generation antipsychotics. These drugs are all strong D2 receptor antagonists. By binding to D2 receptors in the striatum, typical antipsychotics prevent activation of post-synaptic cells by dopamine. This results in altered signaling in several neural pathways, including the mesolimbic pathway, which has been shown to underlie the experience of positive symptoms. Unfortunately, the strong D2 antagonism also affects the mesocortical and nigrostriatal dopamine pathways, leading to unwanted extra-pyramidal (parkinsonian) side effects and secondary negative symptoms (Meltzer, 2013).

Positive symptoms can also be managed with the use of atypical antipsychotics. These drugs are characterized by looser binding capacity to D2 receptors than typical antipsychotics, and additional binding capability with other receptors (eg, muscarinic, histamine) (Kapur & Seeman, 2001). This eliminates the adverse side effects seen in typical antipsychotics, however, due to their binding capacity for other receptors, atypical antipsychotics come with their own adverse side effects such as weight gain and drowsiness.

E. Cognitive Features
While positive, negative and disorganized symptoms are highly variable among individuals diagnosed with schizophrenia, cognitive deficits are nearly always present to some degree (Aquila & Citrome, 2015). Reductions in cognitive function are consistently found in the domains of working memory, verbal learning and memory, attention and vigilance, processing speed, social cognition, problem solving, and visual learning and memory (Aquila & Citrome, 2015). Although the average age of onset for schizophrenia is between 16-30 years (Owen et al., 2016), these cognitive deficits are often present before the onset of symptoms, and are persistent throughout life (Allot et al., 2010).

The high prevalence and severity of cognitive impairment in schizophrenia has encouraged a great deal of research over the past few decades into the nature of these deficits and how to treat them. The current study focuses on one promising method of improving cognitive impairment: cognitive remediation therapy (CR).

**Cognitive Deficits and Functional Outcome.**

Cognitive impairment is an extremely debilitating aspect of schizophrenia. It is notoriously difficult to treat, and there is ample evidence linking it to functional outcome (Bortolato et al. 2015; Allot et al., 2010; Harvey & Strassnig, 2012). A 2010 meta-analysis looking at different domains of cognitive function at illness onset found that for three quarters of studies analyzed, performance on at least one aspect of cognitive function was predictive of functional outcome (Allot et al., 2010). More recently, a study investigating the predictive power of avolition and cognitive impairment on functional outcome for schizophrenia patients found cognitive
impairment to be a statistically significant predictor of functional outcome one year after onset of illness (Chang 2015).

Moderate to severe cognitive impairment directly affects one’s capacity to live independently, go to school, maintain relationships, keep a steady job, and earn money. (Allot et al., 2010). These abilities are known as psychosocial function – a rough measure of general functioning in daily life. The level of general cognitive impairment in patients with schizophrenia has been found to be a valid predictor of functional capacity when cognitive function remains below normal ranges (Moore et al., 2015).

**Cognitive Deficits and Social Cognition.**

Studies have revealed that deficits in social cognition also play a consequential role in influencing functional outcome. Social cognition encompasses a wide range of deficits, including impairment in emotion perception (the ability to intuit another person’s emotional state based on facial expressions and tone of voice), social perception (the ability to pick up on social cues based on the behaviors and emotions of others) and theory of mind (the ability to recognize others as having distinct mental states, and to make correct inferences on those mental states based on context) (Couture, 2006). Deficits in social cognition are very common in schizophrenia, and have a direct impact on one’s ability to communicate with others and to maintain relationships, making it more difficult to stay employed and function as a community member (Couture, 2006).

**Reward Learning.**
Decreased dopamine levels in prefrontal cortical regions of the brain are known to play an important role in the dysfunctional regulation of cognitive and emotional processes in schizophrenia. Dopamine is also a major neurotransmitter in the motivation and reward pathway, which originates in the midbrain, is imperative for learning, and is also essential for higher-level cognitive processes located in the PFC.

Reward learning is a higher-level function associated with motivation, learning, and hedonic response. There is ample evidence to suggest that the mechanism underlying reward learning is located in the prefrontal cortex (Dixon, 2014). For example, reward learning has been shown to be impaired in patients with schizophrenia, especially in those who score higher on negative symptom scales and lower on measures of cognitive function – both symptom domains that can be explained at least in part by dysfunction in the PFC (Nestor, 2014). The connection between reward learning and cognitive impairment has prompted research in training on reward learning in CR as a possible means of normalizing dopamine levels in the PFC (Cella, Reeder & Wykes, 2015).

**Motivation.**

Motivation is closely related to reward learning. Deficits in motivation, sometimes referred to as apathy or avolition, affect as much as 53% of people diagnosed with schizophrenia and directly contribute to poor functioning and quality of life (Raffard et al., 2016). Motivational deficits have been identified as a core negative symptom, along with blunted affect; however, lack of motivation and
decreased goal oriented behavior is also directly linked to cognition and dysfunction in the PFC (Foussias et al., 2015; Simpson et al., 2012).

Motivational deficits in schizophrenia seem to result from a reduced capacity to anticipate pleasure rather than a reduction in the ability to feel pleasure. For example, in a 2012 study of motivation in schizophrenia, a transgenic mouse model of schizophrenia showed unchanged hedonic response to sucrose compared to wild type mice; however, the schizophrenia-model mice were significantly less inclined to press a lever to receive the sucrose compared to wild-type mice (Simpson et al., 2012).

This makes sense when viewed in the context of cognitive deficits. Working memory, defined as the portion of our memory we use while carrying out tasks, is often reduced in schizophrenia. Along with the reward system, working memory is required when attempting to carry out tasks that we deem valuable. In a 2016 study, Raffard et al. showed that decreased motivation was negatively associated with working memory. Furthermore, in 2015, Foussias et al. showed a significant relationship between motivation and global cognition. Foussias et al. were also able to demonstrate that effort exerted on cognitive tests was significantly related both to motivation and to cognitive function (Foussias et al., 2015). These and other studies contribute to a blurring of the line between negative symptoms and cognitive deficits, which is particularly important when thinking about maximizing the effectiveness of CR programs.

