Comparing Intrinsic and Extrinsic Motivation as Targets for Enhancing Cognitive Remediation Outcomes in Schizophrenia

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Abstract

Motivational deficits have long been viewed as a core feature of schizophrenia. In recent years, there has been an increased focus on the role of motivation in cognitive remediation (CR) of schizophrenia, a type of skills-training intervention that focuses on improving cognitive deficits. While it is clear that deficits in both Intrinsic (IM) and Extrinsic (EM) motivation exist in schizophrenia, there is debate about which component is a more effective target for enhancing treatment effects of CR therapy. No published studies directly compare IM- and EM-based interventions in the context of CR therapy. Thus, the purpose of the current research project was to compare the utility of IM- and EM-based methods for enhancing CR outcomes, and also to investigate the effect of manipulating both IM and EM simultaneously. Data was collected from 18 outpatients diagnosed with either schizophrenia or schizoaffective disorder. Along with two CR training sessions targeting working memory deficits, participants either received an IM-enhancing intervention, an EM-based intervention, a combination of both interventions, or neither (a control group). The outcome measures were change in performance on the working memory training task used in the two CR sessions, as well as on working memory tasks not trained in the CR program in order to assess the possibility of generalization of CR effects. These assessments were administered at baseline and immediately post-training, as well as at a three-week follow-up in order to determine if intervention-mediated effects were persistent. The results showed that 1) the EM intervention did not improve CR outcomes, as indicated by change in performance on trained and untrained working memory measures, 2) the IM intervention resulted in some significant improvements, and 3) administering both interventions resulted in more significant and persistent improvements compared to either intervention alone. This suggests that targeting IM and EM simultaneously might be the most effective way to enhance learning and skill-acquisition in CR therapy, providing important insight into how motivational deficits in schizophrenia can be modified to enhance treatment outcome.
Chapter 1. Introduction: Schizophrenia

1.1 Schizophrenia—Diagnosis and Symptoms

Schizophrenia is a disabling mental illness in which those affected experience altered thought processes, perceptions, emotions, and behaviors (Tsuang, 2011). It is a heterogeneous disorder, characterized by delusions, hallucinations, emotional dysregulation, difficulties in interpersonal and occupational functioning, and cognitive impairment. It has a peak age of onset in the early twenties in men, and three or four years later in women (Saha, 2005). In the U.S., the cost of treating people with schizophrenia has been estimated to be USD 62.7 billion per year (Wu, 2005). Among diagnosed individuals, 80-85% are typically unemployed at any given time (Silverstein, 2008), which further adds to the financial burden on the government and society. The risk of dying is two to three times higher in individuals with schizophrenia compared with the general population, resulting from a combination of high rates of suicide and various comorbid somatic conditions; unfortunately, this mortality gap has increased over recent decades (McGrath, 2008). Despite advances in research, there is still so much we don’t know about this disorder—the etiology is unclear, our understanding of risk factors is low, we don’t have reliable preventative mechanisms, and diagnosis is still made late in the course of the disease’s developmental trajectory (Silverstein, 2013).

Due to the current absence of any biological markers, schizophrenia must be diagnosed on the basis of clinical interviews that assess signs and symptoms. The most recent version of the Diagnostic and Statistical Manual, the DSM-5, lists the
five key symptoms of the disorder as 1) delusions, 2) hallucinations, 3) disorganized speech, 4) disorganized or catatonic behavior, and 5) negative symptoms (American Psychiatric Association, 2013). Criterion A states that two of these five symptoms are required and that at least one symptom must be one of the first three (delusions, hallucinations, disorganized speech). These symptoms must be present for a significant portion of time during a 1-month period (or less if successfully treated). Evidence of significant social/occupational dysfunction is also a criterion for diagnosis (American Psychiatric Association, 2013). Despite the heterogeneity of schizophrenia, it has historically been treated as a singular entity (Janicak, 2014). However, the scientific community has recently transitioned towards a belief that our construct of schizophrenia encompasses not one but several diseases (Keshavan, 2011). In past versions of the DSM, the heterogeneity of the illness was accounted for by defining distinct subtypes—paranoid, disorganized, catatonic, simple, and undifferentiated. These subtypes, however, provided an inadequate description of the heterogeneity of this condition (Janicak, 2014), and had virtually no clinical or research utility (Tandon, 2013). For reasons such as these, they have been removed from the classification system in the DSM-5.

1.1.1 Positive Symptoms

The symptoms of schizophrenia can be divided into two main categories: positive and negative symptoms. Positive symptoms are comprised of behaviors that are not observed in usual behavior, such as delusions and hallucinations.
Hallucinations are false perceptions, which commonly take the form of auditory hallucinations; an example would be a voice commenting on a patient’s thoughts or behaviors. Hallucinations can take several other forms, such as visual, sensory, or gustatory hallucinations (Tsuang, 2011). Another common positive symptom is delusions, which are false beliefs that are persistent, irrational, and often quite bizarre. Although people with schizophrenia experience a diverse set of delusions, there are some common themes; for example, many patients experience paranoid delusions consisting of belief that others are trying to harm them (Tsuang, 2011). Another common type is grandiose delusions, which can range from an individual falsely claiming to have an extraordinary talent to an individual who believes he or she is the reincarnation of Jesus Christ. These positive symptoms are often detrimental to a patient’s relationships because the patient views them as real while others see them as bizarre or even frightening (Fletcher, 2009).

Although delusions are the most common form of thought disruption in schizophrenia, patients also often display disorganized or illogical patterns of thinking. For example, affected individuals can demonstrate a loosening of associations, in which they draw connections between seemingly unrelated concepts. In terms of symptoms relating to emotional regulation, individuals with schizophrenia may exhibit inappropriate affect (expressions of emotions that are incongruent with the ideas being expressed) or excessive emotional excitement (appropriate emotions are expressed abnormally intensely). Lastly, motor excitement is another positive symptom of schizophrenia, which consists of disorganized movements such as
excessive gesticulations, stereotypies (repetitive, meaningless movements), and habitual movements like fidgeting with one’s fingers (Tsuang, 2011).

1.1.2 Negative Symptoms

In contrast with positive symptoms, negative symptoms are comprised of reductions or deficiencies in normal emotions or behaviors. Negative symptoms may be more chronic and, in some ways, more devastating than positive symptoms (Tsuang, 2011). While the psychotic symptoms associated with schizophrenia can generally be addressed by pharmacological interventions (Foussias, 2010), negative symptoms are more resistant to current interventions (Foussias, 2015). Negative symptoms can be separated into two classes: Diminished expression and avolition. Diminished expression is comprised of symptoms such as restricted affect (reduced emotional expression) and alogia (diminished speech production). Avolition refers to reduction in motivated or goal-directed behavior (Messinger, 2011). Symptoms in this category are amotivation, anhedonia (reduction in feelings of pleasure), and asociality (social withdrawal or avoidance). These motivational disturbances impact nearly all aspects of behavior, including adherence to treatments and the ability to learn skills necessary for functioning in the community (Barch, 2014).

Negative symptoms adversely impact patients’ longitudinal social, occupational, and functional outcomes, as well their long-term recovery (Nguyen, 2016). Recent research indicates that negative symptoms are important treatment targets since they are associated with a number of positive clinical outcomes,
including subjective well-being, quality of life, and recovery (Meehl, 2001) (Strauss, 2010, 2012, 2013). Despite this growing understanding of the importance of negative symptoms in relation to both poor functional outcome and recovery goals, the underlying mechanisms of these deficits remain poorly understood (Fervaha, 2014). For this reason, research into the causes and potential treatments of these symptoms should be highly prioritized.

1.1.3 Neurocognitive Impairment

In addition to positive and negative symptoms, neurocognitive impairment is considered to be a core feature of schizophrenia. These deficits occur in more than 85% of patients (Isaac, 2016), and impact a wide variety of cognitive functions such as attention, processing speed, executive functioning, verbal fluency, social cognition, theory of mind, and memory (including episodic, verbal, and working memory). Cognitive impairments can be detected in patients during the prodromal phase of the illness (prior to the first psychotic episode), and it has been shown that these deficits deteriorate further around the onset of psychotic symptoms (Shmukler, 2015). Worse cognitive functioning has been related to longer durations of untreated psychosis (Scully, 1997), which suggests that intervening early in the course of illness is important for reducing the severity and impact of cognitive deficits.

Cognitive functioning is a contributing factor to functional outcomes for individuals with schizophrenia. For example, one study found that individuals’ performance in various cognitive domains (including working memory, attention, and
processing speed) strongly predicted their likelihood of returning to work or school by 9 months after clinical stabilization (Neuchterlein, 2011). Other functional outcomes that are strongly related to cognitive impairments are residential independence, self-care skills, and occupational engagement (Fett, 2011) (Harvey, 2012). Cognitive impairment is also one of the greatest contributors to poor social functioning in schizophrenia (Brekke, 2007) (Brekke, 2009). Functional disability results in huge indirect health costs, which may be as much as three times the cost of treating the psychotic symptoms of schizophrenia (Harvey, 2012); since antipsychotics have little to no positive impact on cognitive deficits (Keefe, 2007), behavioral interventions like cognitive remediation (CR) therapy have been a major focus of recent research.

1.2 Incidence & Prevalence

Schizophrenia occurs in diverse populations at comparable rates (Jablensky, 1992), though exact measures of incidence and prevalence vary greatly across studies. A meta-analysis that systematically reviewed over 150 published studies calculated the median incidence to be 15.2 per 100,000 individuals, with a male:female ratio of 1.4:1. The incidence was higher in studies done in exclusively urban settings compared to those done in mixed urban and rural settings, but incidence did not differ according to socioeconomic status (McGrath, 2008). The same meta-analysis calculated the median lifetime prevalence to be 4 per 1,000 persons based on results from 24 studies. This analysis found that prevalence estimates did not differ between
males and females or urban versus rural settings, but showed that developed countries had higher prevalence estimates than those with less developed economies (McGrath, 2008). This observation is supported by a ten-country study conducted by the World Health Organization, which also found that the prognosis of schizophrenia was better in developing countries than in developed countries (Jablensky, 1992).

1.3. Neurochemical Dysfunction in Schizophrenia

1.3.1 The Dopamine Hypothesis

The dopamine hypothesis is a widely known theory explaining the pathophysiology of schizophrenia; it postulates that the symptoms of schizophrenia are caused by dysregulation or dysfunction of the dopaminergic system. This theory arose in the 1950’s based on the observation that dopamine-depleting drugs reduced psychotic symptoms (Campden-Main, 1955) (Arnold, 1956). More concrete evidence arose when researchers began to perform post-mortem analyses of the brain, which revealed that patients with schizophrenia showed increased striatal dopamine levels and increased D2 receptor density (Owen 1978) (Mackay 1982). The simplicity of the original dopamine hypothesis was called into question in the 1990’s when an article called “Dopamine in schizophrenia: a review and reconceptualization” by Davis et al was published (Davis, 1991). These researchers suggested that since different dopamine receptors were distributed differently throughout the brain, the effects of abnormal dopamine transmission in schizophrenia could impact brain regions differently. Based on evidence from a variety of studies, they proposed an updated
dopamine hypothesis that involved reduced dopamine transmission in the prefrontal
cortex (likely cause of negative symptoms) and excess dopamine transmission in the
striatum (likely cause of positive symptoms) (Howes, 2009).

Since neuroimaging technology and techniques for measuring dopamine
levels have greatly improved since 1991, our understanding of dopamine’s role in
schizophrenia has changed drastically. The role of dopamine and its receptors have
been further investigated by studies using a variety of methods such as most-mortem
analysis, PET and SPECT imaging, and measures of radioligand binding. Some
widely replicated findings in regards to dopamine abnormalities are the presence of
elevated presynaptic striatal dopamine availability, and increased release of dopamine
into the synapse in the striatum (Howes, 2009). Some recent studies have supported
the hypothesis that D2 receptors are altered in schizophrenia (Howes, 2015),
including evidence of a link between the DRD2 gene and schizophrenia
(Schizophrenia Working Group of the Psychiatric Genomics, 2014). However, there
are many inconsistencies in this aspect of the dopamine hypothesis; although some
studies have found increased D2 receptor availability in patients with schizophrenia,
others have found no difference from controls (Farde L 1990; Martinot 1990) or that
increases can be attributed to antipsychotic treatment (Silverstri, 2000).

In general, it seems that the previous focus on D2 receptor dysregulation has
been replaced by evidence for dopamine dysregulation at the presynaptic level. In
terms of D1 receptors in the prefrontal cortex, recent studies have been relatively
inconsistent (Howes, 2015); however, there is evidence suggesting that low levels of
dopamine in the prefrontal cortex is related to cognitive deficits in schizophrenia, and that D1 receptors may actually be upregulated in the prefrontal cortex as a compensatory mechanism (Abi-Dargham, 2002). Despite the number of inconsistencies between current research and earlier versions of the dopamine hypothesis, the longstanding idea that antipsychotic drugs primarily work by blocking D2 receptors in the striatum has remained true, although this is likely not the sole mechanism (Howes, 2015).

1.3.2 The Glutamate Hypothesis

The concept that glutamate neurotransmission could be involved with the pathophysiology of schizophrenia stems from the observation of behaviors induced by drugs like PCP and ketamine, which are both NMDA receptor antagonists; these drugs can induce psychotic symptoms, cognitive deficits, and motor abnormalities that are similar to symptoms of schizophrenia (Javitt, 1991). Further, observations of reduced NMDA receptor density in the prefrontal cortex and hippocampus in post-mortem studies led to an increased focus on NMDA receptor dysfunction (Harrison, 1999). NMDA receptor involvement is supported by the fact that when NMDA receptor auto-antibodies are administered to healthy participants, it induces a schizophrenia-like syndrome that resolves upon removal of the antibodies (Dalmau, 2008). Evidence for NMDA receptor hypofunction in schizophrenia is provided by successful clinical trials of drugs that modulate the NMDA receptor, but there has been a fair amount of inconsistency between studies (Tsai, 2010).
A review of recent research pertaining to glutamate dysfunction in schizophrenia found that although there is evidence of morphological alterations in dendrites of glutamatergic neurons in the cerebral cortex of affected individuals, there is not enough evidence to support reductions in glutamate receptors or associated vesicular transporters (Hu, 2015). Also, theories of reduced glutamate transmission in schizophrenia are challenged by studies using magnetic resonance spectroscopy to indirectly measure glutamate levels, which show that tissue levels of glutamate are elevated in the prefrontal cortex (Poels, 2014). These observations do not rule out the role of glutamatergic dysfunction in the etiology of schizophrenia, but they do highlight the need for continued research on glutamate’s role.

1.3.3 The Role of GABA

There is evidence for disruptions in GABA activity in schizophrenia, which are observed in first-episode and antipsychotic-free patients (Wassef, 2003). One study that compared GABA levels between antipsychotic-free patients and healthy controls revealed elevated GABA concentrations in the medial prefrontal cortex of the schizophrenia group (Kegeles, 2012). There also seems to be an association between stage of illness and GABA levels, with a recent proton magnetic resonance spectroscopy study showing increased GABA levels in younger patients with schizophrenia compared with older patients (Rowland, 2013). A more specific theory about GABA’s role in schizophrenia is that dysfunction of GABA interneurons, especially those that contain a calcium-binding protein called parvalbumin (PV),
results in an imbalance between inhibition and excitation in the cerebral cortex (Won, 2015). Various lines of evidence support this theory, including studies that show reduced PV-positive GABA interneurons (Beasley, 1997) and reduced mRNA and protein levels of glutamate decarboxylase 67, the enzyme that synthesizes GABA, in the frontal cortex of schizophrenia patients (Beasley, 2002).

While the dopamine and glutamate hypotheses primarily account for the positive symptoms of schizophrenia, dysfunction of GABAergic neurotransmission likely pertains to neurocognitive dysfunction. PV-positive GABAergic interneurons play a role in synchronous neural activity in the brain, which can produce gamma frequency oscillations in neural networks such as the DLPFC (Won, 2015). These oscillations produced by synchronous neural firing in the DLPFC are considered to underlie cognitive processes such as working memory (Roopun, 2008), an area of cognition that is known to be greatly impaired in schizophrenia (Forbes, 2009). It is important to note that pyramidal glutamatergic neurons are also responsible for synchronous oscillatory activity in the brain, so it is possible that abnormal glutamate transmission may also play a role in neurocognitive deficits. One study provides support for the involvement of both neurotransmitters in cognitive deficits, and suggests that glutamate dysfunction may lie upstream of GABA dysfunction; in rats treated with MK-801, a non-competitive NMDA agonist that results in NDMA receptor hypofunction in PFC neurons and subsequent disinhibition of pyramidal cells, researchers observed an upstream GAD 67 deficit in PV-positive GABA interneurons in the PFC (Homayoun 2007). Future studies should seek to clarify the
nature of these neurochemical abnormalities, especially since current pharmacological interventions for schizophrenia do not treat neurocognitive deficits.

