Salience as a Tool for Cognitive Remediation in Schizophrenia

by

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Abstract

**Introduction:** Processing speed is a measure of cognitive function related to working memory, attention, and psychomotor skills. Schizophrenia patients consistently perform poorly on tests such as the Wechsler Digit Symbol-Coding Test (DSC; Wechsler D., 1997), which is an established measure of processing speed. Recently, studies have shown that patients with schizophrenia have the most significant impairment on the Digit Symbol-Coding Test relative to all common neuropsychological measures, a finding that could not be accounted for by medication exposure. In spite of such significant impairment, the Digit Symbol-Coding Test has rarely been the subject of theoretical review and experimental investigation (Dickinson et al. 2007). One clever remediate strategy has shown the remediate power of salient cues in a continuous performance task (Lee, Park, 2005). The incorporation of salient cues into a computerized DST could enhance encoding of the digit-symbol relationships in the key, allowing subjects to obtain higher scores. **Methods:** 20 healthy controls from the Middletown, CT community were administered a computerized DST designed to test the effect of salient priming on score. **Results:** There was a negative correlation between the number of digit-symbol pairs in the key and total score in the fixed relationship conditions; as the key grew larger, subjects’ scores decreased. Likewise, there was a positive correlation between the number of digit-symbol pairs in the key and reaction time in the fixed relationship conditions; as the key grew larger, subjects took longer to respond to each trial. The number of digit-symbol pairs in the key was not significant in the varying relationship conditions. 10 trials of salient priming with red arrows significantly reduced score but did not significantly affect reaction time in both fixed and varying relationship conditions. **Discussion:** The number of symbols in the key had a significant effect only in fixed relationship conditions. Thus, this study was unable to fully replicate previous results using a computerized DST. Furthermore, salient cues made subjects perform significantly worse on the computerized DST, which indicates that the experiment needs to be completely revised before it is ready to test schizophrenia patients.
Schizophrenia in History:

Insanity is older than civilization. It represents a key conflict in myths, such as the sirens in The Odyssey. More contemporary characters have started entire revolutions, claiming that their divine experiences compelled them to foment a new order. Joan of Arc is considered by many to have experienced auditory hallucinations characteristic of schizophrenia. However, accounts of insanity of all types were vague until standards of diagnoses emerged in the 20th century. Until then, mental illness was most often interpreted as a problem of the spirit and the soul, a superficial manifestation of evil demons, or an imbalance of the vital fluids in the body (Gottesman, 1991).

Before we had the scientific tools to investigate their characteristics, most mental illnesses remained undistinguished from each other. Today, we have only the written accounts of witnesses and the sufferers themselves to understand the experience of madness in the past. The Reverend Mr. George Trosse wrote this account of his hallucinations around 1690:

I was haunted with a great many terrifying and disquieting Visions and voices; which tho’ (I believe) they had no Reality in themselves, yet they seem’d to be such to me, and had the same Effect upon me, as if they had been really what they appear’d to be.

At length, standing up before the Window, I either heard a Voice, which bid me, or had a strong Impulse, which excited me, to cut off my Hair; to which I reply’d, I have no Scissors. It then hinted that a Knife would do it; but I answer’d, I have none. Had I had one, I verily believe, this Voice would have gone from my Hair to my Throat, and commanded me to cut it (Frith, Johnstone, 2003).

These passages describe experiences from the Reverend’s early twenties, when the onset of schizophrenia is most common. The auditory hallucinations along
with their coercive nature are consistent with hallucinations reported by contemporary patients with paranoid schizophrenia. Hallucinations such as these represent some of the most terrifying and disabling characteristics of the disease.