**Treating Cognitive Deficits.**
While progress has been made in treating positive symptoms with typical and atypical antipsychotics, finding ways to improve the cognitive deficits (and negative symptoms) of schizophrenia has proven much more difficult. This has led to a push in recent years to develop both pharmacological and non-pharmacological therapies to treat the cognitive deficits associated with the disease. Pharmacological therapies targeting NMDA receptor function, aiming to normalize the amount of glutamate in the brain, have been developed to alleviate cognitive symptoms, but results are not significant compared to placebo (Aquila & Citrome, 2015).

**F. Cognitive Remediation**

Cognitive Remediation (CR) therapy is one of the most promising means of improving cognitive function in people with schizophrenia. CR programs generally fall into two categories: “drill and practice,” or “strategic.” Drill and practice CR programs are often carried out on a computer, and consist of repetition and training on tasks targeting a specific cognitive domain. The level of difficulty of these tasks can be titrated to each individual’s specific needs. The theory behind drill and practice CR programs is that training on basic tasks in various areas of cognitive impairment could translate to overall enhanced cognition, and therefore better functional outcome (Cella, Reeder & Wykes, 2015).

On the other end of the CR spectrum, strategic programs emphasize the importance of understanding cognitive problems and teach transparent strategies clients can use both in the sessions and in their daily lives to think more efficiently (Cella, Reeder & Wykes, 2015).
Both strategic and drill and practice CR programs have been shown to have merit in improving cognitive deficits. Many CR programs have begun to combine the two methods by incorporating a discussion session led by a therapist into computer-based drill and practice (Medalia & Bowie, 2016).

There is evidence that CR improves brain network activity and increases blood flow in prefrontal, occipital, and anterior cingulate regions (Wykes et al., 2002; Subramaniam et al., 2012; Revell et al., 2015). There is also evidence that it prevents grey matter depletion (Eack et al., 2010). However, the exact mechanisms by which these changes occur remain unclear (Isaac & Januel, 2016; Cella, Reeder & Wykes, 2015). At any rate, improvements in global functioning have consistently been found in meta-analyses (Revell et al., 2015).

**Combining Cognitive Remediation with Other Therapies.**

CR is most effective when combined with other forms of psychiatric rehabilitation (Revell et al., 2015). CR has been combined with vocational support, exercise, and cognitive behavioral therapy with favorable results (Bell et al., 2014; Malchow et al., 2015; Kurtz et al., 2015). In a 2015 meta-analysis focusing on the effects of CR on recently diagnosed schizophrenia patients, larger effect sizes were seen for improvement in the domain of social functioning when CR was combined with one of these rehabilitative programs (Revell et al., 2015). The same meta-analysis also found that CR was most effective when performed in a group rather than one-on-one with a therapist.

**Cognitive Remediation and Different Populations.**
CR has been found to be most beneficial to those who have the most to gain from it. In a 2014 study, Bell et al. compared the effects of CR on clients with either low or high community functioning, which was determined by their score on the QLS, a measure of quality of life. Both groups were divided into two sub-groups; one that received only supported employment (SE) services, and one that received SE and CR. Participants in the low community functioning group who received CR were 2.5 times more likely to be employed at one year follow-up than their counterparts who only received SE. This effect was only significant for the low community functioning group. Those with low community functioning who received CR also worked more than 1.5 times more hours on average at one year follow-up than those who received only SE. All groups showed slight but not significant improvement on tests of negative symptoms, neurocognition, and intrinsic motivation, however, greatest improvement was seen for the low functioning group that received CR (Bell et al., 2014).

Another study published by Bowie et al. in 2013 compared the effects of CR on early stage psychosis patients (within five years of illness onset) and long-term patients (15+ years after illness onset). Both groups participated in computer-based drill and practice exercises and therapist-led discussion sessions. Significant improvement was seen for both recent and long-term psychosis patients for various cognitive domains. However, greatest improvement was seen in the early stage patients in the domains of psychomotor speed and executive functions relating to working memory and planning. Although schizophrenia is no longer considered a degenerative disease, and there is general consensus that cognitive deficits stay
relatively stable throughout the course of the illness, this study suggests that there may be an ideal window in which cognitive function can be improved through certain types of CR. In fact, because cognitive deficits are often found before onset of illness, it may be beneficial to provide CR for at-risk populations not yet diagnosed with schizophrenia (Bowie et al., 2013).

However, Revell et al. found that while cognition, symptoms, and general function did improve, effect sizes for first-episode patients were smaller compared to those found in chronic patients, perhaps due to smaller initial deficits (Revell et al., 2015). Clearly, more research is needed to fully illuminate the effects of CR on different subsets of schizophrenia patients.

**Cognitive Remediation and Genetics.**

As genetic testing becomes standard, healthcare workers could begin to identify ideal combinations of CR programs, medications and other therapies to maximize treatment efficacy for patients based on their specific genotypes, along with variables such as age and level of functioning.

The COMT gene on chromosome 22 directly affects cognition in schizophrenia. This gene produces the enzyme catechol-O-methyltransferase, which breaks down catecholamines (epinephrine, norepinephrine, dopamine) in the PFC. A common single nucleotide polymorphism (SNP) changing a methionine (met) to a valine (val) still produces a functional enzyme, but with a greater ability to break down dopamine. This translates to lower levels of dopamine in the PFC of individuals with either one or two copies of the val SNP (Twamley et al., 2014). Furthermore,
Possession of the val allele has been shown to correspond with upregulation of D1 receptors in cortical regions (Slifstein et al., 2008).

Possession of the val allele has been linked to poorer cognitive performance, not only in schizophrenia, but also in the general population (Green et al., 2012). In a 2014 study, Twamley et al. found a direct, dose-dependent relationship between possession of 0, 1, or 2 copies of the met allele of COMT and performance on cognitive tests in patients with schizophrenia. In other words, people with two copies of the met allele tended to perform better on cognitive tests, those with two copies of the val allele performed worst, and heterozygous individuals fell in the middle (Twamley et al., 2014).