1.4 Etiology

1.4.1. Genetics

For many decades, epidemiological studies have found significant genetic contributions to people’s risks for developing schizophrenia. These conclusions were first drawn based on the observations that the illness runs in families, but this is not sufficient to prove that genes are responsible since family members are often reared in the same environment. For this reason, researchers have studied concordance rates between monozygotic and dizygotic twins in order to clarify the genetic contributions to schizophrenia risk. Results from early studies suggested that genetics account for ~80% of variance in disease susceptibility (Cannon, 1998) (Cardno, 1999). A more recent and larger-scale analysis estimated that variance due to additive genetic effects was ~64% (Lichtenstein, 2009).

Only in the past few years has the technology for genetic analysis been advanced enough to identify specific risk loci for the development of schizophrenia. Methods such as whole-exome sequencing and genomic wide association studies have led to the establishment of more than 128 common single nucleotide polymorphisms (SNPs) and ~15 rare copy number variants (Kotlar, 2015) associated with schizophrenia risk. These findings reveal the complex and polygenic nature of schizophrenia’s genetic etiology, which is not surprising considering the vast
heterogeneity of the illness itself. Several of these discovered risk loci are found in genes coding for dopamine D2 and serotonin receptors (Daisuke, 2015), as well as in genes involved with glutamatergic neurotransmission (Schizophrenia Working Group of the Psychiatric Genomics, 2014) and cytoskeleton-associated scaffold proteins at the postsynaptic density (Purcell, 2014). Despite these numerous findings, a large-scale genetic study of schizophrenia found that the 108 most statistically significant SNPs together could only account for 3.4% of variance (Schizophrenia Working Group of the Psychiatric Genomics, 2014), which is quite small in relation to the estimated heritability rates. However, since this is a rapidly developing field, future studies are likely to shed light on the genetic risk factors for schizophrenia and also inform our understanding of the disease’s underlying neurobiology.

1.4.1. Environmental Risk Factors

As discussed previously, schizophrenia is increasingly being conceptualized as a neurodevelopmental disorder. An early onset of pathogenesis is supported by the presence of minor physical anomalies and neuromotor abnormalities during childhood (Xu, 2011) (Walker, 1994). For a long time, it has been proposed that the pathogenesis of schizophrenia has pre- or perinatal origins, possibly through environmental insults or genetically mediated defects in neuronal migration (Weinberger, 1987). This theory is supported by postmortem studies that indicate alterations in neuronal migration from subcortical to cortical regions, a process that occurs during the second trimester (Kovalenko, 2003). Considering the
conceptualization of schizophrenia as a developmental disorder, it is important to look at environmental risk factors in order to understand the etiology of the disease and to identify possible preventative interventions.

Epidemiologic studies link increased risk of developing schizophrenia to increased paternal age—offspring of fathers who are older than 35 years have up to a three-fold increased risk (Malaspina, 2001) (Wohl, 2007). Another risk factor is nutritional deficiency in-utero, resulting from maternal exposure to famine during pregnancy (Susser, 1992) (St Clair, 2005), and some studies have attributed this to specific deficiencies such as vitamin A, vitamin D, folate, and essential fatty acids (Brown, 2008). Maternal exposure to infectious agents like viruses and bacteria during pregnancy has also been repeatedly shown to significantly increase offspring’s schizophrenia risk (Daisuke, 2015). For example, studies show that there is a 7-fold increase in risk for offspring if mothers are infected with influenza during the first trimester of pregnancy (Brown, 2004). Maternal adverse life events during pregnancy also increase risk, but evidence from animal models suggest that this effect of maternal stress on the offspring is mediated through alterations in the mother’s immune system (Daisuke, 2015). In terms of environmental risk factors that occur during childhood, studies have found that negative rearing environments and high levels of childhood stress increase the risk of developing psychotic disorders (Bart, 2009). Later in development, it appears that cannabis and other drugs of abuse contribute to risk for developing psychotic disorders; cannabis use is related not only to increased risk, but also to decreased age of onset (Sugranyes, 2009).
1.5 Cognitive Remediation Therapy

The symptoms of schizophrenia are treated using pharmacological agents, chiefly antipsychotics, as well as various behavioral therapies. Since remediation of cognitive deficits is a main focus of the research project being discussed in this paper, treatments for only this symptom domain will be reviewed. Cognitive remediation (CR) represents a variety of learning-based interventions that aim to improve and/or sustain various cognitive abilities (Saperstein, 2013). Cognition-enhancing approaches aim to improve cognitive functioning through stimulating impaired areas of cognition, which most commonly use “drill and practice” methods that involve repetitive practice of increasingly difficult cognitive exercises (Janicak, 2014). Some CR programs also utilize a method called strategy-coaching, in which a therapist discusses with the patient how newly acquired cognitive skills can be applied in real-world settings and result in improved community functioning (Wykes, 2007). The ultimate goal of CR is that improvements will generalize to untrained cognitive skills as well as transfer to real-world psychosocial outcomes (Saperstein, 2013).

The efficacy of CR therapies have been evaluated in multiple reviews and meta-analyses, and the findings have consistently described a moderate effect size for improvements in global cognitive functioning, as well as for improvements in real-world psychosocial functioning (McGurk, 2007) (Wykes, 2011). In terms of improvements in functional outcome, studies have consistently shown that the effects of cognitive training are greatly augmented when administered along with more comprehensive psychosocial rehabilitation therapies (Janicak, 2014). In an analysis of
26 studies that showed a mean effect size of .36 for functional outcome measures, the
effect size rose to .47 when only studies with adjunctive psychosocial rehabilitation
were included, and dropped to .04 when including only studies without adjunctive
therapy (McGurk, 2007).

Studies have also examined the effects of CR on the brain; in clinical trials,
researchers have found localized changes in brain activity (Wykes, 1998) (Wykes,
2002) (Wykes, 2011) and structure (Eack, 2010), and more recently, improvements in
the functioning of neural networks (Penades, 2013). A meta-analysis investigating the
neural correlates of CR-driven cognitive improvements in schizophrenia support the
existence of neuroplastic effects of CR on the functional organization of neural
networks. Specifically, it found that CR improves activation in several cortical and
subcortical regions, as well as frontal regions associated with high-level cognitive and
social-cognitive functions (Isaac, 2016). Given that the present research study utilizes
a CR program specifically targeting working memory skills, a recent meta-analysis
investigating the effect of working memory training in schizophrenia is quite relevant.
The results of this investigation suggest a neuroplastic effect of working memory
training in schizophrenia, mainly in the dorsolateral prefrontal cortex (DLPFC), the
precuneus, and the fusiform gyrus (Li, 2015). In summary, given the grave impact
that cognitive deficits have on functional disability in schizophrenia, it is highly
important that future studies explore methods for increasing the efficacy of CR
therapies for improving cognitive skills, functional outcomes, and functional
connectivity in the brain.
Chapter 2. Introduction: Motivation

Motivation is a surprisingly challenging concept to define, and the wide range of theories used to conceptualize motivation throughout history is reflective of this difficulty. In the context of human behavior, motivation can be described as the process by which a need or desire can energize behavior and direct it towards a goal. There are many motivation concepts that have developed and evolved throughout the last century. One of the earliest concepts explained motivation as the drive to maintain homeostatic balance (Cannon, 1932); this theory is most useful for explaining motivation relating to hunger, thirst, or nutrient intake, but may not be sufficient to explain motivation for behaviors more complex than correcting physiological deficits (Berridge, 2004). Many theories of motivation have evolved since the conceptualization of homeostatic drive, but exploring the more recent theories will best help to set the scene for an in-depth discussion of motivational deficits in schizophrenia.

2.1 Incentive Motivation

While earlier theories suggested that motivated behaviors are driven by the need to meet internal needs like homeostatic balance, incentive motivation concepts focus on how behaviors can be motivated by an individual’s desire for reinforcements or rewards. These concepts became popular in the 1960’s when behavioral neuroscientists began to reject the simplicity of earlier drive theories (Berridge, 2004). One of the first steps in developing the concept of incentive motivation was
when a biopsychologist named Robert Bolles posited that individuals are motivated by incentive expectancies, or learned expectations of hedonic reward. He theorized that through Pavlovian or classical conditioning, a neutral stimulus that is repeatedly paired with a hedonic reward would acquire motivational value due to its predictive expectancy of reward (Bolles, 1972). A psychologist Dalbir Bindra built upon this idea by suggesting that this conditioned stimulus does not simply cause expectation of reward, but rather it actually evokes a motivational state similar to what would be evoked by the reward itself (Bindra, 1974); in other words, the individual would actually perceive the previously neutral stimulus as a hedonic reward (Berridge, 2004). As a result of this conditioned incentive, the conditioned stimulus would elicit approach and goal-directed behaviors, explaining the mechanism by which motivation is elicited by these learned expectancies.

2.2. The Incentive Salience Model

According to the above-mentioned theories, the conditioned stimuli are not just “wanted”; since the previously neutral stimuli come to be perceived as hedonic rewards, it can also be said that they are “liked”. This begs the question of whether these two concepts are synonymous or distinct in the context of incentive motivation. Not until 1990 was it proposed that not only are “wanting” and “liking” two distinct components of reward, but also that the neural correlates of these components are also distinct from one another; this theory of motivation is called incentive salience (Robinson, 1993). “Liking” is the hedonic impact—or feeling of pleasure—
experienced after receiving a reward. This hedonic experience can occur for an unconditioned reward such as food, or for a conditioned stimulus that acquired hedonic value after being repeatedly paired with a reward (conditioned ‘liking’). On the other hand, “wanting”—also referred to as incentive salience—is the motivational incentive value of a reward, which is completely distinct from the sensory pleasure associated with that reward (Berridge, 1998).

In most circumstances, both ‘liking’ and ‘wanting’ occur together in relation to a rewarding stimulus; however, the fact that they are distinct components of reward with separate neural circuits means that one can indeed occur without the other. For example, blocking dopamine can reduce ‘wanting’ for rewards like food, sex, or drugs, while leaving the hedonic impact or ‘liking’ response to those rewards intact (Berridge, 2004). Conversely, different brain manipulations can produce ‘wanting’ without ‘liking’ (Berridge, 1998) (Pecina, 2003). This means that incentive salience can be attributed to a reward stimulus—resulting in an increase of goal-directed behaviors towards it—even though the actual reward is not ‘liked’ or could even be disliked. Observing the consequences of having one without the other makes it apparent that both ‘wanting’ and ‘liking’ are necessary for normal experiences of rewards and appropriate reward-seeking motivated behaviors. It is important to note that ‘wanting’ in this context is separate from cognitive forms of wanting, which describe a subjective feeling of desire for a reward based on declarative memories of previously reward and conscious expectations of future reward (Berridge, 2004). In the context of the incentive salience model, ‘wanting’ does not rely on conscious
understanding of causal relationships between a behavior and its hedonic outcome; it is mediated by more simple neural mechanisms, and is triggered by relatively basic stimuli (Berridge, 2003). Similarly, ‘liking’ is different from conscious liking; while the experience of “liking” is often accompanied by subjective feelings of pleasure, ‘liking’ produces objective behavioral or physiological reactions that can occur without conscious recognition of the reward’s hedonic impact (Berridge, 2003) (Dickinson, 2002).

In terms of their neural correlates, ‘wanting’ depends on subcortical mesolimbic dopamine transmission; research has demonstrated that neurochemical lesions in dopaminergic pathways that project to the nucleus accumbens disrupt incentive salience for rewards (Berridge, 1998) (Pecina, 1997). Studies have also suggested more specifically that mesolimbic dopamine activation of GABAergic spiny neurons in regions of the nucleus accumbens is responsible for producing incentive salience (Reynolds, 2002) (Wyvell, 2000). Again, this form of ‘wanting’ is separate from cognitive forms of wanting, which depend on cortical brain regions like the orbitofrontal cortex and insular cortex (Balleine, 1998) (Dickinson, 2002). The neural correlates of ‘liking’ are often specific to the form of pleasure being experienced (i.e. sweetness). Since ‘liking’ in this context is separate from subjective feelings of pleasure, researchers must measure ‘liking’ through objective hedonic reactions that are not consciously mediated, such as facial expressions. Researchers have found that facial expressions that reflect ‘liking’ or ‘disliking’ of taste stimuli are generated in the brain stem, and also that other circuits involving the forebrain can
override the brainstem’s control over affective expressions to taste (Berridge, 2003b). Specific mechanisms in the forebrain that can generate ‘liking’ are opioid neurotransmission onto GABAergic spiny neurons in the shell of the nucleus accumbens (Kaczmarek, 2000) (Pecina, 2000) (Berridge, 2003b), as well as outputs from the nucleus accumbens to the lateral hypothalamus and ventral pallidum (Berridge, 2003b) (Cromwell, 1993). It is important to note that mesolimbic dopamine transmission mediates only incentive salience for rewards (‘wanting’), not hedonic response to sensory pleasure (‘liking’) (Berridge, 2004); the relevance of mesolimbic dopamine transmission to motivational impairments in schizophrenia will become clear in later chapters.

2.3 Self-Determination Theory

While introducing the incentive salience model provides important background information about the behavioral neuroscience of motivation, the basic tenets of motivational psychology must also be reviewed before examining the motivational deficits seen in schizophrenia. The most prominent human motivation science theory is Self-Determination Theory (SDT) (Deci, 1985). While the above-mentioned theories of motivation focus on non-conscious reward processing, SDT is more involved with the conscious aspects of motivation and drive. An important feature of SDT is that both the personality and the environment or social context of the individual are taken into account when evaluating motivated behavior (Patrick, 2012). SDT conceptually separates motivation into different categories based on the
extent to which behaviors are autonomous (originating from the self) versus controlled (driven by external influences). These two categories are referred to as intrinsic motivation (IM) and extrinsic motivation (EM), respectively, and they are a key focus of the present research project.

### 2.3.1 Intrinsic Motivation

Intrinsic motivation (IM) involves the drive to engage in behaviors based on the interest, enjoyment, and satisfaction provided to the participating individual (Deci, 1985). IM is an innate component of human behavior; starting from birth, humans actively learn, play, and explore without the need of any external incentives. SDT posits that intrinsically motivated behaviors are driven by three main intrinsic psychological needs—these are autonomy (motivation for agency and self-expression), competency (motivation to attain skills or knowledge), and relatedness (motivation to build interpersonal connections). According to SDT, these three needs are critical to supporting the process of internalization as well as for developing a proper level of motivation and personal wellbeing (Patrick, 2012).

SDT also says that fulfillment of these needs is closely associated with the social milieu of the present context, meaning that IM is facilitated if other people in the environment support the individual’s needs for autonomy, relatedness, and competence, a concept which is referred to as ‘need support’ (Deci, 2000). For decades, a major research goal has centered on determining what environmental factors facilitate versus undermine IM. This interest in IM is partially based on
consistent findings that more autonomous motivation is associated with more sustained engagement in a behavior (Vansteenkiste, 2004) (Li, 2008), which could be highly relevant in various contexts including education, preventative health, and treatment engagement. Research on this subject has led to identification of the “motivation crowding-out effect,” which describes the observation that extrinsic rewards can undermine people’s IM for a task or behavior (Deci, 1999).

2.3.2 Extrinsic Motivation

In contrast, extrinsic motivation (EM) involves behaviors executed to obtain external reward or to avoid punishment. According to SDT, behaviors that are highly extrinsically motivated can regulate short-term behavior but are ineffective at sustaining those behaviors over time (Deci, 1985). However, it must be noted that these categories of motivation are not entirely black and white, and can be better described as existing on a motivation continuum. In SDT, “internalization” is a term used to describe the process by which behaviors shift over time from being externally controlled to more autonomously regulated. The most controlled forms of motivation are those that are driven exclusively by externally administered rewards and punishments. Still within the category of EM, SDT defines various levels of how “internalized” the regulation of a behavior is, which are termed introjected, identified, and integrated regulation. Introjected regulation involves behaviors that are driven by self-approval. Although these behaviors are somewhat internally regulated, they are performed in order to maintain self-esteem and pride or to avoid feelings of guilt
(Ryan, 2000). Identification regulation is the next most autonomous form of EM; this describes a behavior that is executed not because it is inherently fun or rewarding, but rather because an individual recognizes the value or utility of the behavior. The most autonomous form of EM is integrated regulation, which describes an extrinsically motivated behavior that becomes assimilated with one’s values, goals, or sense of self. Individuals will execute these behaviors because they feel these behaviors are part of who they are (e.g. regularly going to church) (Ryan, 2000). Although this may sound like IM because the behaviors are internally controlled, EM is still involved because the behaviors are being used to achieve a goal or reward rather than for the pure joy of participating (Cox, 2007).