Diagnostic criteria for schizophrenia didn’t emerge until the turn of the 20th century, when Kraepelin described *dementia praecox* as an early onset psychological illness that consisted of hallucinations, cognitive impairment, functional paralysis, and a young death (Kraepelin, 1970). Emil Bleuler continued Kraepelin’s work by describing the manifestation of *dementia praecox* in adults. Through his work, Bleuler contradicted Kraepelin’s notion that the illness always began in the young and that it results in cognitive deficits. In his extensive book, *Dementia Praecox or the Group of Schizophrenias* (1911), Bleuler described the characteristic mental deficits in schizophrenia, which came to be known as the four A’s: association, affectivity, ambivalence, and autism (McGlashan, 2011). The influence of his writings is still visible in the *Diagnostic and Statistical Manual of Mental Disorders*. This manual is the standard reference for the diagnostic criteria of all mental illness. Several editions have been published since the first edition in 1952 (Grob, 1991). The DSM-IV-TR is the most current version and provides extensive characterization of schizophrenia.

**Incidence, Prevalence, and Etiology:**

Incidence is defined as the number of new cases per 1,000 individuals in a given population during one year (First & Tasman, 2004). While the exact
incidence of a mental illness such as schizophrenia is difficult to determine, the rate of diagnosis in various countries can allow epidemiologists to make more global estimates. The World Health Organization, in an International Pilot Study of Schizophrenia, found that schizophrenia is found in all cultures, and that incidence per 1,000 individuals annually ranges from 0.15 in Denmark to 0.42 in India (WHO, 1973).

Prevalence is usually defined as the portion of a population that has ever been diagnosed with the illness. Most populations have a prevalence rate of about 1%. Extremes in population prevalence are important for researchers seeking to understand the genesis of schizophrenia. For example, in the Hutterite community, a Protestant sect living in South Dakota, schizophrenia is almost nonexistent. Epidemiologists theorize that diet, genetics, even maternal age may contribute to this phenomenon (Heinrichs, 2003). However, the causes of schizophrenia remain enigmatic.

Signs of schizophrenia usually begin in individuals in late adolescence and early adulthood, though it tends to start earlier in men than in women by a few years. It can affect individuals of any race or socioeconomic status (Butcher, Mineka, & Hooley, 2010).

There are many hypothesized causes of schizophrenia, ranging from the season in which an individual is born to the alleles of specific genes. One popular theory is the dopamine hypothesis, which proposes that there are elevated levels of dopamine in the brains of individuals with schizophrenia and that this excess dopamine induces psychosis. While the dopamine hypothesis cannot account for
all the symptoms of schizophrenia, it does explain why patients prescribed drugs that act as antagonists on the D₂ dopamine receptor experience reduced psychotic symptoms (First & Tasman, 2004). However, the cause of these elevated levels of dopamine is also unknown.

As mentioned, one hypothesized link is season of birth. Evidence has shown that spring births are correlated with increased risk of schizophrenia because mothers are often infected with influenza in the winter during their second trimester of pregnancy. One study reported a strong correlation between pregnancies during the 1957 influenza epidemic in Finland and the subsequent development of schizophrenia (Mednick, Machon, Huttunen, & Bonett, 1988). It is believed that because the second trimester is critical for the formation of the limbic system, viral infection during this time is disruptive to healthy brain development (First & Tasman, 2004).

Contemporary research has identified several candidate genes that may influence the transmission of schizophrenia. One of these genes is known as catechol-O-methyltransferase (COMT). COMT carries two possible alleles that are designated by the names Val and Met. The methionine (Met) allele is associated with low enzymatic activity, whereas the valine (Val) allele is associated with higher activity. The COMT gene produces an eponymous enzyme that is responsible for breaking down catecholamines, which are chemicals related to the stress response. Homozygosity for the Met allele yields a 3- to 4-fold reduction in COMT activity relative to Val homozygotes, with heterozygotes demonstrating intermediate activity (Strous, 1997). Thus, individuals who are
homozygous for the Met allele do not metabolize stress-related chemicals very effectively, which leads to their prolonged effect in the brain and increased risk of developing psychosis.