Research on the COMT SNP has provided direct evidence that particular genotypes can affect response to CR. In 2007, Bosia et al. demonstrated that in a group of patients with schizophrenia, possession of the met/met allele correlated with greater improvements in measures of cognitive flexibility and quality of life after CR (Bosia et al., 2007). This suggests that the availability of dopamine in the PFC and general PFC activation patterns affected by the COMT gene could mediate some of the positive affects of CR.

Additionally, in 2014, Bosia et al. showed that clozapine (an atypical antipsychotic with unique affinity for D1 receptor binding in the PFC) was able to normalize improvements in cognitive function to met/met allele levels after CR in val/val patients with schizophrenia (Bosia et al., 2014).
These early COMT studies provide hope that the creation of personalized treatment plans based on genetics is possible and potentially effective for patients with schizophrenia.

**Intrinsic and Extrinsic Rewards in Cognitive Remediation Programs.**

Recently, interest in the differences between intrinsic motivation (IM) and extrinsic motivation (EM) in schizophrenia, especially in the context of CR, has grown. In his 2010 review of intrinsic and extrinsic motivation in CR programs, Steven M. Silverstein makes his case for the incorporation of extrinsic rewards in CR aimed at populations with motivational deficits.

Historically, CR programs have shied away from using external motivators (money, food), based on evidence that EM undermines IM (an internal desire to do something for no other reason but to improve oneself or because it is interesting), which is thought to be more valuable in the learning process (Silverstein, 2010). However, experiments examining the interaction between EM and IM in educational environments have for the most part been carried out on populations without motivational deficits (Silverstein, 2010). Therefore, this generalization cannot necessarily be applied to people with schizophrenia.

Silverstein argues, “when the base rate of a desired behavior is low, and IM is low, use of extrinsic reward can be effective in increasing the rate of the behavior, and ultimately of IM, especially when non-tangible rewards (eg, verbal praise, social reinforcement) are used and when reward is contingent on an individualized performance level” (Silverstein, 2010). This argument champions the use of strategic
CR programs with a high level of client-therapist contact for populations with particularly large motivational deficits.

**G. CogSMART**

CogSMART is a strategic CR program developed by Dr. Elizabeth Twamley at UCSD. It was developed to be “brief, practical, low-tech, engaging to clients, and portable enough to be delivered in the community” (Twamley et al., 2012). CogSMART consists of 12, 2-hour sessions, which can be conducted in groups or one-on-one. Each session is designed to train on aspects of prospective memory, attention and vigilance, learning and memory, and executive functioning (Twamley et al., 2012). Sessions require minimal resources outside of the actual manuals (for example: calendars, a deck of cards, a ball). This makes CogSMART a viable, relatively low-cost CR option.

In an initial randomized controlled trial of the CogSMART program, Twamley et al. found significant improvement in attention and functional capacity at 3 month follow-up and significant improvement in verbal memory at post-treatment and follow-up in the CogSMART group. Improvement was also seen in negative symptoms at post-treatment and follow-up, and in subjective quality of life at follow-up (Twamley et al., 2012).

Along with these initial positive results, there is good evidence in support of the principles underlying CogSMART. The program relies heavily on client-therapist interaction, with most of the session time spent discussing goals and strategies and working as a group or in pairs. In a 2016 paper, Cella, Reeder and Wykes argue for the importance of an active therapist role, specifically in strategic CR programs.
Therapists can provide motivation and encouragement, and can work on a personal level with clients to ensure proper understanding of material. This is perhaps particularly important for more severely impaired and symptomatic patients who may find individual computer-based programs overwhelming (Cella, Reeder & Wykes, 2016).

The active role of the therapist and the associated EM provided in the CogSMART program could at least partially explain the improvement seen in negative symptoms and subjective quality of life in Twamley et al.’s 2012 study. This effect could also be attributed to the importance placed on meta-cognition and transferring the skills learned in the sessions to everyday situations (Cella, Reeder & Wykes, 2014).

Verbal learning and memory are often identified as the areas of most severe cognitive impairment in schizophrenia and have been shown to correlate with severity of negative symptoms (Manglam & Das, 2013). The significant improvements observed by Twamley et al. in verbal memory could potentially influence or be influenced by the improvements seen in negative symptoms.

**H. The Present Study**

The aim of our study was to implement and evaluate the efficacy of a pilot CogSMART program at the Gilead Community Services Social Rehabilitation Center in Middletown, CT, which provides outpatient care and activities for community members with psychiatric illnesses. We hypothesized that the clientelle at Gilead would tolerate and attend the sessions, and improve on measures of the CogSMART
targeted domains of cognition (prospective memory, attention, learning/memory, and executive functions), as well as measures of social cognition.

3. Methods

A. Recruitment

All protocols for this study met the Wesleyan University Institutional Review Board requirements for studies with human subjects. Five participants were recruited through Gilead Community Services. Participants were notified of the study in person by the study author during an informational presentation on the grounds of Gilead Community Services. Inclusion criteria consisted of the following: participants must have been stabilized outpatients with a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features, at least 18 years of age, not simultaneously enrolled in another cognitive training program, and not actively using illicit substances.

Participants committed to attending two 2-hour sessions per week for 6 weeks, and all pre and post-training testing (at cessation of training and at a 6-month follow-up). Participants were compensated $30 for three hours of their time during pre and post-testing.

B. Cognitive, Social Cognitive, and Symptom Assessments

Participants were each assessed with a standardized battery of cognitive and social cognitive tests and assessments of attitude, function and symptoms prior to the start of the program, and immediately after completion of the program. Pre-testing began on 12/7/15, and post-testing ended on 3/18/16.
Measures of Cognition and Social Cognition

The Wechsler Test of Adult Reading (WTAR) is used as an estimate of premorbid intelligence through word recognition capability. It consists of a list of 50 irregular words in increasing difficulty. The individual must read the words aloud, and is given either 1 or 0 for correct or incorrect pronunciation of each word (Holdnack, 2001). Raw scores are converted to scaled scores, which can then be used to estimate verbal IQ (VIQ) and full scale IQ (FSIQ).