**Chapter 3. Introduction: Motivational Deficits in Schizophrenia**

In a clinical context, motivational deficits describe a reduction in goal-directed behaviors and their associated internal processes that prompt individuals to plan, initiate, and pursue activities (Andreasen, 1982) (Foussias, 2015). Motivational deficits have long been viewed as a core feature of schizophrenia. The early 20th century psychiatrist Emil Kraepelin distinguished schizophrenia—which at that time was termed ‘dementia praecox’—from other psychotic disorders by a feature he described as “the weakening of the wellsprings of volition” (Kraepelin, 1919). This deficit in motivation was considered to be a distinguishing feature of the disease, leading to the presentation of other symptoms like emotional dullness, lack of occupation, and absence of drive (Carpenter, 2016). Later in the century when the
positive versus negative distinction was applied to the categorization of schizophrenia symptoms, avolition became a part of the negative symptom construct.

3.1 Motivational Deficits and Functional Outcomes

Negative symptoms have profound effects on the lives of individuals with schizophrenia. Out of the two main subdomains of negative symptoms—diminished emotional expression and avolition—researchers have found that avolition contributes more to overall severity of negative symptoms. Further, compared to patients who display diminished emotional expression as their primary negative symptom, those who primarily express apathy and avolition have worse functional outcomes (Strauss, 2013). Motivational deficits have been repeatedly shown to play an important role in predicting functional outcomes in schizophrenia (Fervaha, 2014b) (Foussias, 2011) (Konstantakopoulos, 2011) (Evensen, 2012). A recent study found that over 75% of patients with schizophrenia experience motivational impairments, and also that motivation explains 48% of the variance in global functional outcome. Additionally, it found that change in motivation is the most significant predictor of change in functional outcome at a 6-month follow up (Fervaha 2015), highlighting the influence of motivational deficits on longitudinal functioning in schizophrenia. There is also growing recognition that motivation among individuals with psychosis may influence both participation in and response to psychosocial interventions (Choi, 2010). This suggests that not only do motivational deficits impair everyday functioning, but also that they may impede the potential benefits of treatment, which is one reason that the
present research study is investigating methods for remediating motivational deficits in schizophrenia.

3.2 Motivational Deficits and Cognitive Impairment

Emerging evidence suggests that motivation is a central mediator in the relationship between cognition and functional outcome. A study that examined relationships between motivation, effort exerted in cognitive testing, and cognitive performance in schizophrenia found that amotivation is significantly correlated with global functioning, verbal and working memory, and verbal fluency (Foussias, 2015). Further analysis revealed that amotivation is the most significant predictor of cognitive performance, with effort partially mediating the relationship (Foussias, 2015). Another study also showed that measures of motivation positively correlate with global cognitive test performance across varying domains of cognition, and concluded that motivational deficits account for 6-16% of variance in patients’ neurocognition (Fervaha, 2014). Furthermore, lack of motivation is a significant mediator in the relationship between cognition and real-world skills (Nakagami, 2008), such as the ability to independently manage finances or find employment (Saperstein, 2011). In light of the sizable impact of motivation on functional outcome, treatment efficacy, and cognitive deficits in schizophrenia, the remainder of chapter will explore the specific components of motivation that are impaired in individuals with schizophrenia.
3.3 Deficits in Reinforcement Learning

Deficits in reinforcement learning are common in patients with schizophrenia (Waltz, 2007) (Ziauddeen, 2010) (Dowd, 2012), and may be an important factor underlying motivational impairments. Reinforcement learning refers to the development of associations between originally neutral stimuli or behavioral responses and outcomes that are either rewards or punishments. Studies have shown that patients with schizophrenia are impaired at making trial-by-trial adjustments in response to feedback, and that these impairments are associated with negative symptom severity (Waltz, 2011) (Waltz, 2007). More specifically, it has been demonstrated that learning from positive feedback is more severely impaired in patients with schizophrenia compared to learning from punishment (Strauss, 2011) (Waltz, 2011).

There are several proposed explanations for the mechanisms underlying poor feedback learning in schizophrenia. One explanation could be that patients fail to learn from feedback because of impairments in representation of stimulus value (Strauss, 2015) (Gold, 2012). Impairments in this ability are associated with aberrant activity in the orbito-frontal cortex (OFC), which plays a role in updating mental representations of value for stimuli and possible responses (Strauss, 2016). A different explanation is that reinforcement learning deficits stem from impaired reward anticipation, or the ability to signal reward availability when predictive cues are present, a process depends greatly on striatal dopamine transmission (Strauss, 2014). The existence of impaired reward prediction in schizophrenia is evidenced by
findings that patients have reduced activation in the ventral striatum in response to cues predicting upcoming rewards (Juckel, 2006) (Nielsen, 2012). Another alternative explanation is offered by a study showing that patients with schizophrenia performed poorly on a feedback-learning task compared to controls, despite the fact that both patients and controls met the criteria for learning the reward contingencies (Ciciero, 2014). Based on the participants’ ability to learn the contingencies and failure to apply this information during the task, these researchers suggested that deficits in reinforcement learning in schizophrenia may result from trouble transferring what is learned from feedback to novel stimuli or new environments.

There have been attempts to discover the neural correlates of feedback-learning deficits in schizophrenia. An fMRI study that compared performance on a task in which participants were either monetarily rewarded (motivated condition) or not rewarded (neutral condition) revealed an association between positive feedback learning deficits and aberrant striato-cortical connectivity only in schizophrenia patients. When the task switched from the neutral to the motivation condition, healthy controls showed increased activity in the left inferior frontal gyrus (IFG), while patients showed decreased activation. Patients also showed deficient left IFG to right ventral striatum (VS) connectivity compared to controls during the motivated condition (Reckless, 2015), despite having normal VS response to motivating stimuli. This suggests that impairments in the ability to discern motivationally salient stimuli may result from abnormally high VS to IFG connectivity during neutral events,
supporting past fMRI findings of hyperconnectivity between cortical and subcortical regions in patients with schizophrenia (Salvador, 2010) (Zhang, 2012).

These conclusions are supported by a similar fMRI study, which instead trained participants on a negative feedback learning task. Schizophrenia patients showed inappropriately strong VS activation in response to the neutral (unconditioned) stimulus compared to controls, suggesting an inability to distinguish between cues for aversive vs. neutral outcomes (Jensen, 2008). Parallels can be drawn between these neuroimaging findings and theories regarding the role of dopamine dysregulation in motivational deficits. It is proposed that in schizophrenia, the elevation in presynaptic dopamine leads to its release in the absence of appropriate stimuli (Winton-Brown, 2014). Dysregulated release may lead to the attribution of salience to irrelevant stimuli due to the stimuli’s temporal association with dopaminergic signaling, a phenomenon that would be consistent with the abnormally high responsiveness (both in terms of behavior and neural activity) to neutral stimuli observed in schizophrenia patients.

It has also been suggested that disruptions in goal-directed behaviors in patients with schizophrenia stem from deficits in prediction error signaling (Murray, 2008), which is the neural signal generated when outcomes deviate from prediction that help to guide future decision-making (Walton, 2004) (Behrens, 2007) (Brown, 2005). Positive prediction error signals occur when individuals experience an outcome that is better than expected, which is coded by transient bursts in dopamine (DA) cell firing, while negative prediction error signals occur when individuals
experience a worse than expected outcome, resulting in transient decreases in DA cell firing (Schultz, 1997). The electrophysiological signature of prediction errors is error-related negativity (ERN), a negative potential observed over the medial-frontal cortex following unpredicted outcomes of goal-directed behaviors (Holroyd, 2002) (Frank, 2005). The link between impaired prediction error signaling and feedback learning deficits has been strengthened by a recent study, which found that poor performance on a feedback-learning task correlates with diminished ERN amplitude in patients with schizophrenia. The study further supported this link by showing that twenty minutes of transcranial direct current stimulation (tDCS; a treatment that uses electrical currents to stimulate specific brain areas) across the medial-frontal cortex rescued patients’ low ERN amplitude and effectively restored patients’ ability to learn from feedback (Reinhart, 2015).

3.4 Impaired Representation of Reward Value

3.4.1 Deficits in Anticipatory Pleasure

As mentioned in the previous section, it has been postulated that the observed deficits in reward learning in schizophrenia may result from an inability to represent reward value (Gold, 2008). This deficit is closely linked to deficits in anticipatory pleasure—or pleasure pertaining to anticipation of future activities. Deficits in this component of hedonic experience have been observed in patients with schizophrenia (Gard, 2007), which has been theorized to contribute to low motivation and poor functioning (Foussias, 2011) (Strauss, 2013) (Rocca, 2014). Since anticipatory
pleasure is related to motivational processes that promote goal-directed behaviors (Schultz, 2002), deficits in this system likely play a role in the motivational deficits seen in schizophrenia.

It has been proposed that diminished pleasure experienced while anticipating future events underlies the negative symptom of anhedonia, while consummatory, or “in the moment,” pleasure remains intact (Kring, 2010). This raises questions in regards to the symptom of anhedonia—the inability to experience pleasure—being considered a core feature of schizophrenia (Gard, 2007). With the goal of clarifying this discrepancy, researchers designed a study to assess these two components of hedonic experience in schizophrenia. Patients were asked to rate emotional responses to various images (measure of consummatory pleasure), and then these images were associated with neutral cues through trial-and-error with feedback. After meeting the criteria for learning the associations (to ensure that deficits in feedback learning do not account for the results), patients were presented with a cue and asked to anticipate their emotional response to the associated image (measure of anticipatory pleasure). The results revealed a specific deficit in anticipating future pleasantness, and also supported previous findings that consummatory pleasure is intact in schizophrenia (Tremeau, 2010) (Choi, 2014). More specifically, those with schizophrenia overestimated future pleasure for low-rated images and underestimated future pleasure for high-rated images (Edwards, 2015).

Recent studies have sought to determine the neural correlates associated with deficits in anticipating pleasurable experiences for future rewards. Mucci et al. (2015)
examined the neural correlates of reward anticipation in 28 people with schizophrenia and 22 healthy controls using a task that associated varying magnitudes of monetary gains and losses with previously neutral cues. While controls showed increased response speeds upon seeing reward associated cues, the performance of individuals with schizophrenia was not affected by cue type, despite the fact that both groups learned the reward contingencies (Mucci, 2015). Using fMRI, they found dorsal caudate activity during reward anticipation correlated negatively with measures of avolition in schizophrenia, providing evidence for a link between dorsal caudate hypoactivation and motivational deficits. Also, patients and controls did not differ in measurements of hedonic experience, supporting intact consummatory pleasure in schizophrenia despite impaired transfer of pleasurable experiences to future motivational states (Mucci, 2015).

### 3.4.2 Impaired Effort Allocation

Another hypothesis is that disruptions in goal-directed behaviors in schizophrenia may result from failure to mobilize effort in response to maximally rewarding cues, or impaired effort allocation (Fervaha, 2013) (Gold, 2013) (Barch, 2014). In a recent study that utilized an effort-based decision-making task in which reward probability and reward magnitude varied across trials, healthy controls were more likely to choose high-effort tasks when the probability and magnitude of the reward were high. However, participants with schizophrenia failed to use probability and magnitude of reward to guide their choices, despite having no global reduction in
effort expenditure. These deficits in effort allocation correlated with negative symptom severity (Treadway, 2015), supporting past studies asserting that reduced effort exertion in maximally rewarding situations correlates with negative symptom severity and poor functional outcome (Fervaha, 2013) (Barch, 2014) (Gold, 2013) (Hartmann, 2015) (Strauss, 2015).

The anticipation of a future pleasurable experience is undoubtedly related to the effort that an individual will expend in order to obtain that rewarding experience. A recent study investigated whether probability and magnitude of reward would influence both effort allocation and anticipatory pleasure experienced by patients with schizophrenia. The results supported previous findings of impaired reward-maximizing effort allocation, and also revealed that patients with prominent negative symptoms experienced less anticipatory pleasure than controls when anticipating even high magnitude and probability rewards (Wang, 2015). This incongruity between the magnitude of the anticipated reward and the anticipatory pleasure experienced may explain why patients with severe negative symptoms lack motivation to allocate effort despite the potential for highly rewarding experiences.

The willingness to exert effort in order to receive rewards has been associated with several neural mechanisms, with dopamine transmission and anterior cingulate cortex (ACC) structure and function being keys players (Strauss, 2014). The ACC has been associated with effort allocation through both animal studies and human neuroimaging studies (Strauss, 2014). The ACC’s role in motivational deficits in schizophrenia is supported by structural MRI studies showing that patients have
reduced ACC volume, as well as from post-mortem studies (Benes, 2000) (Barch, 2000). However, research directly linking effort computations and ACC function in schizophrenia is needed. In terms of dopamine’s role in effort allocation, research has shown that dopamine depletion in the nucleus accumbens causes animals to make low effort, low reward choices over higher rewards options that require more effort (Barch, 2010). Although the presence of dopaminergic abnormalities in schizophrenia is well known, it is not clear exactly how they relate to impaired effort allocation.

Schizophrenia is characterized by increased striatal dopamine levels as well as increased release of dopamine in response to dopamine-enhancing agents, yet reduced effortful behavior is associated with decreased striatal dopamine release and receptor availability (Strauss, 2014). A few theories have been proposed in an attempt to reconcile this inconsistency. For example, researchers found that mice genetically altered to overexpress post-synaptic D2 receptors displayed reduced motivation to work for rewards despite intact hedonic reactions, much like what is observed in schizophrenia (Ward, 2012). Based on the fact that individuals with schizophrenia do in fact display an increase in D2 receptor availability (Fusar-Poli, 2013), the researchers suggested that overexpression of postsynaptic D2 receptors contribute to patients’ reduced effort to obtain rewards (Ward, 2012). An alternative theory is that both positive and negative symptoms result from irregular—rather than enhanced or reduced—striatal dopamine release, resulting in the failure to respond selectively and appropriately to rewarding stimuli (Treadway, 2015). This explanation is consistent
with the fact that studies on effort allocation find that patients do not display a global reduction of effort (Fervaha, 2013) (Gold, 2013) (Barch, 2014).

### 3.4.3 Integrating Learned Reward Value with Goal-directed Actions

As discussed, research has shown that schizophrenia patients demonstrate intact hedonic experiences (Kring, 1993) (Gard, 2007), indicating that deficits in goal-directed action do not result from diminished experience of rewards. Alternatively, it has been proposed that these deficits may result from disruptions in the ability to integrate knowledge of an action’s consequences with previously experienced value of those consequences (Kring, 2013) (Gold, 2008) (Dowd, 2012).

It is unknown whether this deficit results from failure to maintain memories of rewarding events or from a failure to use predictive cues to anticipate rewards, an issue that a recent study sought to clarify (Morris, 2015). This study evaluated the participants’ ability to use past experience and learned reward cues to guide goal-directed actions, using fMRI to explore the neural correlates of these cognitive processes. Both schizophrenia patients and controls were equally successful at learning the reward cues associated with liked snack foods, and also performed equally on explicit memory tests of the reward contingencies at the end of the experiment; however, the schizophrenia group was far less able to use reward cues to guide reward-seeking actions. This failure to use predictive cues to guide choices strongly correlated with reduced amygdala activity during cue presentation. Additionally, the schizophrenia group demonstrated hyperactivity in the medial OFC.
during non-reward cues, suggesting that the inability to use predictive cues to guide choice may result from a deficit in withholding the reward-seeking response to non-reward cues (Morris, 2015).

In a second part of the same experiment, a previously rewarding snack food was devaluated through association with unpleasant imagery. Although devaluation reduced the participants’ food ratings equally in both groups, only the controls demonstrated reduced reward seeking-behavior for that food during testing, indicating a deficit in integrating changes in experienced value with previously learned action-outcome associations in schizophrenia. This deficit corresponded to right caudate hypoactivation in the schizophrenia group, which also correlated with negative symptom severity and avolition scores. In addition to revealing specific deficits in integrating revised reward values with future goal-directed actions in schizophrenia, the study results highlight that limbic-striatal circuits mediate cue-guided choice impairments in schizophrenia, while corticostriatal circuits mediate goal-directed choice deficits (Morris, 2015).