**Symptomatology and Diagnosis:**

Schizophrenia exists on a spectrum of severity and can have a combination of symptoms. These symptoms can be manifested in a variety of ways, which makes the diagnosis of schizophrenia subjective. Furthermore, there are a variety of similar conditions such as schizoaffective disorder, mood disorder with psychotic features, and bipolar disorder.

The Diagnostic Statistical Manual IV (DSM-IV) defines the diagnostic criteria for schizophrenia based on its characteristic symptoms. These symptoms include delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (affective flattening, alogia, or avolition). Two or more of these symptoms must be present for a significant portion of time during a one-month period and continuous signs of the disturbance must persist for at least six months. If there are periods of remission during these six months, the signs of the disturbance may be manifested by only negative symptoms or two or more characteristic symptoms in an attenuated form (First & Tasman, 2004).

Most clinicians separate symptoms of schizophrenia into two main categories: *positive* and *negative*. Positive symptoms encompass the more expressive and psychotic manifestations of the illness. They include symptoms
such as hallucinations and delusions, thought disorder, bizarre behavior, and inappropriate affect. Negative symptoms are often the most disabling feature of schizophrenia. These symptoms include blunted affect, asociality, anhedonia, alogia, and avolition. Individuals with profound negative symptoms will often refrain from speaking at all. Individuals with schizophrenia never display only positive or negative symptoms, but display some degree of heterogeneity (First & Tasman, 2004). Although the distinction between these two sets of symptoms is incomplete, they are useful designations for understanding the symptomatology of schizophrenia.

Additionally, a third accepted category of symptoms has been introduced into the vocabulary. This third category, disorganization, classifies inappropriate affect, bizarre behavior, flight of ideas, disturbances in thought, and loose associations as separate from other positive symptoms (Lenzenweger et al., 1991).

Positive symptoms are the most responsive to medication. Most theories suggest that delusions and hallucinations are a symptom of hyperdopaminergia, elevated levels of dopamine in the brain. This is often referred to as the dopamine hypothesis. However, the dopamine hypothesis is under debate. Neuroleptic drugs target the dopamine systems in the brain, but their effectiveness varies. In addition, these anti-psychotic drugs are often effective in treating psychoses unrelated to schizophrenia, such as drug-induced psychosis (Johnstone, Humphreys, Lang, Lawrie, & Sandler, 1999). Since each case is different, clinicians are often forced to experiment with different cocktails of
neuroleptics before a successful regimen can be recommended. In one study, only 40-53% of patients reported that their positive symptoms were well controlled by their neuroleptics (Lecrubier et al., 2007). These inconsistencies reveal how little we understand about the neurological etiology of the disease. Luckily, some studies have shown that positive symptoms tend to decrease as the disease progresses (Harrow & Jobe, 2008; Szymanski et al., 1996).

Negative symptoms refer to the absence of behaviors that healthy people exhibit. These symptoms contribute to social withdrawal and a lack of desire to initiate goal-related activities. These symptoms are just as prevalent as positive ones and are just as debilitating. Individuals with profound negative symptoms are difficult to treat. There are no neuroleptic drugs that can ameliorate negative symptoms and they tend to be related with poor functional outcome after treatment (Ho et al., 1998). Early-onset schizophrenia tends to be associated with the development of more negative symptoms as the disease progresses throughout an individual’s life (Mancevski et al., 2007). Most importantly, negative symptoms are a stronger predictor of functional outcome than positive symptoms; individuals with milder negative symptoms do better in social and occupational settings throughout life (Rabinowitz et al., 2006).

**Neuropsychological Deficits:**

It is worth noting that in much of the documented history of the study of schizophrenia, cognitive deficits were overlooked or seen as subordinate to psychotic symptoms. Influential psychiatrists of the late 19th century saw ‘feeble-
mindedness’ as non-progressive and treatable. This view was accepted for many decades even in the face of poor performance on neuropsychological tests, which was determined to stem from a lack of motivation or a failure to cooperate with the examination (Johnstone, Humphreys, Lang, Lawrie, & Sandler, 1999). Beginning in the 1960’s, however, neuropsychological tests gained increased use for screening and as adjuncts to medical procedures meant to diagnose mental illnesses such as schizophrenia (Heaton, Baade, & Johnson, 1978).