The Wechsler Adult Intelligence Scale (WAIS-IV; selected subtests) was used to assess attention, processing speed and working memory. Measures from this scale include the Digit Span subtest, which measures attention through recall of short sequences of digits; The WAIS-IV Digit Symbol test, which is used to measure processing speed; and the WAIS-IV Letter-Number Sequencing Test, which is used to measure working memory (Wechsler, 2008). Scaled scores for the WAIS are reported in Table 2.

The Hopkins Verbal Learning Test (HVLT) was used to assess verbal learning and memory. The HVLT consists of a list of 12 words that belong to three categories (i.e. animals, spices, weapons). The words are read aloud at a steady 1-second per item pace and the individual is asked to recall as many words as they can. This process is repeated three times (Brandt, 1991). Scaled scores for the HVLT are available, however, all participants included in the statistical analyses in Table 2 scored below threshold for the lowest scaled score in both pre and post-testing. Raw scores were used in order to detect any changes.
The Controlled Oral Word Association Test (COWAT) is a measure of verbal fluency. Individuals are asked to spontaneously recall words in response to a phonemic cue (F, A or S), or belonging to a specific category (animals) (Golden et al., 2000). Raw scores were converted to scaled scores and are reported in Table 2.

The 64-card version of the Wisconsin Card Sorting Test was used to test executive functioning. Executive functions can be defined as the skills necessary to regulate and control cognitive processes. This includes planning, mental flexibility and problem solving. The Wisconsin Card Sorting Test uses a deck of cards to measure executive function. The individual must formulate a sorting rule, and be able to switch sorting methods based on negative or positive feedback from the test administrator (Grant et al., 1993). We reported the scaled scores for total mistakes made and raw scores for categories completed in Table 2.

The Awareness of Social Inference Test (TASIT) consists of a series of short vignettes and corresponding questions to assess social perception. The test comprises three sections: Emotion Evaluation, Social Inference (minimal), and Social Inference (enhanced). Each section has a different series of scenes depicting real life social situations portrayed by professional actors, and questions on the videos (McDonald et al., 2003). Raw scores are reported in Table 2.

The Memory for Intentions Screening Test (MIST) tests prospective memory, which is defined as the ability to remember to do something in the future. The MIST consists of a series of tasks the individual must remember to carry out at various points in the immediate future (Raskin, 2009). A score is given for prospective memory as well as retrospective memory in the form of percentiles.
Measure of Attitude

The Self-Efficacy Scale (SES) measures the individual's belief that he or she has the psychological, biological, and cognitive capabilities to execute a certain behavior through a series of questions, which can be answered on a scale from 0-100% in increments of 10. The questionnaire is divided into three subscales: positive, negative and social, each with 19 questions (McDermott, 1995). The test is scored by adding the percentages for each subscale and dividing the total by the number of questions answered. These scores are reported in Table 2.

Measures of Function

The Social Functioning Scale (SFS) consists of 79 questions designed to assess the level of impairment of social function in patients with schizophrenia. The items on the scale assess seven areas of impairment in social functioning: social engagement, interpersonal communication, activities of daily living, recreation, social activities, competence at independent living, and occupation/employment (Birchwood et al. 1990). Raw scores for the SFS are reported in Table 2.

The UCSD Performance-based Skills Assessment-Brief (UPSA-B) is used to assess the ability to perform certain everyday living tasks. Participants are asked to role-play skills in finances, including tasks such as writing a check, and communicative skills, with tasks such as dialing for help in an emergency and rescheduling an appointment with a doctor. Participants receive a score ranging from zero to twenty (Mausbach et al., 2006).

Symptoms Measure.
The Positive and Negative Syndrome Scale (PANSS) is a comprehensive questionnaire designed to measure the severity of the positive, negative and general symptom domains of individuals with schizophrenia. Answers to the questions on the PANSS are used to rate seven positive, seven negative and 16 general symptom items on a seven-point scale (from absent to extreme) (Kay et al., 1987).

C. CogSMART Sessions

The CogSMART program took place over 6 weeks, with two 2-hour sessions each week. The sessions were located in a conference room at the Gilead Community Services Social Rehabilitation Center in Middletown, CT. At least two research assistants trained in the ethics of research with human subjects were present for each session. The study author was the primary instructor for the sessions, and had experience and extensive training working with patients with psychotic disorders for studies in Dr. Kurtz’s lab prior to commencement of the CogSMART sessions. All participants received the same training, and were expected to complete simple homework assignments between sessions.

Topics covered in the sessions were calendar use; to-do lists; prioritizing tasks; linking tasks by using planned cues; automatic places; using routines to automate tasks; eye contact, paraphrasing, asking questions during conversations; self-talk during tasks; taking breaks to refocus; taking notes; association; chunking; categorization; acronyms; visual imagery; over-learning; six-step problem-solving method; self-talk and self-monitoring while solving problems; hypothesis testing using pro and con evidence; set shifting; and set maintenance.
Each session was audio recorded to ensure proper instruction methods, and the integrity of session administration was maintained by review of the sessions with Dr. Elizabeth Twamley, developer of the CogSmart program.