Findings from a study using a mouse model of the negative symptoms in schizophrenia support the hypothesis that striatal dysfunction underlies motivational deficits relating to cue-guided choices. Researchers found that mice that overexpress D2 receptors in the striatum (D2R-OE mice) failed to use previously learned reward cues to guide performance on a sustained attention task, despite demonstrating no deficits in sustained attention or working memory maintenance. This suggests that the D2R-OE mice could maintain information about reward cues, but were unable to use
these representations to guide decision-making (Ward, 2015). The mice also showed an overall decrease in motivation during the task, aligning with previous studies showing that genetic D2R overexpression decreases motivation (Drew, 2007) (Ward, 2012). Further implicating striatal dopamine dysfunction in this motivational deficit, the researchers found that 2 weeks of doxycycline treatment to normalize D2R levels rescued the animals’ ability to modulate attention using learned reward signals (Ward, 2015). Based on these results, it should be considered that abnormal striatal dopamine transmission in schizophrenia could play a significant role in motivational deficits, especially in light of previously discussed findings that phasic dopamine signaling plays a role in modulation of behavior by cues signaling high-reward probabilities (Day, 2010) (Gan, 2010).

Chapter 4. IM vs. EM as Targets for Enhancing Motivation

It is clear that various components of motivated behavior and reward processing are impaired in schizophrenia; it is also clear that methods forremediating these deficits would have a high level of clinical utility. Despite a growing focus on the role of motivation in enhancing treatment outcomes in schizophrenia, there remains disagreement about which methods should be used to target motivation. Specifically, there is disagreement about the relative utility of interventions that target intrinsic motivation (IM) and those that target extrinsic motivation (EM) (Robinson, 2012). As discussed previously, IM is based on the innate needs for competence and self-determination. IM motivates people to seek out inherently fulfilling activities in
the absence of rewards, while EM describes how goal-directed behaviors are executed in order to obtain an external reward or to avoid punishment (Deci, 1985). The remainder of this introduction will review research on the utility of IM and EM as targets for enhancing learning and treatment outcomes for individuals with schizophrenia, which is the main focus of the current research project.

4.1 IM as a Treatment Target

IM has been established as a core deficit in schizophrenia, as well as a significant mediator of the relationship between cognition and functional outcome (Gard, 2009) (Nakagami, 2008). Recent studies have found a robust negative correlation between IM and amotivation, as well as between IM and overall negative symptom severity (Fervaha, 2015). Thus, targeting IM may serve as a way to reduce amotivation and overall negative symptomatology. However, while this correlation suggests that IM and amotivation share underlying processes, IM seems to have unique predictive power in explaining future cognitive and global functioning (Saperstein, 2011). This evidence that IM deficits and amotivation may be distinct offers a promising treatment pathway since it is known that amotivation is difficult to change, while IM has been shown to be malleable (Choi, 2014b). IM has been shown to change over time during treatment, with increases in IM correlating strongly with positive changes in psychosocial functioning (Nakagami, 2010), further emphasizing the clinical significance of IM.
Targeting IM has been shown to have many positive effects in the context of treatment. For example, studies have found that learning programs that promote IM by raising perceptions of competency are associated with improved attendance and more durable improvements in mental illnesses (Gooding, 2016). Additionally, a recently published study examining group-based behavioral therapies for work rehabilitation found that targeting feelings of autonomy and competence for learning vocational skills led to better vocational and social outcomes compared to programs that focused on vocational skills alone (Mervis, 2016). These studies show that components of IM such as autonomy and agency are malleable, and suggest that targeting these psychological needs can increase adherence to therapeutic programs and contribute to successful psychiatric rehabilitation (Choi, 2010).

The clinical utility of IM is further supported by evidence that it can be used to promote participation in and learning from CR therapy. It has been shown that patients with high IM are more likely to attend cognitive training sessions without extrinsic reinforcement and more likely to learn from certain treatments (Silverstein, 2010) (Choi, 2010). Strategies for promoting IM for CR therapy include allowing patients to establish personalized treatment goals, and also emphasizing the link between treatment activities and those individual recovery goals (Medalia, 2009). A recent study successfully increased IM for cognitive training using a brief psychoeducational intervention (two 45-minute sessions) modeled after motivational interviewing, a counseling style that aims to increase an individual’s IM for a specific goal. When the intervention was given at the beginning of cognitive training, it
significantly improved both IM and attendance for the CR program. The participants’ level of IM right after they received the intervention strongly predicted attendance, suggesting that targeting IM in patients with schizophrenia can result in increased adherence to therapeutic programs like CR therapy (Fiszdon, 2016).

4.2 EM as a Treatment Target

External motivators have been successfully used for over 50 years in treatments for schizophrenia (Robinson, 2012). Interventions that target EM are designed to attenuate the impact of motivational deficits via positive social feedback and tangible reinforcers (Velligan, 2006). Extrinsic motivators can be used to gradually increase or decrease a behavior, improve basic cognitive and social skills in those who are receiving intensive psychiatric care (Silverstein, 2014), and also to build momentum for IM when there is low motivation to tackle a challenging task (Silverstein, 2010). Recent neuroscience research has investigated the mechanisms by which rewards and changes in motivation can modulate neurocognitive processing, and studies shows that extrinsic rewards can be utilized in the context of cognitive training. There is evidence that performing tasks while receiving reward incentives leads to enhanced cognitive processes including working memory, anticipatory attention, episodic encoding, and decision making (Locke, 2010) (Maddox, 2010) (Pessoa, 2009) (Pessoa, 2010) (Shohamy, 2010). These changes in cognition are hypothesized to occur through modulation of neural circuits involving the prefrontal cortex, the midbrain dopamine system, and related subcortical structures (Braver,
For individuals with schizophrenia, studies have shown that extrinsic rewards have the potential to improve performance on various cognitive measures, such as attention, executive functioning, learning (Silverstein, 2001, 2005, 2009).

EM-based interventions have been studied over the past two decades as a way to target sustained attention, a cognitive deficit that interferes with the ability to engage in and benefit from psychosocial treatments (Silverstein, 1998). Studies have used a reward-based learning procedure called attention shaping (AS) to augment attention, task performance, and skill acquisition in psychosocial therapies. AS uses extrinsic reinforcement for successive approximations toward a desired behavior (e.g. paying attention for 2 min, then 3 min, then 4 min, and so on), beginning with reinforcement of behavior that is at the upper end of what the person can already do. Reinforcement in AS is typically in the form of small amounts of money for meeting goals, but rewards like snacks and social reinforcement have also been used. Studies have shown that patients receiving social skills training augmented with AS demonstrated significantly higher degrees of attentiveness, longer durations of attentiveness, and greater social skill acquisition compared to patients receiving training alone (Silverstein, 2009). Changes in attentiveness and learning of behavioral skills were significantly correlated, suggesting that AS-mediated improvements in attention successfully enhanced patients’ ability to learn from the training.

However, it remained unclear whether using this EM-based method is still effective when AS is done outside of the inpatient setting. In a more recent study of psychosocial training with AS, the same researcher sought to study the potential
generalizability of this EM-based intervention for schizophrenia patients in a partial hospital program who were participating in conversation skills therapy. The patients who most strongly responded to AS procedures (defined by greatest improvements in attentiveness over the course of treatment) showed significantly greater negative symptom reduction, social engagement, and skill acquisition compared to patients who responded less strongly. It is important to note that the patients experiencing these enhanced improvements represented a diverse set of symptom profiles, suggesting that a wide range of patients with attentional impairments could benefit from using AS procedures to augment psychosocial therapies (Silverstein, 2014). However, lack of follow-up data warrants future research on the long-term durability of AS-related benefits.

4.3 Comparison of IM and EM as Targets

As previously referenced, researchers disagree on the utility of EM-based versus IM-based methods for targeting motivational deficits in schizophrenia. Critics of EM-based methods for behavioral change characterize EM as providing no lasting benefit to patients, a view that is reinforced by studies showing that external rewards can undermine IM (Deci, 1999). However, this finding—termed the ‘motivation crowding out effect’—may not generalize to populations with low baseline IM, such as populations of individuals with severe mental illness. An alternative view is that intrinsic and extrinsic rewards can have additive effects (Mawhinney, 1990), especially in patients with severe motivational and cognitive deficits who are not
motivated to participate in therapy. Self-Determination Theory posits that people can engage in a behavior due to EM, and once the intrinsically rewarding aspects are experienced, IM can maintain the behavior (Ryan, 2000). In the context of treatment, EM can be used to promote a patient’s participation in therapeutic activities, and as intrinsically rewarding behaviors become sustained by IM, tangible rewards can become less necessary.

A direct comparison between EM and IM regarding how best to enhance CR outcomes in schizophrenia is being investigated in an ongoing and yet to be published research study by Choi et al. The study’s goal is to examine how administration of intrinsic and extrinsic rewards impact learning performance in adults with schizophrenia enrolled in a computerized arithmetic-learning program. Participants were randomized into learning conditions that manipulated presence/absence of an intrinsically rewarding learning environment (learning was made to be more enjoyable with an emphasis on self-efficacy for outcome) and cash payments (present or absent) as an extrinsic reward for better task performance. The data collected suggests that external reward was related to greater arithmetic learning compared to intrinsic rewards. Importantly, for those with low motivation at the beginning, external rewards promoted greater learning and enjoyment for learning even after the external reward was discontinued. Intrinsic reward was modestly associated with greater learning, but only in patients who had high levels of motivation prior to the start of the program (Choi, personal communication, 2016). While the results of this ongoing study are helping to answer the question of which component of motivation
is the most useful target for improving treatment outcomes in schizophrenia, it is clear that more research directly comparing the utility of IM- and EM-based interventions must be done.

4.4. Overview of Present Study

Development of the present study was motivated by the need for research that directly compares the utility of EM and IM for remediating motivational deficits in schizophrenia, specifically in the context of CR therapy. The central goal of the research project was to investigate the effects of manipulating IM and EM on learning and skill acquisition from CR therapy in adults with schizophrenia. Specific objectives were to clarify which of these two types of motivations is a more effective target for enhancing learning and skill acquisition from cognitive training and whether the combination of these treatments would provide additional incremental value on treatment outcome in CR. Based on the various consequences motivational deficits have on individuals with schizophrenia, investigating how to ameliorate motivational deficits in the context of treatment has a clear relationship to the improvement of clinical care for this patient population.

4.4.1. Research Questions & Hypothesis

The goal of the present study was to investigate the effects of manipulating IM and EM on the enhancement of learning and skill acquisition from CR therapy in adults with schizophrenia. The research question was comprised of two main parts:
which of these two manipulations is most effective at improving learning and skill acquisition during a CR program targeting working memory, and what effect does the combination of the two manipulations have compared to either manipulation alone? Various measures were used to investigate changes in performance on the trained working memory task as well as on untrained working memory tasks. The study investigated both the immediate effects of the interventions as well as whether the effects persisted three weeks after the completion of cognitive training.

The hypothesis was that groups receiving one of the two interventions would demonstrate greater gains in performance on the cognitive training task, as well as greater improvements on untrained working memory measures, compared to the control group receiving no intervention. Furthermore, it was also hypothesized that participants’ receiving both the IM and EM interventions simultaneously would have greater gains in performance on the training task, as well as greater improvements on untrained working memory measures, compared to both the control group and groups receiving only one of the two interventions.

Chapter 5. Methods

The present investigation was a randomized, controlled, single-blind study consisting of two behavioral interventions (IM and EM) targeting enhancement of CR therapy outcomes. Participants were randomly assigned by the researcher into one of four groups through an online random number generator, in a 2 x 2 design that manipulated both extrinsic and intrinsic motivation; group 1 received the IM
manipulation, group 2 received the EM manipulation, group 3 received both manipulations, and group 4 received neither (a control group). The randomization was done by the researcher administering the intervention and cognitive training, and the immediate and 3-week follow-up assessments were administered by a researcher who was blind to group assignment. This was a minimal risk study; there were no medical or any other dangers associated with participating, and the likelihood of harm or discomfort was no greater than that which would be encountered in everyday life. Written informed consent was collected from all participants prior to their participation in the study, and the participants were asked a series of questions towards the end of the consenting process to ensure that they understood the primary purpose of the research, the voluntary nature of their participation, and the amount of time that they would spend participating in the study. Patients also signed a release of protected health information (PHI). All procedures for the study met relevant institutional review board (IRB) approval at Hartford Hospital and Wesleyan University.

5.1 Participants

The population of interest was individuals 18 and older with a diagnosis of schizophrenia or schizoaffective disorder. The sampling in this study was convenience sampling, and consisted of 18 clinically stable adults that were recruited from either the Institute of Living at Hartford Hospital (n=9) or Gilead Community Services in Middletown, CT (n=9). Participants were recommended to participate in
the study by clinicians or staff at either of the sites from which we recruited participants. The inclusion criteria included having either Schizophrenia or Schizoaffective disorder, as confirmed by clinicians or staff who were familiar with the participants’ diagnoses. The exclusion criteria included uncorrected auditory or visual impairment, intellectual disability as evidenced by a documented history of services, lack of proficiency in English, other neurological disorders, history of major head trauma or loss of consciousness, and current substance abuse or dependence. Those with a lack of proficiency in English were excluded because many of the neurocognitive tests being used require fluency in the English language.

We evaluated the presence of current substance abuse or dependence from self-report, along with verification through the participants’ medical records when possible. Medical history was collected through a combination of patient interview and reviewing patients’ health records; diagnosis, age of onset/first hospitalization, number of hospitalizations, diagnosis, medications, presence of other neurological or medical conditions, and history of head trauma were recorded. Demographic characteristics were collected through patient interview, including age, gender, race/ethnicity, level of education, and parents’ levels of education.

5.2 Cognitive Remediation Program

The CR training in the present study utilized a working memory-training module within an online CR program called PSSCogRehab (Bracy, 1994). This cognitive training exercise is an element of comprehensive program of CR that has
been shown to improve cognitive deficits in working memory (Kurtz, 2007) (Kurtz, 2015). The computerized task involved remembering sequences of numbers, which were presented visually on the computer screen one number at a time. After the sequence was presented, participants used the mouse to click on the numbers they recalled seeing. The sequences began at a length of 2 digits, and then increased by one digit each time the participant answered 3 sequences in a row correctly. Participants continued to complete trials of increasing lengths until they met the discontinuation criteria, which signified the completion of that round; a round of the task ends when the participant provides 3 incorrect answers in a row or 6 incorrect answers of the same sequence length.

In the following round, instead of starting with a sequence that is 2-digits long, the first sequence they were presented with were two digits shorter than the longest sequence they completed in the previous round; the effect of this feature is that the task becomes increasingly more difficult as the participant improves. This cognitive training exercise relies on a “drill and practice” method, which involves repetitive practice of increasingly difficult cognitive exercises (Janicak, 2014). Participants were trained on two variations of the task, one that asked the participant to recall the sequence of numbers in the same order that they were presented, and one that asked participants to recall the sequence of numbers in reverse order. The participants repeated multiple rounds of both variations of the task during the two cognitive training sessions. Task-performance was quantified as the length of the longest sequence recalled correctly on a first try.
6.3 Intervention Procedures

Those assigned to the IM manipulation received a brief psychoeducational intervention prior to engaging in CR that was designed to increase IM for cognitive training. This intervention consisted of a motivation-enhancing interview given immediately prior to the start of the CR training (See Appendix A). The interview was developed based on the principles of motivational interviewing, a counseling style that aims to increase IM for a specific goal or behavioral change; in this case, the interview was being used to increase participants’ IM to engage in the CR program and improve their working memory skills. This method was chosen because motivational interviewing has been successful in past studies at increasing IM for CR therapy in schizophrenia (Fiszdon, 2016). The interview is semi-structured; there are guiding questions that pertain to participants’ motivation for cognitive training (e.g. "why do you feel that it is important to improve your cognition?" or "do you feel that impairments in your cognition have an effect on your every-day life?"), but interviewers were allowed to continue a conversation about a topic based on the individual patient's desire to provide information about it. At the end of the interview, the researcher summarized the most important points discussed in the interview aloud to the participant, and the participant was provided a written summary of the topics discussed and allowed to look over it before continuing.

Participants assigned to conditions that do not include the IM manipulation received a “sham” interview. This interview consisted of meeting with an experimenter for an identical period of time as the psychoeducational intervention,
but discussing neutral topics such as current events and weather (See Appendix B). This sham procedure was meant to ensure that all groups had equal exposure to interactions with the research personnel, in order to minimize potential confounds.

At the start of the second training session (1 week later), those who received the IM intervention were given a recap of what was talked about during the motivational interviewing session based on notes taken during the interview. The interviewers were instructed to choose parts of the interview that were most relevant to the participant’s motivation to participate in and benefit from cognitive training. The participants who were not assigned to receive the IM manipulation were given a “sham” recap of equal length about the topics discussed during the sham interview.