Today, it is agreed that cognitive impairment is relatively independent of psychotic features of schizophrenia and that it is central to the enduring features of the illness. Furthermore, the extent of cognitive impairment seems to determine the rate of functional improvement in patients (Goldberg et al., 1993). We recognize that the vast majority of individuals with schizophrenia have impairment in at least one cognitive area, but impairment ranges from severe to negligible. Cognitive deficits are found in the following six categories: general intellectual ability, memory, executive function, motor function, attention, and language (Frangou & Murray, 2000). Cognitive impairments that result from schizophrenia have a profound impact on the ability of individuals with schizophrenia to find and maintain employment and social contacts. These disqualifications have a high direct cost for cognitively low-functioning patients (Grant et al., 2012).

While schizophrenia can affect individuals of all IQs, patients with schizophrenia experience general intellectual impairment and deterioration (Kondel, Mortimer, Leeson, Laws, & Hirsch, 2003). It is generally believed that
global intellectual impairments precede the onset of psychotic symptoms that
eventually lead to diagnosis (Dunkley & Rogers, 1994). Additionally, some
research suggests that general intellectual ability declines throughout the course
of the illness. As patients age, the probability that they will be able to even
complete standardized IQ tests such as the Weschler Adult Intelligence Test
(WAIS) gradually declines (Dunkley & Rogers, 1994). However, other research
has indicated that intelligence remains relatively constant throughout the course
of the disease. In one study, 12 patients were administered the WAIS once upon
entry into the study and again 10 years later. Scores did not differ significantly
between the two tests (Kurtz, Seltzer, Ferrand, & Wexler, 2005). This would
suggest that intelligence in schizophrenia is unlinked to most other symptoms,
which change throughout the course of the disease. Conflicting studies make it
difficult to understand the relationship between intelligence and the progression
of schizophrenia.

Memory deficits in schizophrenia are complex due in part to the many
distinct types of memory recognized by researchers and clinicians. In addition,
there is disagreement as to whether memory impairment in patients is a
primary symptom or if it is secondary to deficits in attention and executive
function. Regardless, memory deficits are one of the most reliable findings in
neuropsychological examinations (Gourovitch & Goldberg 1996; Aleman et al.,
1999). Memory is divided into short and long-term, explicit, implicit, and
working. All of these types of memory have been shown to be impaired and
Impairments are more pronounced in individuals with heavy negative symptoms (Sander, 2008).

Implicit memory refers to conditioning, priming and procedural learning. Unlike working memory, implicit procedural memories are mostly preserved in schizophrenia patients (Sander, 2008). These unconscious memories require very little mental effort to perform, like riding a bike. However, explicit memory deficits are common and are a major cognitive deficit of the disease. Patients are poor spontaneous encoders of information during learning sessions and this is the case for verbal and non-verbal material (Conklin, Curtis, Katsaris, & Ianco, 2000). Some theories suggest that the decreased activity of the dorsolateral prefrontal cortex prevents patients from processing information long enough in their working memory to build contextual links and then store the new material for recall (Vinogradov et al., 1997).

Working memory is a cognitive process that holds a limited amount of information while an individual manipulates that information. Remembering a phone number long enough to dial it is an example of a working memory process. Cognitive psychologists define working memory as being made up of two components. One of these is the phonological loop. This component is active when one mentally repeats a phone number to remember it. The other component is the visuospatial sketchpad, which allows for the recall and manipulation of visual stimuli. During working memory tasks with fMRI monitoring, schizophrenia patients show dysregulation relative to controls of the dorsolateral prefrontal cortex, which is thought to be a locus of processing
and working memory (Spitzer, 1993). Research has shown that working memory deficits underlie a vast range of impairments in schizophrenia, including sensorimotor function, visual retention, executive function, and negative symptoms (Silver, Feldman, Bilker, & Gur, 2003).