D. Participants

Table 1: Participant Demographics (N=5)

<table>
<thead>
<tr>
<th>Participant Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35</td>
<td>53</td>
<td>48</td>
<td>48</td>
<td>54</td>
<td>47.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(±7.57)</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>80% male</td>
</tr>
<tr>
<td>Education</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>11</td>
<td>11</td>
<td>10.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(±.837)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>6</td>
<td>3</td>
<td>6.5</td>
<td>5</td>
<td>&gt;50</td>
<td>5.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(±1.55)</td>
</tr>
<tr>
<td>Age of onset</td>
<td>21</td>
<td>17</td>
<td>18</td>
<td>18</td>
<td>42</td>
<td>23.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(±10.62)</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>14</td>
<td>35</td>
<td>30</td>
<td>30</td>
<td>12</td>
<td>24.2</td>
</tr>
<tr>
<td>(years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(±10.45)</td>
</tr>
<tr>
<td>FSIQ initial</td>
<td>73</td>
<td>79</td>
<td>86</td>
<td>80</td>
<td>92</td>
<td>82 (±7.25)</td>
</tr>
<tr>
<td>Sessions Attended</td>
<td>9</td>
<td>7</td>
<td>0</td>
<td>8</td>
<td>6</td>
<td>7.5/12**</td>
</tr>
</tbody>
</table>

Note: *Excluding CS005  **Excluding CS003

Participants were all stabilized outpatients with a diagnosis of schizophrenia or schizoaffective disorder. Four out of five were male. After participant 3 dropped out of CogSMART sessions, all participants were male. The age of the participants ranged from 35 to 54 years old, with mean age 47.6 years old. Only participant 3 had graduated from high school. All other participants completed up to 10 or 11 grade. None of the participants were currently employed. Participant 5 had a dual diagnosis of schizophrenia and substance abuse disorder, but, to our knowledge, was not currently using illicit substances. The mean pre-morbid FSIQ was 82, which is 1.2 standard deviations below the population mean of 100.
F. Statistics

Statistical analyses were run using The Statistical Package for Social Sciences (SPSS 23.0). Raw scores on the assessments were converted to scaled scores when available. A paired samples T-test with a 95% confidence interval was conducted for each assessment to determine whether significant change occurred on any measures between pre and post-testing (Table 2). Effect size was calculated by hand using Cohen’s d. CS003 and CS005, who had each dropped out of the protocol at different time points, were excluded from the analysis.

4: Results

A. Attrition

After pretesting, participant 3 decided not to attend the CogSMART sessions. We continued with post-testing for this participant and saved her data for potential use as a control. Each of the other four participants attended at least 50% of the sessions. Participant 1 had the highest attendance with 9/12 sessions. Participant 4 had second highest attendance with 8/12 sessions. Participant 2 attended 7/12 sessions, and participant 5 attended 6/12 sessions. Ensuring attendance was one of the biggest challenges of this study. Clients are not required to come to Gilead each day, and almost all of them rely on a morning shuttle to get there. Furthermore, few of the participants had their own phone. The two participants with highest attendance lived in a group home with round the clock staff. The Gilead staff was able to work with the staff at the group home to remind these participants to attend the CogSMART sessions, however this was not foolproof. At one point, participant 5 was unable to be
contacted by Gilead staff and missed three consecutive sessions (3, 4 and 5). For similar reasons, we were unable to complete post-testing for participant 5.

The participants in this study were quite symptomatic, which at times prevented them from attending sessions. Participant 2 refused to participate in the last four sessions. There were also some issues with participant 4’s attendance due to psychotic episodes.

B. Results of Cognitive Assessments Pre and Post CogSMART

Table 2: Means, effect size and Paired-Samples T-test for assessments pre and post intervention

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Mean pre-testing (±SD) (N=3)</th>
<th>Mean post-testing (±SD) (N=3)</th>
<th>Cohen’s d</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS positive</td>
<td>24.67 (±1.15)</td>
<td>22.33 (±5.86)</td>
<td>.561</td>
<td>.607</td>
<td>.606</td>
</tr>
<tr>
<td>PANSS negative</td>
<td>17.33 (±3.51)</td>
<td>19.33 (±5.03)</td>
<td>.454</td>
<td>-.795</td>
<td>.510</td>
</tr>
<tr>
<td>TASIT 1</td>
<td>12.67 (±6.66)</td>
<td>19.33 (±5.78)</td>
<td>1.14</td>
<td>-1.696</td>
<td>.232</td>
</tr>
<tr>
<td>TASIT 2</td>
<td>27.33 (±10.12)</td>
<td>37.00 (±5.29)</td>
<td>1.12</td>
<td>-3.263</td>
<td>.082</td>
</tr>
<tr>
<td>TASIT 3</td>
<td>35.33 (±6.03)</td>
<td>31.67 (±8.33)</td>
<td>.503</td>
<td>1.000</td>
<td>.423</td>
</tr>
<tr>
<td>WTAR</td>
<td>68.67 (±4.93)</td>
<td>66.00 (±3.00)</td>
<td>.654</td>
<td>.839</td>
<td>.490</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>77.33 (±3.79)</td>
<td>75.33 (±2.52)</td>
<td>.621</td>
<td>.866</td>
<td>.478</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>77.33 (±3.79)</td>
<td>75.33 (±2.08)</td>
<td>.654</td>
<td>.756</td>
<td>.529</td>
</tr>
<tr>
<td>COWAT (animals)</td>
<td>33.67 (±8.02)</td>
<td>42.00 (±6.93)</td>
<td>1.11</td>
<td>-3.201</td>
<td>.085</td>
</tr>
<tr>
<td>COWAT (letters)</td>
<td>35.33 (±5.69)</td>
<td>39.00 (±12.29)</td>
<td>.383</td>
<td>-.954</td>
<td>.441</td>
</tr>
<tr>
<td>WCST categories</td>
<td>1.33 (±0.78)</td>
<td>2.00 (±0.00)</td>
<td>1.64</td>
<td>-2.000</td>
<td>.184</td>
</tr>
<tr>
<td>WCST errors T score</td>
<td>36.33 (±5.77)</td>
<td>37.33 (±5.13)</td>
<td>.183</td>
<td>-1.000</td>
<td>.423</td>
</tr>
<tr>
<td>MIST PMT percentile</td>
<td>19.67 (±16.17)</td>
<td>35.00 (±55.46)</td>
<td>.375</td>
<td>-.544</td>
<td>.641</td>
</tr>
</tbody>
</table>
Pilot Testing CogSMART