The EM manipulation consisted of giving participants monetary rewards for correct answers and improvements in the working memory CR program. This reward consisted of 5 cents for each correct answer, and 10 cents for a correct answer that resulted in moving up a level in the program (3 correct answers in a row results in a level-up). Nickels and dimes were displayed to participants as they earned money in order to make the reward more tangible, since research has shown that individuals with schizophrenia have impairments in mentally representing reward value (Gold, 2008). Before the start of cognitive training, the experimenter explained to the participant that they would earn additional money during the session based on their performance on the cognitive training task, specifying the amount they would earn for correct answers and improvements. The researcher informed the participant of how much money they earned at the end of each round of training, and the total amount
earned at the end of the session was added to the amount they were being compensated for their participation.

5.4 Scales & Measures

*Intrinsic Motivation Inventory for Schizophrenia Research (IMI-SR)*

The IMI-SR is a self-report IM scale that gauges the central motivational structures identified by Self-determination Theory as pertinent to cognitive task engagement, skill acquisition, treatment compliance, and remediation outcome, and was validated by a study by Choi et al. (2010). It was found to possess good internal consistency (alpha = .92) and test-retest reliability (intraclass correlation = .77) (Choi, 2010). In the present study, it was used to measure task-specific IM in regards to the cognitive training task 1-week before, directly after, and 1-week after the interventions were administered (See Appendix C).

*Perceived Competency Scale (PCS)*

The PCS is a self-report scale that gauges the participant's level of perceived competency in completing the computer task. Competency is one of the main psychological needs driving IM as described in Self-determination theory. Two examples of studies that have used the PCS are by Williams, Freedman, & Deci for management of glucose levels among patients with diabetes (Williams, 1998), and by Williams and Deci for medical students learning the material in an interviewing course (Wiliams, 1996). The alpha measure of internal consistency for the perceived
competence items in these studies was above 0.80. In the present study, it was used to measure this component of IM in regards to the cognitive training task 1 week before, directly after, and 1 week after the interventions were administered (See Appendix D).

QLS-3

The QLS-3 is an interview-based measure derived from 3 subsections of the Quality of Life Scale that measures general state intrinsic motivation (Heinrichs, 1984). This QLS index has been used in a number of schizophrenia studies (Nakagami, 2010) (Wechsler, 2008), and research has shown that it may predict rehabilitation outcomes (Saperstein, 2011). In the present study, this QLS-3 was administered at the start of the study as a baseline measurement for general-state IM (in contrast with the above-mentioned measurements of task-specific IM, which related specifically to cognitive training). This measure was included for the purpose of eventually exploring whether general-state motivation levels are predictive of how participants respond to the different interventions.

The Wechsler Test of Adult Reading (WTAR)

The WTAR (Holdnack, 2001) is a proxy for premorbid intelligence quotient (IQ), which estimates intellectual functioning before the onset of an injury or illness. The task involves reading 50 words with atypical grapheme to phoneme translations. The WTAR will be used to generate an estimated FSIQ score for each participant that
is continuous and ranges from 64 to 124. The FSIQ score is calculated by standardizing the raw score against data from a large normative sample that factors in demographic characteristics. The purpose of using the WTAR in this study was to ensure that differences observed between the four groups did not stem from between-group differences in IQ level.

The Wechsler Adults Intelligence Scale (WAIS-IV)

The Wechsler Adult Intelligence Scale has been used extensively to study impairment across a range of cognitive domains in schizophrenia. A study by Michel et al. (2013) found that the most current version of this measure, the WAIS-IV (Wechsler, 2008), revealed a pattern of impairments in adults with schizophrenia consistent with patterns identified using the previous version, the WAIS-III (Michel, 2013). The working memory index of the WAIS-IV measures the participant’s ability to hold information in their immediate awareness and then perform a mental operation on the information. The 3 subtests that were administered in this study as part of the working memory index were the Digit Span, Letter-number Sequencing, and Arithmetic tasks. The digit span has three parts: forwards (individual must repeat digits forwards), backwards (individual must repeat digits backwards, and sequencing (individual must repeat digits in ascending order). The Letter-number Sequencing task requires the individual to listen to a series of numbers and letters, and then recall the numbers in ascending order and the letters in alphabetical order. The Arithmetic task involves the individual mentally solving a series of arithmetic problems of
increasing difficulty without the use of a pencil and paper. In the present study, these tests were used in order to investigate whether intervention-mediated increases in learning from CR therapy would generalize to working memory tasks that were not part of cognitive training.

**Grooved Peg Board**

The Grooved Pegboard task is a standardized measure used to quantify motor functioning of the upper limbs (Klove, 1963). It measures the length of time it takes an individual to put a set of pegs into holes in a pegboard, and requires the individual to fill the pegboard first with their dominant hand and then with their non-dominant hand. In this study, it was expected that the motivation-enhancing interventions would result in improvements only in skills specific to working memory, since that was the skill being targeted by the CR program. Thus, this measure was included as a control task in order to ensure that the motivation-enhancing effects were specific.

### 5.5 Study Design and Procedures

![General Timeline of Study](image)

**Figure 1**: General Timeline of Study
Session 1:

After written informed consent was obtained, all relevant demographic and clinical information were collected through patient interview. Then, participants were given a set of tests to determine baseline motivational characteristics and cognitive abilities. Weschsler Test of Adult Reading (WTAR) was given as an estimation of premorbid IQ. As a gauge of baseline motivational characteristics, researchers administered the QLS-3, an interview-based measure that quantifies general-state IM (Nakagami, 2010). While the above two measures were only administered during the first session, the remaining measures were administered at multiple time points throughout the four sessions in order to measure intervention-mediated changes.

In order to quantify working memory abilities at baseline, 3 subtests from the WAIS-IV that assess working memory were administered to all patients during session 1. These included the Digit Span, Letter-number Sequencing, and Arithmetic tasks. In order to ensure that the intervention targeted working memory specifically, performance on the Grooved Pegboard task was assessed as a control measure. Then, participants were introduced to the working memory-training module within the computerized CR program PSSCogRehab (Bracy, 1994), and a baseline measure of performance on this task was recorded. Performance was quantified as the length of the longest sequence that participants correctly recalled on their first try. Participants completed one round of each of the two variations of the task, one that required the participant to recall the sequence of numbers in the same order that they were
presented, and one that required participants to recall the sequence of numbers in reverse order.

At the end of the session, the participants completed two questionnaires—The Intrinsic Motivation Inventory for Schizophrenia Research (IMI-SR), which measures task-specific IM, and the Perceived Competency Scale (PCS), which assesses participants’ feelings of competence (a component of IM) about the specific task they are engaging in. On both surveys, the questions pertained to the cognitive training exercise that the participants just completed. At the end of the session, the participants were compensated $10 for their participation.

**Session 2:**

At the start of session 2 (approximately 1 week later), participants were randomly assigned to one of four groups through an online random number generator. Group 1 received the IM intervention only, group 2 received the EM intervention only, group 3 received both interventions, and group 4 (control group) received neither intervention. After the researcher administered either the motivational interviewing script or the “sham interview,” the participant began the cognitive training session. The session consisted of five rounds of the forwards recall variation and five rounds of the reverse recall variation. Participants assigned to the EM or IM+EM groups received monetary rewards throughout the session. After the end of the cognitive training, participants completed the IMI-SR and PCS questionnaires again, in order to assess whether group assignment had an impact on task-specific IM.
At the end of the session, the participants were compensated $15 for their participation, and those who received the EM manipulation had the amount they earned during the cognitive training added to the $15 payment.

<table>
<thead>
<tr>
<th>Group 1: IM only</th>
<th>Group 2: EM only</th>
<th>Group 3: IM + EM</th>
<th>Group 4: Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Psychoeducational intervention (Motivational Interviewing)</td>
<td>• Sham interview</td>
<td>• Psychoeducational intervention (Motivational Interviewing)</td>
<td>• Sham interview</td>
</tr>
<tr>
<td>• 5 rounds of each version of cognitive training with no monetary incentive.</td>
<td>• 4 rounds of each version of cognitive training with performance-based monetary reinforcement</td>
<td>• 4 rounds of each version of cognitive training with performance-based monetary reinforcement</td>
<td>• 5 rounds of each version of cognitive training with no monetary incentive.</td>
</tr>
<tr>
<td>• IMI-SR &amp; PCS (task-specific IM measures)</td>
<td>• IMI-SR &amp; PCS</td>
<td>• IMI-SR &amp; PCS</td>
<td>• IMI-SR &amp; PCS</td>
</tr>
</tbody>
</table>

Table 1: Summary of study procedures for session 2, second week of cognitive training (assessment point= immediate follow-up).

Session 3:

During the third session one week later, researchers administered the second session of the cognitive training program, which consisted of four rounds of the forward recall variation and four rounds of the reverse recall variation (the fifth round of each variation would occur later in the session). Immediately prior to the start of cognitive training, the researcher provided a “recap” of the main points discussed in either the motivation-enhancing interview or the sham interview. Those who were assigned to the EM manipulation continued to earn additional money throughout the training session. Afterwards, participants again completed the IMI-SR and PCS in
order to assess changes in task-specific IM after the second cognitive training session; this would reveal whether changes in task-specific IM persisted over the 1-week since receiving the IM-enhancing (or sham) interview.

The second half of session 3 was the same for all four groups; since both cognitive training sessions had been completed at this point, the researchers collected immediate follow-up measurements by re-administering the tasks given at baseline. Participants repeated the Digit Span, Letter-number Sequencing, and Arithmetic tasks from the WAIS-IV in order to determine if the intervention-mediated improvements generalized to untrained working memory tasks. They also completed one more round of each variation of the cognitive training task in order to assess changes in task performance immediately following cognitive training. Lastly, participants repeated the Grooved Pegboard task in order to determine if only skills specific to the cognitive training changed based on group assignment. At the end of the session, the participants were compensated $15 for their participation, and those assigned to the EM manipulation had the amount they earned during the cognitive training added to the $15 payment.
Group 1: IM only  |  Group 2: EM only  |  Group 3: IM + EM  |  Group 4: Control
--- | --- | --- | ---
- Recap of main points from motivational interviewing
- 4 rounds of each version of cognitive training exercise with no monetary incentive.
- IMI-SR & PCS
- Post-intervention administration of:
  - Grooved Pegboard
  - 3 Working Memory Tasks from WAIS-IV
  - Cognitive training task (1 round of each version)
- Recap of sham interview
- 4 rounds of each version of cognitive training with performance-based monetary reinforcement
- IMI-SR & PCS
- Post-intervention administration of:
  - Grooved Pegboard
  - 3 Working Memory Tasks from WAIS-IV
  - Cognitive training task (1 round of each version, no longer with monetary incentive)
- Recap of main points from motivational interviewing
- 4 rounds of each version of cognitive training with performance-based monetary reinforcement
- IMI-SR & PCS
- Post-intervention administration of:
  - Grooved Pegboard
  - 3 Working Memory Tasks from WAIS-IV
  - Cognitive training task (1 round of each version, no longer with monetary incentive)
- Recap of sham interview
- 4 rounds of each version of cognitive training exercise with no monetary incentive.
- IMI-SR & PCS
- Post-intervention administration of:
  - Grooved Pegboard
  - 3 Working Memory Tasks from WAIS-IV
  - Cognitive training task (1 round of each version)

Table 2: Summary of study procedures for session 3, the second week of cognitive training (assessment point= immediate follow-up).

Session 4:

The fourth session was a 3-week follow up, intended to gauge whether changes in working memory and computer task performance were persistent even after the cognitive training had ended. Participants in all four groups completed follow-up assessments of performance on the cognitive training task, the three untrained working memory tasks from the WAIS-IV, and the Grooved Pegboard task.

At the end, all participants were compensated $15 for their participation.
5.6 Statistical Analysis Plan

The SPSS statistical package (V.19) was used for data analysis. Descriptive statistics including mean, SD and range were obtained for all groups on all measures at each time point in the study. An alpha level of $p = .05$ was used *a priori* to indicate statistical significance on all statistical tests. An alpha level of $p=.07$ was used to indicate a trend-level of statistical significance on all statistical tests. If necessary, the appropriate data transformations would have been used on the outcome measures prior to statistical analysis. ANOVA was used to assess baseline differences in all demographic and clinical variables and chi-square was used to assess baseline differences in categorical variables. Any variables differing between groups at baseline would have been entered as covariates into a mixed design ANCOVA. Also, Cohen’s $d$ effect sizes were calculated as an indicator of practical significance when interpreting the effects of the interventions. This analysis evaluates effect size as the difference between the means of two independent groups divided by standard deviation. For effect size analysis of within-subject analyses (matched-pairs comparisons between pre-test and post-test scores), the correlation between the two means was factored into the Cohen’s $d$ calculation so that direct comparisons could be made to effect sizes of independent-groups analyses (Morris, 2002). The conventional cut-offs for Cohen’s $d$ values were used to determine effect size (.2=small, .5=moderate, .8=large). Error bars on all graphs represented the standard deviations of the data being depicted.
In order to assess the impact of the interventions on task-specific IM, IMI-SR and PCS scores at the three assessment points were compared using matched-pairs t-tests. Specifically, comparisons were made between score at baseline and immediately after the first training session (in the same session as the MI or sham interview), as well as between baseline and after the second training session (one week after MI or the sham interview). The primary purpose of this analysis was to evaluate whether the IM intervention successfully increased task-specific IM, but it was also to reveal whether any of the four groups demonstrated significant changes in task-specific IM. In addition, the change scores between the three assessment points from each group were compared using independent group t-tests in order to determine if changes were significantly different between groups. These t-tests were conducted on all two-group combinations (1 vs. 2, 1 vs. 3, 1 vs. 4, 2 vs. 3, 2 vs. 4, and 3 vs. 4). The reason for using multiple t-tests instead of an ANOVA between the four independent groups is because of the small sample size and the resulting low level of power of the statistical analyses; we acknowledge that there is a higher risk for type 1 errors by doing multiple t-tests, but these analyses are exploratory in nature since the number of subjects in each group is quite low.

In order to evaluate intervention-mediated changes in performance on the cognitive training task, change scores were compared using matched-pairs t-tests within each group. Task-performance was quantified as the length of the longest sequence recalled correctly on a first try. Scores on the subtests of the WAIS-IV were also compared using matched-pairs t-tests, in order to evaluate intervention-mediated
changes in generalization measures of working memory. The same comparisons were used to evaluate changes on the control measure, the Grooved Pegboard task. Comparisons for all of the above measures were made between performance at baseline and immediate follow-up, as well as between baseline and 3-week follow up. In order to assess whether there are significant differences between the four groups on these outcome measures, the immediate and 3-week follow-up change scores from each group were compared using independent group t-tests. These t-tests were conducted on all combinations of two groups (1 vs. 2, 1 vs. 3, 1 vs. 4, 2 vs. 3, 2 vs. 4, and 3 vs. 4). All of the above-mentioned measures—with the exception of performance on the cognitive training task—have standardized scores calculated from a normal sample, so differences in standard scores or T-scores (as opposed to raw scores) will be evaluated in the statistical analyses.

Chapter 6. Results

6.1 Demographic and Clinical Characteristics

There were no significant differences between the four different experimental groups with regard to demographic or clinical characteristics. Using a one-way ANOVA, it was determined that the four groups were comparable with regard to the demographic variables of age (p=.854), education (p=.988), mother’s education (p=.517), father’s education (p=.744), community living status (p=.927), gender (p=.093), and race/ethnicity (p=.652). The sample had a higher percentage of male participants, with 14 of the 18 participants being male.
<table>
<thead>
<tr>
<th>Variable</th>
<th>IM only (n=5)</th>
<th>EM only (n=5)</th>
<th>IM+EM (n=5)</th>
<th>Control (n=3)</th>
<th>F-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.2 ± 10.4</td>
<td>39 ± 17.1</td>
<td>41 ± 12.1</td>
<td>39.6 ± 8.14</td>
<td>.259</td>
<td>.854</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.4 ± 2.97</td>
<td>12.4 ± 1.67</td>
<td>12.6 ± .89</td>
<td>13 ± 4.58</td>
<td>.043</td>
<td>.988</td>
</tr>
<tr>
<td>Mother’s Education</td>
<td>14.2 ± 3.70</td>
<td>12.7 ± 3.06</td>
<td>15 ± 2.00</td>
<td>11.5 ± .707</td>
<td>.810</td>
<td>.517</td>
</tr>
<tr>
<td>Father’s Education</td>
<td>14 ± .63</td>
<td>11.5 ± 6.36</td>
<td>14.7 ± 2.31</td>
<td>14 ± 3.46</td>
<td>.42</td>
<td>.744</td>
</tr>
</tbody>
</table>

**Table 3:** Demographic characteristics of the four groups (ANOVA).

In terms of clinical variables, there were no significant differences between groups in duration of illness (p=.631), age of onset (p=.327), number of hospitalizations for schizophrenia (p=.773), or diagnosis (schizophrenia versus schizoaffective disorder) (p=.817). The four groups also were not significantly different on measures of premorbid IQ (p=.147) or general-state IM (p=.166).