Studies employing continuous performance tasks have repeatedly demonstrated attention and executive functioning deficits in patients with schizophrenia. Continuous performance tasks require an individual to perform simple visual vigilance exercises that test one’s ability to devote sustained attention to stimuli. Both medicated and unmedicated individuals show deficiencies in these tests (First & Tasman, 2004). Some research has shown that even those who are at risk for psychosis but have no symptoms, such as first-degree relatives of schizophrenia patients, perform worse on tests of attention (Wolf & Cornblatt, 1996). Processing speed is also adversely affected. Tasks such as word production and verbal fluency have shown that the number of words produced by patients is consistently lower than in healthy controls (Gruzelić et al., 1988).

Processing speed is a measure of cognitive function related to working memory, attention, and psychomotor skills. Patients consistently perform poorly on tests such as the Wechsler Digit Symbol-Coding Test (DSC; Wechsler D., 1997), which is an established measure of processing speed. Recently, studies have shown that patients with schizophrenia have the most significant impairment on the Digit Symbol-Coding Test relative to all common neuropsychological measures, a finding that could not be accounted for by
medication exposure. In spite of such significant impairment, the Digit Symbol-Coding Test has rarely been the subject of theoretical review and experimental investigation (Dickinson et al., 2007). One study showed that the correlation between processing speed and working memory deficits remained constant even when memory span was partialled out. This suggests that a slowing of the elementary operations involved in information processing is the most basic limiting factor of cognitive deficits and that processing speed deterioration is the basis of all working memory deficits (Brebion, Amador, Smith, & Gordon, 1997).

Psychomotor deficits also play a role in the cognitive impairments in patients. However, there are other more disabling motor impairments in the schizophrenia symptomatology. Relative to controls, patients show longer reaction times in volitional tasks, indicating a general difficulty in initiating movement for tasks (Frecska, Symer, White, Piscani, & Kulcsar, 2004).

The most tangible and accessible way to understand the cognitive deficits in schizophrenia patients is through language. Some patients are effervescent speakers, with seemingly endless monologues, while others rarely utter a word. The influential psychiatrist and schizophrenia theorist Eugen Bleuler observed, “Of the thousands of associative threads which guide our thinking, this disease seems to interrupt, quite haphazardly, sometimes single threads, sometimes a whole group... in this way thinking becomes illogical and often bizarre” (Bleuler, 1911). These disjointed threads refer to the loose associations that many patients make when they talk. Indeed, there is some evidence that there is a lack of inhibition in the semantic networks of the brain. For example, in one
experiment, subjects were primed with the discordant words “tree-palm-wrist” and later “hand-palm-wrist.” The healthy controls required more presentations of the former words than the patients with schizophrenia to recognize the alternative meaning of “palm.” This suggests that the multiple meanings of “palm” were not inhibited when presented with “wrist” in patients as they were in controls (Bullen & Hemsley, 1987). Thus, language deficits in patients can be best understood as a lack of semantic inhibition normally present in healthy individuals.

There is general consensus among clinicians that neuropsychological deficits are a primary characteristic of schizophrenia and are not just consequences of deficits in motivation, cooperation, or psychosis (Gourovitch & Goldberg, 1996). The cognitive impairments that result from schizophrenia are a central feature of the disease and are just as disabling as the more traditionally studied positive and negative symptoms. Study after study has shown that low cognitive functioning is related to poor functional outcomes in quality of life and rehabilitation (Evans et al., 2004; Green, Kern, & Heaton, 2004; Milev, Ho, Arndt, & Andreasen, 2005).

**Cognitive Dysfunction and Functional Outcome:**

The cost of cognitive impairment to the individual is manifested in his or her inability to work and maintain social contacts. These disabilities represent multidimensional impairments that cannot be understood by performance on one cognitive test. Functional outcome refers to the extent that a patient’s
behavior could be considered healthy and normal. Numerous studies have indicated that cognitive dysfunction and functional outcome are inextricably related. Measuring functional outcome is an important step in determining the efficacy of rehabilitation programs. First, it is important to understand how functional outcome is measured and its relevance to treatment.