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean ± SD</th>
<th>Pearson Corr</th>
<th>t-value</th>
<th>p-value</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIST RRT percentile</td>
<td>18.67 (±9.07)</td>
<td>.403</td>
<td>-.383</td>
<td>.739</td>
<td></td>
</tr>
<tr>
<td>UPSA</td>
<td>45.28 (±8.18)</td>
<td>.355</td>
<td>-.891</td>
<td>.467</td>
<td></td>
</tr>
<tr>
<td>WAIS Digit Span</td>
<td>3.00 (±2.00)</td>
<td>0</td>
<td>.000</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>WAIS Letter-number seq.</td>
<td>2.33 (±2.31)</td>
<td>2.19</td>
<td>-3.464</td>
<td>.074</td>
<td></td>
</tr>
<tr>
<td>WAIS Coding</td>
<td>4.67 (±2.08)</td>
<td>.639</td>
<td>-4.000</td>
<td>.057</td>
<td></td>
</tr>
<tr>
<td>SFS total</td>
<td>126.00 (±15.52)</td>
<td>.155</td>
<td>-.327</td>
<td>.775</td>
<td></td>
</tr>
<tr>
<td>HVLT raw</td>
<td>7.67 (±.578)</td>
<td>3.30</td>
<td>-3.00</td>
<td>.095</td>
<td></td>
</tr>
<tr>
<td>SES total</td>
<td>59.60 (±24.01)</td>
<td>.038</td>
<td>-.833</td>
<td>.493</td>
<td></td>
</tr>
</tbody>
</table>

Note: For explanatory purposes, p values < 0.10 have been bolded and classified as “trends.”

Though no results of our paired samples T-tests yielded a p-value below .05, we saw trends toward significance (p-value < 0.10) and large effect sizes for the TASIT 2 (social inference – minimal) [d=1.12, t=-3.263, p=.082], COWAT animals category [d=1.11, t=-3.201, p=.085], WAIS letter-number sequencing [d=2.19, t=-3.464, p=.074], and HVLT [d=3.3, t=-3.00, p=.095]. Additionally, we saw trends toward significance and moderate effect size for the WAIS digit-symbol coding subtest [d=.639, t=-4.00, p=.057], and large effect size for WCST categories [d=1.64, t=-2.00, p=.184] and TASIT 1 (emotion evaluation) [d=1.41, t=-1.696, p=.232].

No significant change was observed for the PANSS positive or negative symptoms scores, and no trends were observed for the UPSA, MIST, SFS or SES.

5. Discussion

A. Our Results in Context

WTAR – FSIQ and VIQ.
The mean crystallized FSIQ (and VIQ) of all participants was 1.2 standard deviations below the mean population IQ, and significantly lower than the mean FSIQ of participants in Twamley et al.’s 2012 pilot study. Additionally, the mean score on the positive symptoms section of the PANSS was significantly higher than the mean positive symptoms score for participants in Twamley et al.’s 2012 pilot study (table 2). The mean age of our participants was about the same as those in the Twamley et al. study, though our group had on average about 2 years less education than Twamley et al.’s, likely contributing to lower FSIQ. These scores could also reflect level and quality of education as well as intelligence (Silverberg et al., 2013). The low scores are unlikely to be a result of decreased effort or lack of motivation, as the WTAR has been shown to remain valid regardless of effort level (Whitney et al., 2010).

WAIS – processing speed, working memory and attention/concentration.

A large effect size with a low p value was observed for the WAIS Letter-number Sequencing subtest, and a moderate effect size and near-significance was observed for the WAIS Coding subtest. These findings suggest improvements in processing speed, working memory, and attention and concentration (Wechsler, 2008) as a function of the CogSMART training. Improvements in these higher-level functions might also explain the overall better performance and substantial effect sizes observed on most of our measures.

Although Twamley et al. did not observe significant improvement on the WAIS Letter-number Sequencing and WAIS Coding subtests, our results are supported by a comprehensive meta-analysis of 40 studies of cognitive remediation
Pilot Testing CogSMART

for schizophrenia published in 2011 by Wykes et al, which found overall small to moderate effect size for improvement in global cognition, and small effect sizes for improvement in processing speed, attention/vigilance, working memory, and verbal learning/memory (Wykes, 2011).

It should also be mentioned that we saw modest improvement in the number of categories participants were able to complete in the WCST. Two participants who had completed one category in pre-testing successfully completed two categories in post-testing, while one participant who had completed two categories in pre-testing again completed two categories in post-testing. These results could reflect improvement in executive functions, but in this case, especially because no reduction was seen in the number of errors made, they are may be more likely a result of practice on this specific measure.

**HVLT and COWAT – verbal learning, memory and fluency.**

A very large effect size was observed for the HVLT, which could reflect enhanced verbal episodic memory, however, for the three participants included in the analysis, scores on the HVLT at both pre and post-testing were so low that standardized scores could not be used. In order to detect changes, statistics were run using the raw scores. We must therefore proceed with caution when discussing improvements on the HVLT. In their 2012 randomized controlled trial of CogSMART, Twamley et al. also saw significant improvement on the HVLT at post-treatment. This is encouraging, as verbal memory was a cognitive domain specifically targeted for improvement by CogSMART and has been a well-established area of improvement in other CR programs (Wykes, 2011). These results suggest that the
CogSMART sessions at Gilead may have been effective in training on strategies to improve verbal memory.

A trend toward improvement and large effect size were observed for the COWAT categories (animals) section, but not for the COWAT phonemic cue section. The COWAT is a measure of verbal fluency. To do well on the COWAT, subjects must rapidly generate words and determine whether they fit all of the given criteria. On a basic level, this task requires that subjects successfully utilize internal speech to retrieve potential responses (Golden et al., 2000). Cognitive flexibility, self awareness and inhibition are also crucial for elimination of inappropriate responses (Golden et al., 2000). The improvements observed in the category section reflect changes in semantic fluency rather than phonemic fluency. Several studies investigating differences between semantic and phonemic fluency in schizophrenia using the COWAT have found greater impairment in semantic fluency than phonemic fluency when compared to healthy controls (Gourovitch et al., 1996; Philips, 2004; Bozikas et al., 2005). This could explain why trends toward improvement were only seen in the category section; a greater initial deficit would leave more room to improve. Furthermore, the number of responses for categories both for subjects with schizophrenia and healthy controls is virtually always higher than the number of responses for individual letters, which suggests that semantic retrieval is an easier cognitive process than phonemic retrieval (Bozikas et al., 2005). This too would support greater capacity for change in the categories section.