<table>
<thead>
<tr>
<th>Variable</th>
<th>IM only (n=5)</th>
<th>EM only (n=5)</th>
<th>IM+EM (n=5)</th>
<th>Control (n=3)</th>
<th>F-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Illness</td>
<td>13.5 ± 11.8</td>
<td>21.6 ± 18.6</td>
<td>15.5 ± 11.4</td>
<td>19.7 ± 6.43</td>
<td>.595</td>
<td>.789</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>20.8 ± 2.86</td>
<td>17 ± 2.0</td>
<td>21.8 ± 5.84</td>
<td>20 ± 2.65</td>
<td>1.267</td>
<td>.327</td>
</tr>
<tr>
<td># of times in Hospital</td>
<td>6 ± 5.87</td>
<td>6 ± 4.62</td>
<td>8.4 ± 6.58</td>
<td>4.3 ± 3.21</td>
<td>.373</td>
<td>.773</td>
</tr>
<tr>
<td>FSIQ (IQ measure)</td>
<td>85.8 ± 12.0</td>
<td>93.2 ± 14.3</td>
<td>103.8 ± 13.5</td>
<td>85 ± 9.54</td>
<td>2.019</td>
<td>.147</td>
</tr>
<tr>
<td>QLS-3 Score</td>
<td>11.2 ± 2.49</td>
<td>7 ± 3.94</td>
<td>8.4 ± 4.62</td>
<td>5.33 ± 2.31</td>
<td>1.966</td>
<td>.166</td>
</tr>
</tbody>
</table>

**Table 4:** Clinical characteristics of the four groups (ANOVA).
Table 5: Analysis of categorical values for demographic and clinical characteristics (Chi-square Test for Independence)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percentage of total sample (n=18)</th>
<th>Pearson Chi-Square Value (χ)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>22% Female 78% Male</td>
<td>χ = .259</td>
<td>.854</td>
</tr>
<tr>
<td>Ethnicity/Race</td>
<td>44% Caucasian 39% African American 11% Latino 6% Asian</td>
<td>χ = .043</td>
<td>.988</td>
</tr>
<tr>
<td>Community Living Status</td>
<td>22% Living With Family 22% Living in Group Home 56% Living On Own</td>
<td>χ = .879</td>
<td>.481</td>
</tr>
<tr>
<td>Psychiatric Diagnosis</td>
<td>50% Schizophrenia 50% Schizoaffective Disorder</td>
<td>χ = .42</td>
<td>.744</td>
</tr>
</tbody>
</table>

6.2 Comparing Change in Task-specific IM

In order to assess the impact of the interventions on task-specific IM, IMI-SR and PCS scores at the different assessment points were compared using matched-pairs t-tests. First, comparisons were made between score at baseline and immediately after the first training session (same session as motivational or sham interview). This analysis revealed no significant changes in IMI-SR or PCS scores in any of the four groups (p ≥ .113 for all comparisons). Analysis of change in PCS score between these time points was not done for the control group due to the number of subjects being less than 3 (n=2) (1 subject in the control group did not fill out PCS questionnaire after the first training session). Next, comparisons were made between scores at baseline and immediately after the second training session (one week after motivational or sham interview). This revealed no significant changes in IMI-SR score in any of the four groups (p ≥ .346 for all comparisons). While there were no
significant changes in PCS score in the IM, EM, or control groups, the group receiving both the IM and EM interventions demonstrated significant improvement in PCS score at the end of the second training session (p=.017). Effect size analysis suggests that this intervention had a large effect on increasing PCS scores between these two assessment points (d=1.761).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Subjects</th>
<th>PCS Change Score ((\bar{x} \pm SD))</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM only</td>
<td>n=5</td>
<td>-0.24 ± .517</td>
<td>t=-1.037</td>
<td>p=.358</td>
</tr>
<tr>
<td>EM only</td>
<td>n=5</td>
<td>-0.08 ± 1.14</td>
<td>t=-.157</td>
<td>p=.883</td>
</tr>
<tr>
<td>IM+EM</td>
<td>n=5</td>
<td>1.18 ± .572</td>
<td>t=3.925</td>
<td>p=.017**</td>
</tr>
<tr>
<td>Control</td>
<td>n=3</td>
<td>.20 ± .346</td>
<td>t=1</td>
<td>p=.423</td>
</tr>
</tbody>
</table>

Table 6. Results from matched-pairs t-test on change in PCS score from baseline to immediate after the second cognitive training session.

Figure 2. Change in PCS score from baseline to immediate after session 2 of training. Note: **=p<.05, *=p<.07 (matched-pairs t-test between scores at 2 assessment points)
In order to determine if task-specific IM changes were significantly different between groups, independent t-tests on IMI-SR and PCS change scores were conducted on all combinations of two groups (1 vs. 2, 1 vs. 3, 1 vs. 4, 2 vs. 3, 2 vs. 4, and 3 vs. 4). These analyses revealed that change in IMI-SR and PCS scores between baseline and after the first training session were not significantly different between any set of two groups (p ≥ .11 for all comparisons). Changes in IMI-SR scores between baseline and after the second training session were also not significantly different between any of the groups (p ≥ .552 for all comparisons). However, the IM+EM group demonstrated significantly greater increases in PCS score compared to the IM group (t=3.742; p=.006), as well as greater increases at a trend-level of significance compared to the control group (t=2.297; p=.061) and the EM group (t= 2.133; p=.065), with large effect sizes for all 3 comparisons (d=2.602; d=1.097; d=1.40, respectively) (p ≥ .245 for all other comparisons).

### 6.3 Comparing Change in Performance on Cognitive Training Task

In order to evaluate the effect of the interventions on changes in cognitive training task performance, matched-pairs t-tests were used to compare performance between baseline and immediate follow-up, as well as between baseline and 3-week follow up. Task-performance was quantified as the length of the longest sequence recalled correctly on a first try for both the forwards and reverse variations of the task. For the forward recall variation, only the IM+EM group showed significant improvement at the immediate follow-up (p=.034). Effect size analysis suggests that
this intervention had a large effect on task-performance between these assessment points (d=1.433). None of the groups showed significant change for the reverse recall variation at the immediate follow-up, but the IM group demonstrated improvement at a trend level of significance with a large effect-size (p=.056; d=1.303). Lastly, none of the groups demonstrated significant change in either variation of the task between baseline and 3-week follow-up (p≥.184 for all comparisons).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Subjects</th>
<th>Forward Recall Change Score (x±SD)</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM only</td>
<td>n=5</td>
<td>0 ± .707</td>
<td>t= 0</td>
<td>p= 1</td>
</tr>
<tr>
<td>EM only</td>
<td>n=5</td>
<td>1 ± 2.35</td>
<td>t=.953</td>
<td>p=.394</td>
</tr>
<tr>
<td>IM+EM</td>
<td>n=5</td>
<td>1 ± .707</td>
<td>t= 3.162</td>
<td>p=.034**</td>
</tr>
<tr>
<td>Control</td>
<td>n=3</td>
<td>1 ± 1.73</td>
<td>t= 1</td>
<td>p=.423</td>
</tr>
</tbody>
</table>

**Table 7.** Results from matched-pairs t-test on change in forward recall variation of cognitive training task from baseline to immediate follow-up.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Subjects</th>
<th>Reverse Recall Change Score (x±SD)</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM only</td>
<td>n=5</td>
<td>1.6 ± 1.34</td>
<td>t= 2.667</td>
<td>p=.056*</td>
</tr>
<tr>
<td>EM only</td>
<td>n=5</td>
<td>1 ± 1.87</td>
<td>t= 1.195</td>
<td>p=.298</td>
</tr>
<tr>
<td>IM+EM</td>
<td>n=4</td>
<td>0 ± .817</td>
<td>t= 0</td>
<td>p= 1</td>
</tr>
<tr>
<td>Control</td>
<td>n=3</td>
<td>1.33 ± 1.15</td>
<td>t= 2</td>
<td>p=.184</td>
</tr>
</tbody>
</table>

**Table 8.** Results from matched-pairs t-test on change in reverse recall variation of cognitive training task from baseline to immediate follow-up.

Independent group t-tests on all combinations of two groups were used to determine if changes in task performance were significantly different between the four groups. The only difference revealed for the forward variation was between the IM group and the IM+EM group at the immediate follow-up; the IM+EM group showed greater improvement at a trend level of significance (t=2.694; p=.056) with a large effect size (d=1.414) (p≥.281 for all other comparisons). No significant
differences were found between any of the groups for reverse recall performance at either of the assessment points (p ≥ 0.076 for all comparisons).

6.4 Comparing Change in Generalization Measures of Working Memory

To evaluate the impact of the interventions on untrained measures of working memory, matched-pairs t-tests were used to compare scores on the three WAIS-IV subtests. Letter-number Sequencing (LNS) scores between baseline and immediate follow-up were significantly increased only in the IM group, with a large effect size (p = 0.002; d = 4.207). In the IM+EM group, Arithmetic scores were significantly increased with a large effect size (p = 0.035; d = 1.486), and Digit Span scores were increased at a trend-level of significance with a large effect size (p = 0.07; d = 1.097) (p ≥ 0.135 for all other comparisons). Between baseline and 3-week follow-up, the only significant change was in the IM+EM group, which demonstrated significant improvement in Arithmetic scores with a large effect size (p = 0.02; d = 4.963) (p ≥ 0.093 for all other comparisons).
Figure 3: Change in scores on Digit Span task from baseline to immediate follow-up. Note: **=p<.05, *=p<.07 (matched-pairs t-test between scores at 2 assessment points)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Subjects</th>
<th>Digit Span Change Score (x±SD)</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM only</td>
<td>n=5</td>
<td>0 ± 2.24</td>
<td>t= 0</td>
<td>p= 1</td>
</tr>
<tr>
<td>EM only</td>
<td>n=5</td>
<td>-1.6 ± 3.97</td>
<td>t= -0.9</td>
<td>p=.419</td>
</tr>
<tr>
<td>IM+EM</td>
<td>n=5</td>
<td>1.8 ± 1.64</td>
<td>t= 2.449</td>
<td><strong>p=.07</strong></td>
</tr>
<tr>
<td>Control</td>
<td>n=3</td>
<td>-0.33 ± 2.31</td>
<td>t= -.25</td>
<td>p=.826</td>
</tr>
</tbody>
</table>

Table 9. Results from matched-pairs t-test on change in Digit Span score from baseline to immediate follow-up.
Figure 4: Change in scores on Letter Number Sequencing task from baseline. Note: **=p<.05, *=p<.07 (matched-pairs t-test between scores at 2 assessment points)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Subjects</th>
<th>LNS Change Score (x±SD)</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM only</td>
<td>n=5</td>
<td>1.8± .447</td>
<td>t= 9</td>
<td>p=.001**</td>
</tr>
<tr>
<td>EM only</td>
<td>n=5</td>
<td>-1± 1.73</td>
<td>t= -1.291</td>
<td>p=.266</td>
</tr>
<tr>
<td>IM+EM</td>
<td>n=5</td>
<td>.8± 1.92</td>
<td>t=.93</td>
<td>p=.405</td>
</tr>
<tr>
<td>Control</td>
<td>n=3</td>
<td>0.33± 2.31</td>
<td>t=.25</td>
<td>p=.826</td>
</tr>
</tbody>
</table>

Table 10. Results from matched-pairs t-test on change in Letter Number Sequencing score from baseline to immediate follow-up.
Figure 5: Change in scores on Arithmetic task from baseline to immediate follow-up. Note: **=p<.05, *=p<.07 (matched-pairs t-test between scores at 2 assessment points)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Subjects</th>
<th>Arithmetic Change Score (x±SD)</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM only</td>
<td>n=5</td>
<td>1.4 ± 1.67</td>
<td>t= 1.871</td>
<td>p=.135</td>
</tr>
<tr>
<td>EM only</td>
<td>n=5</td>
<td>0.4 ± 1.82</td>
<td>t= -.8124</td>
<td>p=.266</td>
</tr>
<tr>
<td>IM+EM</td>
<td>n=5</td>
<td>1.6 ± 1.14</td>
<td>t= 3.138</td>
<td>p=.035**</td>
</tr>
<tr>
<td>Control</td>
<td>n=2</td>
<td>Excluded from Analysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 11. Results from matched-pairs t-test on change in Arithmetic score from baseline to immediate follow-up.
Figure 6: Change in scores on Arithmetic task from baseline to 3-week follow-up. Note: **=p<.05, *=p<.07 (matched-pairs t-test between scores at 2 assessment points)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Subjects</th>
<th>LNS Change Score (x±SD)</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM only</td>
<td>n=4</td>
<td>1.5 ± 1.29</td>
<td>t= 2.324</td>
<td>p=.103</td>
</tr>
<tr>
<td>EM only</td>
<td>n=5</td>
<td>-0.8 ± 1.64</td>
<td>t= -1.089</td>
<td>p=.338</td>
</tr>
<tr>
<td>IM+EM</td>
<td>n=3</td>
<td>2.3 ± .577</td>
<td>t= 7</td>
<td><strong>p=.02</strong></td>
</tr>
<tr>
<td>Control</td>
<td>n=2</td>
<td>Excluded from Analysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 12. Results from matched-pairs t-test on change in Arithmetic score from baseline to 3-week follow-up.

Independent group t-tests were used to determine if changes were significantly different between the four groups. The only significant difference in immediate follow-up change was in LNS scores between the EM group and the IM group; the IM group improved significantly more (t=3.5; p=.008) with a large effect size (d=2.214) (p≥.115 for all other comparisons). There were significant differences in 3-week follow-up changes between the IM+EM group and the other groups. The IM+EM group improved significantly more on the Arithmetic task compared to the
EM group (t=3.104; p=.021), on the Digit Span compared to the IM group (t=3.287; p=.022), and also on the Digit Span at a trend-level of significance compared to the control group (t=2.573; p=.056), with large effect sizes for all three comparisons (d=2.544; d=2.319; d=2.182, respectively). In addition, the analysis revealed trend-level significance in Arithmetic change scores between the IM group and EM group, with the IM group showing greater improvement with a large effect size (p=.056; d=1.557) (p≥.168 for all other comparisons).

6.5 Comparing Change in Performance on Control Task

In order to evaluate changes on the control task, matched-pairs t-tests were used to compare scores on both variations of the Grooved Pegboard task for each group. At the immediate follow-up, the control group demonstrated significant improvement in dominant hand performance (t=6; p=.027) with a large effect size (d=3.64) (p≥.11 for all other comparisons). At the 3-week follow-up, there were significant improvements in dominant hand performance in both the control group (t=11.129; p=.008) and the IM+EM group (t=14; p=.005) with large effect sizes (d=.691; d=.729, respectively) (p≥.11 for all comparisons).

To determine between-group differences, change scores from each group were compared using independent group t-tests. This analysis revealed that the control group was the only group that differed significantly from the others in terms of Grooved Pegboard performance. At the immediate follow-up, the control group improved significantly more than the EM group (t=2.6; p=.041), and also at a trend-
level of significance compared to the IM+EM group (t=2.274; p=.063) on the non-dominant hand version, with both changes having large effect sizes (d=1.89; d=1.44, respectively) (p≥.114 for all other comparisons). There were no significant differences between groups on dominant hand performance (p≥.243 for all comparisons). At the 3-week follow-up, the control group improved significantly more than the IM (t=3.195; p=.024), EM (t=2.772; p=.035), and IM+EM (t=7.888; p=.001) groups on the dominant hand version, and also significantly more than the EM group on the non-dominant hand version (t=2.649; p=.038), with all four changes having large effect sizes (d=2.616; d=2.25; d=6.44; d=1.80, respectively) (p≥.176 for all other comparisons).

**Chapter 7. Discussion**

7.1 Evaluating the Results

There has been an increased focus in recent years on the role of motivation in CR therapy for schizophrenia; specifically, a major focus has been on the utility of IM versus EM as targets for enhancing motivation. The discussion has been largely dominated by conversations on IM, perhaps based on the relationship between IM and cognitive functioning (Saperstein, 2011), and also based on evidence that promoting IM is associated with improved attendance and more durable improvements for patients in learning programs like CR therapy (Choi, 2010) (Gooding, 2016). However, there is a long history demonstrating the utility of extrinsic rewards for promoting behavioral change and cognitive enhancement in
schizophrenia (Silverstein, 2010)(Penn, 2000). It has been shown that extrinsic rewards have the potential to improve performance on various cognitive measures, such as attention, executive functioning, and learning (Silverstein, 2001, 2005, 2009). As summarized earlier, a reward-based learning procedure called attention shaping (AS) has repeatedly been shown to effectively enhance the ability of schizophrenia patients to learn from psychosocial training (Silverstein, 2009).