Functional outcome measures can be assessed in a variety of ways, however, according to Green et al., most of those measures fall into three general categories: “(1) success in psychosocial rehabilitation programs, (2) studies of laboratory assessment of social problem solving ability or analog measures of instrumental skills, and (3) studies that have considered broader aspects of behavior in community outcome and activities of daily living” (Green, Kern, Braff, & Mintz, 2000).

The first two measures are important because they refer to a patient’s ability to practice and demonstrate cognitive skills. Psychosocial skill acquisition trains patients to develop essential life skills, such as basic conversation skills, leisure skills, and financial management. These rehabilitation programs utilize a highly structured curriculum that aims to provide patients with greater functional independence. Similarly, studies of laboratory assessment of social problem solving ability test a patient’s ability to use logic to dissect and resolve everyday conflicts. In a typical exercise, a patient watches a video depicting a social conflict and then resolves the conflict using role-play. The third measure is more subjective and thus must be determined based on self or caregiver’s reports. Assessments include degree of independent living, social attainment,
and occupational functioning (Green, Kern, Braff, & Mintz, 2000). This measure is of paramount importance because it indicates the degree to which a patient will be self-sufficient in non-laboratory settings in the real world.

Green et al. compiled 37 studies that indicated relationships between specific neurocognitive measures and types of functional outcome (see fig. 2). For example, one study of 40 schizophrenia and schizoaffective outpatients found that the Stroop test of selective attention, verbal fluency tests, and WAIS tests of general cognition were all correlated with functional outcomes in independent living and vocation (Brekke et al., 1997). Other studies examined more global measures of neurocognition. Velligan et al. assessed the relationship between positive and negative symptoms, cognitive impairment and daily activities in two different samples of patients. They showed that differences in cognitive impairment independent of positive and negative symptoms accounted for 48 and 42 percent of the variance in daily activities in the two samples, respectively. This provides strong evidence that cognitive impairment, not symptoms, is most closely linked with functional outcome (Velligan et al., 1997).

**Behavioral Treatment:**

There is no golden handbook for the treatment of schizophrenia. Clinicians are ultimately responsible to inform themselves with current protocols and update themselves with new strategies. Because each case is unique, treatment decisions are subjective and often experimental. It often takes years to find the perfect cocktail of pharmaceuticals and the capricious nature of
the illness can quickly necessitate further experimentation. Additionally, the therapeutic relationship between the clinician and the patient is of paramount importance. The clinician has to work to establish a relationship in which he or she can be seen as a trustworthy mentor and healer. In the tumultuous world of the patient, the clinician must seek to provide consistency and anchoring. The DSM-IV recommends that the relationship include “consistency, acceptance, appropriate levels of warmth that respect the individual’s needs for titrating emotional intensity, nonintrusiveness, and, most important, caring” (First & Tasman, 2004). Effective treatment hinges on the coordination of psychosocial therapeutics and a proven pharmacological regimen.

The patient-clinician relationship is difficult to document and even more difficult to study. Additionally, the efficacies of different psychopharmaceuticals are not relevant to this discussion. Thus, this review focuses on broad population studies of the efficacy of different rehabilitation strategies. Specifically, this review aims to assess the efficacy of holistic rehabilitation and cognitive remediation strategies that hone pragmatic skills in patients. Deinstitutionalization has necessitated patients to acquire the skills for independent living. Effective remediation should identify and promote these capabilities.