However, in their 2012 pilot study of CogSMART, Twamley et al. did not observe improvement in COWAT scores at post-treatment or 3-month follow-up
This discrepancy could potentially be explained by our cohort’s lower level of initial functioning, and hence, their greater capacity for improvement.

**TASIT – social cognition.**

While scores on the TASIT 3 (social inference – enhanced) did not change significantly, we saw a large effect size for TASIT 1 (emotion evaluation) and a large effect size trending toward significant improvement for the TASIT 2 (social inference – minimal), which assesses the subject’s ability to distinguish between sincerity and sarcasm (McDonald et al., 2003). To control for practice effects, alternate versions of the TASIT (a and b) were used during pre and post-testing. Because no change was seen for the TASIT 3, improvement due to practice is unlikely. Twamley et al. did not include a measure of social cognition in their 2012 study, however, we expected to see improvement in this domain based on previous findings. In their 2011 meta-analysis of cognitive remediation therapies for schizophrenia, Wykes et al. reported a moderate effect size for improvement on measures of social cognition (Wykes, 2011).

Social cognition has been shown to be associated with subjective quality of life (Maat et al., 2012; Tas et al., 2013), a domain that Twamley et al. did test for and found improvement in at 3-month follow-up (Twamley et al., 2012). The improvements we saw in social cognition could have implications for our participants’ subjective quality of life, and validate the effectiveness of CogSMART at Gilead.

**Symptoms and Functional Capacity.**
Unlike Twamley et al., we did not observe any changes in negative symptoms between pre and post-testing. In fact, negative symptoms slightly increased in the group of 3 included in our analysis. The lack of change could be a result of imperfect PANSS scoring on the part of the principal investigator at post-testing due to possible bias (see limitations). More likely, the number of participants included in our statistical analysis was simply too small to allow us to reliably detect any trends on the PANSS, which can vary greatly from week to week.

Twamley et al. included a measure of social function (The Social Skills Performance Assessment) in their 2012 pilot study and found no significant effects of CogSMART on this outcome (Twamley et al., 2012). Similarly, we saw no change in scores on the SFS, another assessment of social functioning. However, unlike Twamley et al., we saw no significant improvement in functional capacity as measured by the UPSA. This could relate to the lack of significant improvement we saw on the MIST, a measure of prospective memory. In 2008, Twamley et al. showed that prospective memory (measured by the MIST) was predictive of functional capacity (measured by the UPSA) (Twamley et al., 2008). Improvements on these two tests would consequently be expected to coincide. The lack of significant or near-significant improvement seen on the MIST and UPSA was likely related to our small sample size. Our participants did generally perform better on these measures between pre and post-testing, but there was a large amount of variability in scores, leading to large SD values (see Table 2) and reducing the power of our statistical analyses.

B. Evaluating the Hypothesis: Was CogSMART successful at Gilead?
While none of our results were statistically significant, near-significance and large effect sizes were observed for a number of cognitive measures assessing performance in the CogSMART targeted domains of attention, learning/memory, and executive functions. Unlike Twamley et al., we did not see improvement in negative symptoms or prospective memory. Overall, the results of the statistical analyses are encouraging, given our small sample size. However, a larger sample size and control group will be necessary to determine whether these results are valid, and not an artifact of practice.

The current study aimed to assess the feasibility and overall success of running the CogSMART cognitive remediation program at Gilead Community Services in Middletown, CT. Statistical analysis of changes on social, cognitive and symptoms measures between pre and post-testing are useful in assessing how well the CogSMART program was implemented and what impact, if any, it had on our participants. Quantitative analysis is also necessary in order to compare our results to previous studies. However, not all benefits or drawbacks involved in conducting the CogSMART program at Gilead can be quantified.

One serious consideration when determining whether or not this pilot study was successful is the participants’ overall satisfaction with the program. Although attrition was an issue and on a day-to-day basis motivation to complete the sessions seemed low, participants repeatedly reported a desire to improve some aspect of their cognitive function (especially memory), and to see the program through to its completion. Additionally, participants were quite proud of their accomplishments by the end of the sessions, and expressed intentions of displaying the certificates of
completion in their homes. Participants also enjoyed choosing calendars and for the most part remembered to bring them to each session. This suggests that, despite some bad days, participants were invested in the CogSMART program and understood its value.

The importance of the social aspect of the CogSMART sessions cannot be understated. Although Gilead is a community center, and clients generally consider each other good friends, there is not much spontaneous conversation. Clients can often be found sitting in silence with one another listening to the radio, drinking coffee, smoking a cigarette, or eating a meal. Clients can also spend time by themselves on the computer. Staff members will often engage clients in conversation, but this can only be for a few minutes at a time.

As a discussion-based, strategic cognitive remediation program, CogSMART provided participants with the opportunity to engage in deeper conversation with each other and with the instructors. CogSMART also trained on conversational skills, emphasizing eye contact and active listening. Rapport was built over the course of the sessions and participants developed meaningful relationships with each other and the instructors. It was inspiring to see one higher functioning participant assist and praise lower functioning participants in various group activities. These kinds of connections likely increased both extrinsic and intrinsic motivation to attend the sessions; participants would receive praise and companionship from each other and instructors, which might later translate to a deeper internal desire to attend the sessions and improve cognition.
Gilead staff members were also a major source of support and extrinsic motivation for participants. The staff would encourage and remind participants to attend the sessions, and were incredibly accommodating. They provided coffee and snacks and cleared a quiet room specifically for the sessions to be held. Staff members also personally called participants or their group homes when they were absent. The Gilead team was an incredibly important and effective bridge between the instructors and the clients, and it is safe to say that the CogSMART sessions would not nearly have been as well attended or effective had they not been present.