Despite the wealth of studies evaluating the efficacy of both IM- and EM-based interventions, there are currently no published studies directly comparing these two targets for enhancing motivation in the context of CR therapy for schizophrenia. The goal of the study was to clarify which of these two components of motivations is a more effective target for enhancing learning and skill acquisition in a working memory cognitive training task. Also, in order to address the criticism that external rewards can have an undermining effect on IM, the study also aimed to evaluate the effects of manipulating both IM and EM simultaneously.

### 7.1.1 Evaluating the IM Intervention

The motivational interviewing procedure was designed to increase participant’s IM for the cognitive training task; however, change scores on the IMI-SR indicated that there were no significant increases in task-specific IM immediately after either the first or second week of cognitive training. Also, change scores on the PCS indicated that there were no significant increases in perceived competency, a component of IM, at either time point. This may suggest that the intervention was not
effective at increasing IM, but may also be a result of the small sample size (n=5). Analysis of effect size showed that the IM intervention had a large effect on change in IMI-SR score both after the first training session (d=.984) and after the second training session 1 week later (d=1.117). Considering that none of the other groups demonstrated large effect sizes for change in IMI-SR score at either assessment point, it is possible that the impact of motivational interviewing on task-specific IM will emerge as significant when the subject number increases.

Although it is unclear whether the motivational interviewing procedure was successful at manipulating IM, the intervention’s effect on cognitive training task performance was assessed. At the immediate follow-up, the IM group demonstrated improvement at a trend level of significance for the reverse recall variation. None of the groups showed significant change on either variation of the task at the 3-week follow-up. This may suggest that the IM intervention was effective at increasing task performance, but since the significance was only at a trend level and there were no significant between-group differences, the level of efficacy is unclear.

Next, analyses were performed in order to determine if the IM intervention resulted in improvements that generalized to untrained working memory tasks. LNS scores between baseline and immediate follow-up were significantly increased in the IM group, and were not increased in any other group; additionally, between-group comparisons revealed that the IM group improved on this measure significantly more than the EM group. The analysis also revealed that the IM group improved more than EM group on the Arithmetic task from baseline to 3-week follow up at a trend level
of significance. These results suggest that the IM intervention increased gains in working memory skills significantly more than the EM intervention.

7.1.2 Evaluating the EM intervention

For the group receiving only the EM manipulation, matched pairs t-tests did not show any significant changes in measures of task-specific IM, performance on the cognitive training task, or performance on the untrained working memory tasks at any of the assessment points. The between-group comparisons revealed that the EM intervention alone was not significantly more effective than any other condition at improving task-specific IM, performance on the cognitive training task, or performance on the untrained working memory tasks.

7.1.3 Evaluating the Combination of Both Interventions

Although the IM intervention alone did not produce significant changes in measures of task-specific IM, the group receiving both IM and EM interventions demonstrated a significant improvement in PCS score from baseline to the end of the second training session. In addition, between-group comparisons revealed that the IM+EM group showed significantly greater increases in PCS score compared to the IM group, as well as greater increases at a trend-level of significance compared to both the control group and the EM group. This information suggests that receiving both the IM and EM manipulations most effectively raised perceived competency levels for the cognitive training task.
Even though this component of task-specific IM was increased in the IM+EM group, task-specific motivation as measured by the IMI-SR did not demonstrate significant change. Since effect size analysis showed that the IM intervention produced large effects while the combination of both interventions did not produce moderate or large effects, it is possible that the EM intervention undermined the ability of the IM intervention to increase IM for the task; however, no concrete conclusions about this relationship can be drawn since the matched-pairs t-tests revealed no significant change in IMI-SR score for any group.

In terms of performance on the cognitive training task, the IM+EM group showed significant improvement on the forward recall variation of the task at the immediate follow-up. In addition, between-group comparisons showed that the IM+EM group improved more on the forward variation at immediate follow-up compared to the IM group at a trend level of significance, suggesting that the combination of both interventions was more effective at improving performance on the cognitive training task compared to the IM intervention alone.

In terms of performance on untrained working memory tasks, the combination of both interventions resulted in significant improvements in Arithmetic score and increases in Digit Span score at a trend level of significance at the immediate follow-up. Between baseline and 3-week follow-up, the combination of both interventions resulted in significant improvements in Arithmetic score. Between-group analysis of 3-week follow-up revealed that the IM+EM group improved significantly more on the Arithmetic task compared to the EM group, on the Digit Span compared to the IM
group, and also improved on the Digit Span at a trend-level of significance compared to the control group. These results indicate that the combination of the IM and EM interventions resulted in improvements that generalized to untrained working memory tasks immediately after training, and also that the combination of the interventions was more effective at producing long-lasting improvements on the untrained working memory tasks compared to either intervention alone.

### 7.1.4 Evaluating the Control Condition

For the group receiving neither intervention, matched-pairs t-tests did not show any significant changes in measures of task-specific IM, performance on the cognitive training task, or performance on the untrained working memory tasks at any of the assessment points. The between-group comparisons revealed that the control condition was not significantly more effective than any other condition at improving task-specific IM, performance on the cognitive training task, or performance on the untrained working memory tasks.

### 7.2 Evaluating the Hypothesis

The hypothesis of the present study was that participants’ receiving interventions targeting both IM and EM would have the greatest gains in performance on the training task, as well as the greatest improvements in generalized measures of working memory compared to both controls and to groups receiving only one of the two interventions. Also, it was hypothesized that groups receiving either of the
interventions would demonstrate greater improvements compared to the control group receiving no intervention. These hypotheses concerned both the immediate effects of the interventions as well as whether the effects would persist at a follow-up three weeks after cognitive training was completed.

In terms of the effect of the interventions on improving task-performance immediately after training, the combination of both interventions was the most effective. Both the control group and the EM only group showed no evidence of being able to improve task performance. Although the IM intervention had some impact on reverse recall scores, the significance was only at a trend level. On the other hand, the IM+EM group showed significant improvement on the forward recall variation of the task, and also improved significantly more than those receiving the IM intervention alone. These results show that although there is some evidence that manipulating IM could enhance learning from cognitive training, the addition of extrinsic motivators significantly increases the likelihood of improvement on the cognitive training task. This supports the hypothesis that the combination of the two interventions would be most effective at enhancing performance on the trained task, but it is important to note that this was only observed for immediate follow-up changes; improvements in task performance did not persist three weeks after the end of cognitive training in any of the groups, possible due to the extremely brief nature of the 2-session cognitive training intervention.

The hypothesis also concerned whether or not the interventions would result in cognitive gains that generalize to untrained working memory tasks. Immediately
after training, neither the control condition nor the EM intervention resulted in significant improvements in any of the three working memory sub-tests of the WAIS-IV. The IM intervention produced significant improvements in Letter-number Sequencing scores, and also improved scores on this sub-test significantly more than the EM intervention. The IM intervention was also more effective than the EM intervention at improving Arithmetic scores at the 3-week follow up, but only at a trend level of significance. These results suggest that the IM intervention was more effective than the EM intervention in terms of enhancing cognitive gains immediately after training, and possibly more effective than the EM intervention in terms of cognitive gains that persist three weeks after the completion of cognitive training.

However, the combination of the two interventions appears to be the most effective at creating both immediate and long-lasting improvements on untrained working memory tasks. At the immediate follow-up, the combination of both interventions resulted in significant improvements in Arithmetic score as well as increases in Digit Span score at a trend level of significance. Between baseline and 3-week follow up, the combination resulted in significant improvements in Arithmetic score. Also, the IM+EM group improved significantly more on the Arithmetic task compared to the EM group, on the Digit Span compared to the IM group, and also improved on the Digit Span at a trend-level of significance compared to the control group. Although the IM intervention was the only intervention that significantly improved Letter-number Sequencing scores, the combination of both interventions led to both immediate and long-term improvements on two of the three WAIS-IV
subtests. Also, improvements on these subtests at the 3-week follow up were significantly greater than improvements from either intervention alone. Together, these findings show that combining both interventions resulted in the greatest and most persistent improvements on untrained working memory tasks, supporting the hypothesis that the combination of both IM and EM interventions would most effectively improve CR outcomes.

7.3 Analysis of Major Findings

A major goal of this study was to clarify which of these two types of motivations is a more effective target for enhancing learning and skill acquisition in a working memory cognitive training task; based on the results, the IM intervention was more effective. While the IM manipulation resulted in significant improvement on some of the measures, the EM manipulation did not result in significant improvement on any of the measures used. The other main goal of the study was to evaluate the effect of manipulating both IM and EM simultaneously, in order to evaluate whether or not external rewards actually have an undermining effect on IM in this patient population. The results revealed that manipulating both EM and IM simultaneously resulted in greater and more durable improvements than either intervention alone and the control condition a variety of measures; this supports both the primary hypothesis as well as the view that intrinsic and extrinsic rewards can have additive effects on an individual’s motivation to engage in a task (Mawhinney, 1990).
The present study’s results contradict widely held beliefs that EM-based methods for changing behaviors provide no lasting benefits (Bandura, 1969) and that extrinsic rewards can undermine IM and performance when applied to learning environments (Deci, 1999). Most of the studies that support the undermining effect of tangible rewards are done in healthy populations and with individuals who have high baseline IM for the target behavior (Silverstein, 2010). Since IM has been established as a core deficit in schizophrenia, it makes sense that the results of these studies would have limited generalizability to this patient population, especially to patients with prominent negative symptoms. This criticism of the undermining effect’s validity is not meant to downplay the utility of IM-based interventions; reports that patients with high levels of IM and self-competence at baseline are more likely to attend and learn from CR therapy sessions highlight the importance of IM for enhancing CR outcomes (Choi, 2009). However, these reports also highlight the need to establish methods for enhancing CR therapy outcomes in individuals with low IM and self-competence at baseline (Silverstein, 2010). Based on the results of the present study, integrating extrinsic rewards and IM-based methods may represent a possible solution.

In addition to this study’s results, previous research supports the idea that intrinsic and extrinsic rewards can have additive effects in the context of CR therapy for schizophrenia. There is a wealth of research on the benefits of extrinsic reward on treatment response in schizophrenia. As previously discussed, methods such as attention shaping procedures utilize tangible and nontangible rewards to increase
engagement and allow participants to have the experience of success in a learning program (Silverstein, 2001, 2005, 2009). This method is an example of how extrinsic rewards can be used to build momentum for IM, which is consistent with an important aspect of Self Determination Theory; SDT posits that people can engage in a behavior due to EM, and once the intrinsically rewarding aspects are experienced, IM can maintain the behavior (Ryan, 2000).

To reflect on the possible mechanisms by which extrinsic rewards enhance IM-based interventions for individuals with schizophrenia, it is helpful to consider various reward-processing deficits that were reviewed in the introduction. The reviewed studies provided strong evidence of deficits in anticipating pleasurable experiences for future rewards despite having intact consummatory pleasure in schizophrenia. This is consistent with research showing that impaired functional connectivity between prefrontal cortex and the mesolimbic dopamine system underlies reward-processing deficits (Breiter, 2001), since it is known that anticipatory pleasure relies heavily on mesolimbic dopamine pathways (Berridge, 1998). Considering that schizophrenia patients have impaired mental representations of future rewards (Gold, 2008), and also that intrinsically rewarding aspects of therapeutic programs are not often immediately available (e.g. CR therapy will lead to improved functioning in daily life), it is plausible that immediate tangible rewards may have relatively increased motivational salience and a greater ability to guide behavior in this context (Silverstein, 2010).
Also reviewed in the introduction, it is proposed that elevation of presynaptic dopamine in schizophrenia leads to release of dopamine the absence of appropriate stimuli (Winton-Brown, 2014), which would result in the attribution of salience to irrelevant stimuli due to the stimuli’s temporal association with dopaminergic signaling. Based on this observation, it is plausible that the physical delivery of a reward that is temporally paired with a desired behavior may help to normalize dopaminergic tone and strengthen communication between subcortical reward processing circuits and the prefrontal cortex (Silverstein, 2010). The use of extrinsic reward would be especially relevant in the context cognitive training if this were the case, since the frontal circuits being activated by the reward system are also involved in attention and working memory (Locke, 2008). Since the present study focused specifically on remediating working memory deficits, this could be an explanation for why adding the EM manipulation enhanced learning outcomes compared those receiving the IM intervention alone. This possibility is supported by neuroscience research, which has shown that EM-driven improvements in various cognitive skills occur through modulation of neural circuits involving the prefrontal cortex, the midbrain dopamine system, and related subcortical structures (Braver, 2014). Although the above explanations for the observed additive effects of IM and EM in the present study are speculative, the study’s results do suggest that a combination of EM- and IM-based interventions could be most useful for enhancing learning and skill-acquisition from CR therapy in schizophrenia.
7.4 Limitations

The most obvious limitation of this study was the small sample size, especially since the total sample was divided into four groups. The small size of each group and the subsequently large standard deviations of group means resulted in the statistical analyses having relatively low power. The power of the statistical analyses was even further limited by the fact that only three participants were placed in the control group upon random assignment; having a larger control group would have been much more effective in the between-group comparisons for determining if any of the interventions were effective at increasing learning or skill-acquisition from cognitive training. However, the fact that numerous significant results on the matched-pairs t-tests were obtained from such a small pool of participants in each group (n ≤ 5) highlights the potential efficacy of the intervention procedures, and ultimately indicates that investigating these methods for enhancing motivation for cognitive training is a worthwhile avenue of research.

Another major limitation of the study was that the motivational interviewing intervention did not significantly increase participants’ IM for the cognitive training task; there were no significant increases in IMI-SR score after either the first or second cognitive training session. Also, change scores on the PCS indicated that there were no significant increases in perceived competency, a component of IM, at either time point. This may suggest that the intervention was not effective at increasing IM. On the other hand, the fact that PCS scores were increased between baseline and the end of cognitive training in the group receiving both IM and EM interventions
suggests that the motivational interviewing may have had some ability to increase perceived competency, a subcomponent of IM. Still, the lack of significant improvements in the group receiving only the IM intervention begs the question of whether working memory improvements brought about by the motivational interviewing procedure were truly a result of IM manipulation.

It is possible that the lack of a significant change in task-specific IM may be a result of the small sample size (n=5). Analysis of effect size showed that the IM intervention had a large effect on change in IMI-SR score both immediately after the first cognitive training session and after the second training session 1 week later. Considering that none of the other groups demonstrated large effect sizes for change in IMI-SR score at either time point, it is possible that the impact of the IM-intervention on task-specific IM will emerge as significant when the subject number increases. On the other hand, a similar trend would be expected to occur in the IM+EM group, since they are also receiving the IM-manipulating procedure; yet, the combination of both interventions did not have a large effect on change in IMI-SR score at either time point. While this discrepancy in effect size between the IM group and the group receiving both interventions could suggest that the EM intervention undermined the ability of the IM intervention to increase IM for cognitive training, it is also possible that the lack of significant IM changes stemmed from limitations of the motivational interviewing procedure itself.

The technique of motivational interviewing was chosen as the IM intervention for this study based on a recent study that successfully increased IM for CR therapy.
using a brief intervention modeled after this counseling technique. In this study, two 45-minute sessions of the intervention were given to participants at the start of cognitive training, which led to significant improvements in both IM and attendance, with post-intervention IM levels strongly predicting attendance (Fiszdon, 2015).

Another reason that motivational interviewing was chosen for the IM intervention in the present study is because the client-centered interview style allows for the inclusion of strategies known to promote IM for CR therapy in schizophrenia; these included allowing patients to establish personalized treatment goals, and having the interviewer emphasize the link between the cognitive training activity and those individual recovery goals (Medalia, 2009).

Despite the fact that the IM intervention was developed based on previously successful methods for increasing IM in schizophrenia, the short length of the motivational interviewing procedure may have limited its ability to increase task-specific IM. Compared to the two 45-minute sessions given in the previous study that used motivational interviewing, the present study only administered a 10-minute interview prior to the first cognitive training session and a brief recap of the interview’s main points before the second session. Although the feasibility of a longer interview was limited by the length of time patients were available to meet with researchers, the intervention may have been more effective at increasing task-specific IM over the two training sessions if a 10-minute interview was administered at the beginning of both sessions. Relatedly, another limitation of the study design is that while the EM intervention was administered throughout both cognitive training
sessions, the full IM intervention was administered only at the start of the first session. Considering that the immediate follow-up data was collected at the end of the second session, the fact that session two only included a brief recap of the motivational interview may have led to results that underestimated the intervention’s effect on IM levels, task performance, and generalized working memory measures.