As previously stated, our participants were greatly impaired in multiple cognitive domains. Additionally, the mean age was 47.6 years, mean duration of illness 24.2 years, and mean years of education 10.8. All of the participants had been out of school for decades, and were currently unemployed. As a result, although the sessions seemed rather straightforward, most participants found aspects of them to be quiet challenging – especially being asked to focus on one task for an extended period of time. The difficulty of the sessions for some participants combined with motivational deficits occasionally prevented the completion of certain activities. This also altered the pace and length of the sessions. Sometimes participants were quite distracted and would need frequent water or smoke breaks. On occasion, participants would express fatigue or distress and would request to leave the session early.

Instructors made an effort to encourage participants to try and complete the entire session, but did not force participants to stay in the sessions against their will. Resistance to performing cognitive tasks has been reported in patients of similar age, duration of illness, schooling, and functioning (Rangel et al., 2015).
C. Limitations and Future Directions

I, Sofia Zaidman, the primary instructor and author of this paper, had extensive experience working with subjects diagnosed with schizophrenia and/or other primary psychotic disorders on other research protocols for the Kurtz Schizophrenia Cognition Lab prior to this study. I also had prior experience tutoring small groups and was well versed in the basic principles of teaching and interacting with students in such a setting. However, I had never been trained to specifically teach a strategic cognitive remediation program prior to this study, and neither had anyone else in our lab. Thus, questions regarding the fidelity of our administration of the CogSMART program could be raised. While the CogSMART sessions are designed to be very straightforward, leading them and ensuring that each participant gets as much out of the material as possible takes quite a lot of skill. Now that a precedent has been set and we have received detailed and thoughtful feedback from Dr. Twamley, instruction of sessions will continue to improve and evolve. However, the very “pilot” nature of this study cannot be ignored, and potentially detracted from the quality of the sessions.

As this was an exploratory study designed to assess the feasibility of employing the CogSMART program at Gilead and/or other community centers in the Middletown area, a small number of participants was inherent to the study’s design. While this limited the power of our statistical analyses, we were still able to obtain enough quantitative and qualitative data to make informed observations on the success/failure of running CogSMART at Gilead. If this project is continued, either at Gilead or other local outpatient centers, our sample size will continue to grow and our
statistical analyses and ability to make conclusions on the effectiveness of CogSMART will be strengthened.

This study lacked a control group, which prevents us from making definitive conclusions based on the results in Table 2. Without a no-CogSMART control group, we cannot say with confidence that these results were not at least in part a product of practice on specific measures, or some other unidentified factor such as the non-specific effects of interacting with a team leader on a regular basis or of being enrolled in a study you believe will improve your cognition. However, improvements in the specific domains of verbal learning, attention/concentration, and social cognition had been cited in previous studies (Wykes et al., 2011), and could have been expected. Moving forward, the addition of a control or alternate condition group will greatly strengthen this study.

It must be noted that at the time of the study, I was the only research assistant approved to administer many of the tests in our battery. This became an issue during post-testing, as the participants and I were well acquainted with each other, which could have affected their ratings on the subjectively scored outcome measures (PANSS, SES, SFS). In the future, the tester should not be involved in the administration of the CogSMART sessions.

Time was perhaps the largest limitation in this study. Dr. Twamley designed the CogSMART program to last 12 weeks with one session per week. However, due to difficulty organizing the logistics of the sessions with Gilead and compatibility issues with the semester system at Wesleyan, we had to condense the program into six weeks with two sessions per week. Dr. Twamley approved this decision and did
not say the integrity of the program would be affected. However, by condensing the sessions, we also condensed the time between pre and post-testing, and left less time for participants to complete homework assignments between sessions. This also made the program more intensive, which could have impacted the degree of improvement seen in post-testing and the tolerability of the program for participants. More frequent sessions over a shorter period of time could also have negatively impacted attendance, as participants had to remember to attend sessions multiple days a week. Moving forward, timing the start and end date of the sessions so that they could be completed over twelve weeks would be ideal.

In order to accurately assess the effectiveness of CogSMART and CogSMART alone, we were careful not to employ additional extrinsic motivators not specified in the CogSMART manual during the sessions. This means that participants were only paid for their time spent during pre and post-testing, and not for their attendance of the actual sessions. Although all participants elected to attend the sessions and understood that they would not be paid for their attendance, they frequently expressed a desire to be compensated for their time. Gilead staff also suggested that attendance would improve if participants were compensated even a few dollars for their presence at each session.

Opinion on the use of “hard” extrinsic motivators (money) in CR programs is mixed at best. In a 2011 article evaluating motivation’s role in CR programs for schizophrenia, Medalia and Saperstein argue that the use of “soft” extrinsic motivation (eg, points and certificates) could be more effective in encouraging sustained learning than monetary rewards (Medalia & Saperstein, 2011).
Additionally, in his 2010 review of motivation in CR programs, Silverstein argues for the importance of soft (non-tangible) rather than hard rewards for clients with low IM and greater cognitive impairment (Silverstein, 2010).

Within the sessions, participants did respond well to soft rewards such as praise, being able to select a personal calendar, and certificates of completion. With this in mind, perhaps the establishment of a point system would be more appropriate than monetary compensation for encouraging attendance. Further, greater personalization and community building within the program (e.g., more creative activities or opportunities for participants to share things they do well or are proud of) could create incentive for participants to attend the sessions in the absence of extrinsic motivators.

D. Conclusions

Though limited by a small sample size, our results are encouraging, and support the continuation of the CogSMART program for remediation of cognitive and social cognitive deficits for clients at the Gilead Community Services Social Rehabilitation Center in Middletown, and potentially other outpatient community centers. The high level of therapist-client interaction and associated motivation and support inherent to CogSMART’s design made the program especially well suited to the participants of this pilot study.
References


Seeman, P. (1987). Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse, 1*(2), 133-152.