Another limitation of the study is the presence of significant changes in Grooved Pegboard task performance. This measure was included in order to serve as a control task—or a task that group assignment was not expected to effect—for the purpose of ensuring that the interventions led to specific improvements in the cognitive skill being targeted by the CR program. The control group demonstrated significant improvement in dominant hand performance at the immediate follow-up, and there were also significant improvements in dominant hand performance in both the control group and the IM+EM group at the 3-week follow-up. The concern is that if an intervention enhances performance on any task regardless of the skill it is measuring, then improvements on the various working memory measures would not necessarily reflect the intervention’s ability to enhance learning and skill acquisition from CR therapy.

Fortunately, between group analysis of 3-week follow-up changes showed that the control group improved significantly more than all three groups on the dominant hand version and significantly more than the EM group on the non-dominant hand version. The specificity of the intervention would be called into question if one of the intervention groups improved significantly more than the other groups on the control
task; however, the fact that the control group improved more than any other group suggests that the interventions are likely not leading to acquisition of skills that are unrelated to the CR program. While analyzing these results, the fact that the control group is comprised of only three subjects must be considered; it is likely that when more subjects are added, the within-group variability will decrease and the changes in Grooved Pegboard performance will no longer be statistically significant.

The brief nature of the cognitive training procedure serves as another limitation in this study. Much like the limited length of the motivational interviewing procedure, the feasibility of including more than two brief training sessions was limited by the amount of time patients could commit to meeting with researchers. Although a two-session training represents an extremely short exposure to CR therapy, it was advantageous that participants were able to participate in multiple sessions since it is unlikely that a single training session would have led to measurable improvements in working memory skills. Aside from brevity, there were other limitations associated with the inclusion of this specific cognitive training program in the study design. On one hand, working memory is a good choice for the target of CR therapy based on evidence that CR therapy is effective at improving working memory skills, and also based on research showing that CR-mediated improvements in working memory may also benefit cognitive and global functioning more generally (Hubacher, 2013) (Subramanian, 2014) (Fisher, 2009). On the other hand, the training task used in the present study was limiting in the sense that the potential for improvement on the task was restricted to a very narrow range;
improvement on sequence length recalled was limited to 1, 2, or at maximum 3 digits. If the chosen cognitive training task had a wider range of possible scores and therefore greater variation in the participants’ change scores, it may have been easier to detect differences in task improvement between the four groups.

One of the study’s strengths is that the four groups did not differ significantly on any of the demographic or clinical variables analyzed, suggesting that the results were not likely driven by confounding factors. However, there are a variety of demographic and clinical characteristics that were not accounted for that could influence participants’ responses to the intervention procedures. For example, although the presence of drug abuse or dependence was evaluated using patient interview and medical records, this procedure does not qualify as a formal screen. Some clients may not have been honest about their drug use, which could be a confounding factor since drugs of abuse undoubtedly interact with the brain’s reward circuits and could impact participant’s response to the EM or IM manipulations. The study was also limited in the number of clinical characteristics that were analyzed, especially in regards to variations in type and severity of psychiatric symptoms.

7.5 Future Directions

Analyzing the strengths and limitations of the present study highlights important future directions for both the study itself and for this area of schizophrenia research. In terms of the study, the immediate goal for the future is to increase the subject number to around 15-20 patients per group; reaching this accrual goal would
make the statistical analyses more powerful and the results more reliable. A long-term future goal for the study is to examine the relationship between baseline motivational characteristics and response to the interventions, which could not be done at the present time due to the small sample size. The predictive value of baseline motivation is being explored in an ongoing study by Choi et al. (discussed in chapter 4), which also directly compares EM- and IM-based methods for enhancing CR outcomes. Preliminary findings revealed that for those with low baseline motivation, external rewards promoted greater learning and enjoyment for learning even after the external reward was discontinued. Conversely, intrinsic reward was associated with greater learning only in patients who had high levels of motivation prior to the start of the program.

The QLS-3, a measure of general-state intrinsic motivation, was included in the present study for the purpose of eventually examining this relationship. Within each of the groups, subjects can be separated into either a ‘high baseline IM’ or ‘low baseline IM’ category based on whether they scored in the top or bottom 50 percent of QLS-3 scores; then, all of the statistical analyses can be repeated on these groups in order to determine if high baseline IM patients respond to the interventions differently than those with low baseline IM. The results of this analysis could be highly useful in clinical settings where CR therapy is administered. If a clear relationship between baseline motivational characteristics and intervention efficacy were to be established, then clinicians could evaluate motivation at the onset of
treatment to determine whether targeting IM, EM, or both simultaneously would be most likely to increase a patient’s motivation for and ability to learn from CR therapy.

Future research should continue to investigate the clinical utility of interventions targeting IM and EM for enhancing CR therapy outcomes in schizophrenia, especially in specific subpopulations of patients. One of the present study’s limitations was that information about type and severity of symptoms was not measured. Relatedly, an issue with the current research on IM and EM for CR therapy is that studies demonstrating the utility of IM are most often done in relatively asymptomatic patients, while studies investigating EM are most often done in highly symptomatic patients (Silverstein, 2010). Future studies should use psychiatric rating scales to characterize symptoms (e.g. severe, mild, predominantly positive, predominantly negative, disorganized), in order to explore the relationships between symptomology and response to different types of motivation-enhancing interventions. Just as clarifying the impact of baseline motivational characteristics on intervention response could be valuable in clinical settings, clarifying the subtypes of patients that respond optimally to IM versus EM manipulations could help clinicians determine at the start of CR therapy which approach would be most useful for a patient. Limiting the use of extrinsic rewards to those who are likely to benefit from them would be practical in clinical settings, seeing as that integrating extrinsic reinforcers into treatment would be expensive if done for all patients.

On a related note, future studies should continue to investigate the utility of IM and EM both individually and in combination, but while using a different
reinforcer in the EM manipulation. Although monetary incentives are a reliable way to manipulate EM, it is not often practical or realistic to use them in treatment settings. Also, a serious confound in the current study’s design was that all participants were being monetarily compensated for their time and participation, so participants were earning money regardless of group assignment. This confound could be avoided in future research if non-monetary reinforcers are used. Future studies could investigate the efficacy of other rewards like praise, positive social reinforcement, or any extrinsic reward that could be easily applied in a treatment setting. It would be interesting to see whether or not the additive effects of the IM and EM interventions on CR outcomes observed in the present study would remain if the extrinsic reinforcers being used were less tangible.

The present study investigated the effects of manipulating IM and EM on CR outcomes in the context of a very brief training that targeted one specific cognitive skill. While administering a targeted intervention was useful for investigating ways to augment learning and skill-acquisition in CR therapy, future studies should aim to apply these methods to more comprehensive and larger-scale CR programs that aim to improve general cognitive functioning in schizophrenia. Research on how to most effectively use these motivation-enhancing strategies in this broader treatment context would have a much higher level of clinical utility compared to research that focuses on a single cognitive training task. Research on IM and EM interventions in larger-scale CR programs should aim to investigate not only the effects of the interventions on cognitive enhancement, but also on symptom reduction and global functional
outcome. Furthermore, longitudinal research studies in this area would help to determine the long-term impacts of these interventions and provide insight into whether cognitive gains mediated by these interventions are maintained.

Lastly, future research should aim to examine how these motivation-enhancing interventions are impacting the brain both functionally and structurally. As described in the introduction, many studies that have investigated the neural responses to extrinsic reinforcement in schizophrenia, and it is clear that the brains of individuals with schizophrenia demonstrate many reward processing abnormalities. Although there is evidence that IM levels have an impact on the neural processing of reward (Linke, 2010), there is certainly a need for more imaging data on the neural correlates of IM. Future research should aim to determine how both IM- and EM-based interventions impact brain functioning during cognitive training, as well as whether any structural changes correlate with intervention-mediated increases in learning and skill acquisition. In addition, research investigating the effects of combining both IM- and EM-based interventions on brain activation during cognitive training could help to clarify the mechanism by which the two interventions in the present study interacted to produce greater improvements in CR outcomes compared to either intervention alone.
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doi:10.1097/YCO.0b013e328336661b
Appendix A: Motivational Interviewing Script

“I am going to ask you some questions about your reasoning for wanting to participate in this cognitive remediation program as part of this study, as well as more general questions about your motivation regarding cognitive training therapy. This interview will take about 10 minutes. We encourage you to speak freely about your feelings and opinions.”

How do you feel about your memory skills, are you good at remember things? *pause* What things in particular are you good at or not so good at remembering? *pause, If applicable, does your inability to remember things impact your daily life? If so, in what ways?* *pause, If applicable, have you ever done or thought about doing something to help you improve your memory skills? (again, praise patient for attempts to improve skills in the past).*

_____________________________________________________________________
_____________________________________________________________________

Can you tell me what led you to participate in a study involving cognitive remediation therapy?

_____________________________________________________________________
_____________________________________________________________________

Do you have any goals for your participation in this cognitive training? Is there anything you hope to learn or achieve?

_____________________________________________________________________
_____________________________________________________________________

Do you mind if I tell you a little more about what cognitive remediation therapy is? *If yes,* Cognitive Remediation is a type of therapy that aims to improve cognitive skills such as attention, memory, planning, problem solving, etc. Improving these skills can help contribute to more general recovery goals, like improved functioning in daily life. You will be participating in two sessions of Cognitive Remediation, but you will have the opportunity to continue the therapy in a longer study in the future, which could really help you achieve improvements in your cognitive skills. Does this sound like something you could benefit from? *pause.* Do you have any observations or concerns about your cognitive skills, or any cognitive skills that you think are particularly weak? *pause.* Have you done anything in the past to improve your cognitive skills? *(praise for anything they’ve done to improve cognition in the past).* People who put time and effort into these cognitive training programs often see improvements their cognitive skills. Do you feel like you are capable of improving your cognitive abilities? *pause.*
As you know, the cognitive training we’ll be doing is focused on memory. Do you mind if I tell you some information about what memory skills are useful for? If yes, memory is used for reading comprehension, planning activities, problem solving, learning, and following instructions. Having impaired memory skills can have negative effects on all of these cognitive skills. Does this make sense? If no, try rephrasing until they understand. So based on the information I’ve told you, can you me some of the skills that memory is used for? If they can’t think of many, repeat the list again.

Based on that information, do you think improving your memory would be important to you? Can you tell me one-way that memory skills can be improved? (if they don’t say CRT, remind them that attending cognitive training sessions, such as the two they will be participating in shortly and the longer one that will be offered in the future, often helps people improve cognitive skills like memory). Do you feel that you have the ability to make improvements in your memory skills? Regardless of answer, Your decision to attend these training sessions is a great step towards improvement.

Now I’m going to ask you some questions about the specific cognitive skills that are related to memory. Can you tell me about your planning skills? For instance, do you feel capable of effectively planning your daily activities, or planning an event? Do you have trouble following through with plans that you made for yourself? Any examples of when difficulty to plan effectively has impacted your daily life? Do you think that improvements in these skills would be beneficial in your daily life, or would things be different for you if you made changes to improve your planning skills?

What about reading comprehension? When you are reading a book or a newspaper article, do you have trouble keeping track of what’s happening? Do you sometimes get to the bottom of the page and realize you don’t really remember anything you just read? Do you feel that difficulties in reading comprehension negatively impact your daily life? If so, how/in what ways? Do you think that improvements in these skills benefit you in your daily life, or would things be different for you if you made changes to improve your reading comprehension skills?
Have you ever noticed that you have trouble paying attention or concentrating? *pause*
Well, memory plays an important role in concentration. Often, everyday memory problems result from not paying enough attention in the first place—you have to pay attention to something first in order to remember it later, right? In what contexts do you notice that you have difficulties in paying attention or concentrating? *pause* Do these difficulties impact your daily life or get in the way of things? *pause* Do you think that things would be different for you if you made changes to improve your ability to pay attention? *pause* Do you feel that you are capable of making positive changes in your attention skills?

After learning a little more about memory and reflecting on your cognitive skills, how do you feel about participating in this study’s cognitive training? Are you excited? Apprehensive? Unsure? Explain. *(Regardless of answer, say that it is awesome that the participant is deciding to spend time doing something that could help them improve their cognition).*

On a scale of 1-10, how confident are you in your ability to improve your cognitive abilities through participating in cognitive training therapy? *If confidence is low,* probe what they think is standing in the way and brainstorm ways to overcome those challenges—ensure that the ideas are coming from the patient, not the interviewer. On the same scale, how motivated are you to make these improvements? *If low,* question why they aren’t motivated to make positive changes. On the same scale, how much would you value a improvements in your cognitive skills, whether it be memory, planning skills, reading skills, attention/concentration, etc.

*(provide document with summary of main points)* Summarize at the end what areas they want to work on, what changes they anticipate could come from improving cognitive skills, and remind them that attending cognitive remediation will help them to progress towards their improvement goals *(if they have goals)*. Do you have any further input you’d like to share with me on any of the topics we discussed?

Do you have any other questions about cognitive remediation therapy in general, or specific questions about the memory training activity? Do you have any other comments regarding your feelings about participating in this study?
Appendix B: Sham Interview Script

“I’m going to ask you some questions so I can learn a little bit more about your daily life and interests. This interview will take about 10 minutes. We encourage you to speak freely about your feelings and opinions.”

Where did you grow up? What did you like about growing up there. Was there anything you disliked about it? Have you lived in that area for your whole life, or have you moved?

______________________________

Do you have siblings? If so, how many? Are they older or younger than you? Tell me about them, i.e. what are they doing now, or where do they live/where do they work?

______________________________

Do you have any pets? If so, inquire about what kinds and how many. If not, did you have any pets growing up? If so, inquire about them, i.e. what were their names?. If no pets at all, if you were to get a pet, what kind would you choose? Why?

______________________________

Do you have a job currently? If so, what do you do at your job? How often do you work? Do you like working there? Why/why not? If doesn’t have a job, what was your most recent job? Did you like working there? Why/why not?

______________________________

Can you describe what you do on a normal day? For example, what do you do first thing when you get up in the morning? What types of activities do you do at home throughout the day? Do you have any hobbies, like crafting or collecting things or playing an instrument? If no, were there any hobbies that you had in the past that you spent a lot of time doing?

______________________________

Do you watch television often? Do you have any favorite television shows? If so, what do you like about that show? What about movies, do you watch them often or have a favorite?
Do you watch sports? If so, which sports are your favorites to watch? Do you have any favorite teams? Did you play any sports in high school or when you were a kid? *If multiple,* what was your favorite sport to play?

____________________________________________________________________

____________________________________________________________________

____________________________________________________________________

Do you like to cook? If so, what kinds of things do you usually make? Do you have a favorite food? What about a favorite dessert? *If no,* did you used to cook more often? What did you like to make when you did cook? Do you eat breakfast in the morning? *If so,* what do you usually have?

____________________________________________________________________

____________________________________________________________________

____________________________________________________________________

How often do you partake in physical activity or exercise? *If no,* did you exercise sometimes in the past? What is/was your favorite type of exercise, i.e. playing sports, going on walks, working out at home? Do you think that exercising regularly is important?

____________________________________________________________________

____________________________________________________________________

____________________________________________________________________
Appendix C: Intrinsic Motivation Inventory for Schizophrenia Research (IMI-SR)

For each of the following statements, please indicate how true it was for you in regards to completing the computer learning activity.

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1. I enjoyed doing this activity very much.

2. This activity was fun to do.

3. This was a boring activity. (R)

4. I believe doing this activity could be beneficial to me.

5. This activity did not hold my attention at all. (R)

....

21. I did this activity because I had to. (R)

Reverse score (R) items (subtract item response from 8, use resulting number as score)

Total IMI score: \( \text{(Sum of Q1 through Q21; 21-147 range)} \)  

Average IMI score: \( \text{(Divide total IMI score by 21)} \)
Appendix D: Perceived Competency Scale (PCS)

For each of the following statements, please indicate how true it was for you in regards to completing today's computer learning activity.

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1. I felt confident in my ability to do these computer tasks.
   
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2. I felt capable of doing these computer tasks.

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3. I was able to achieve the goals in these computer tasks.

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4. I felt I was able to meet the challenges of performing well on these computer tasks.

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5. I believe I can do well on future computer tasks like these.

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Total score: *(Sum of Q1 through Q4; 7 - 35 range)*

Average Score: *(Divide Q5 by 5)*