Rehabilitation regimens have existed for a long time. The Assertive Community Treatment (Test & Stein, 1976), Choose-Get-Keep model (Danley et al., 1992) and Intensive Psychiatric Rehabilitation Treatment (Lamberti et al., 1998) are all examples of rehabilitation programs that emphasize
comprehensive treatment, including social skills training, independent living, and behavioral intervention. Most remediation strategies acknowledge the predictive power of cognitive ability and hold cognitive remediation to be a core focus of treatment. Examining an established and empirically effective protocol is the best way to understand the dogma of cognitive remediation strategies. The Neuropsychological Educational Approach to Remediation (NEAR) is one such current approach developed by Alice Medalia in 1999.

NEAR is a group-based treatment program that aims to encourage independent learning and promote pragmatic cognitive functioning on a day-to-day basis. This cognitive remediation program focuses on motivation and learning by implementing strategies such as positive reinforcement, allowance for choice, encouragement of independent learning, and contextualization of learning. Remediation in NEAR is built around the administration of computer games that are adjusted to each individual’s strengths and weaknesses, which are assessed at the beginning of the program. The games’ focus on independence and applicability to real-word scenarios presents patients with tasks related to everyday problem solving or vocational situations. Furthermore, NEAR hinges upon collective learning by utilizing a group format. The group format fosters regular social interaction, which improves social skills while relieving the tediousness of some of the computer games. Participants normally attend hour-long groups twice per week for 10 weeks (Naismith et al., 2010).

Cognitive remediation programs like NEAR show significant patient improvement in all cognitive domains tested. Even though improvement is
heterogeneous among cognitive areas and is still below normal levels, patients improve more than patient controls tested twice with cognitive batteries, indicating a large potential for remediation in individuals with schizophrenia (Ikezawa et al., 2011). However, with half-staffed and overcrowded institutions becoming the norm, we need reliable cognitive remediation that can be administered in an outpatient setting with minimal staff to administer it. Luckily, treatment protocols exist for these requirements, and some have shown just as much promise as programs such as NEAR.

Some methods of treatment focus directly on restoring impaired cognitive function independent of social skills. Researchers develop and test behavioral approaches as a possible method to mitigate profound cognitive dysfunction associated with schizophrenia. These methods are heterogeneous, hinging on both group and individualized protocols and computerized and paper-based administrations. Regardless of its form, any method that seeks to treat cognitive dysfunction as a means for improving the functional outcome of the patient is known as cognitive remediation (Kurtz et al., 2007).

While the first studies of cognitive remediation showed that it had no significant effect on neurocognitive measures (Benedict et al., 1994), more recent studies are encouraging. Most contemporary studies of cognitive remediation show improvement in one or more areas of cognitive functioning, regardless of the design of the study or the profile of the subjects (Twamley, Jeste, & Bellack, 2003). The implementation of cognitive remediation into the
treatment protocol for patients is undoubtedly an essential step to improving functional outcome.

Wexler and Bell have developed and tested one particularly promising program that combines cognitive remediation with vocational remediation to outpatients for six months. Cognitive Remediation Therapy (CRT) consists of computerized tasks that exercise cognitive faculties in attention, memory, language, category formation, and planning. The computer program is designed to assess patients’ strengths and weaknesses and then administer tasks so that patients spend the most time exercising their weakest skills while still maintaining their strengths. Each task is comprised of varying levels of difficulty, allowing patients to improve incrementally.

In their study, Wexler and Bell assigned patients to participate in CRT and a Work Therapy (WT) program, CRT and a community Supported Employment (SE) program, or just WT or SE alone. Predictably, the patients enrolled in both CRT and an employment program showed more improvement on cognitive measures than individuals only enrolled in an employment program. To show that these gains were not specific to the computerized tests, alternative measures of cognition were administered to the patients. In some categories, patients improved almost an entire standard deviation. Furthermore, these gains were shown to be durable and, in some cases, continuous. In a follow-up study a year later, subjects from the WT and CRT condition showed significantly greater improvements in executive function and working memory in comparison to the group that only received WT. As many as 60% of the WT and CRT group showed
sustained improvement in at least one neuropsychological measure. These remarkable results suggest that the application of trained cognitive skills to independent real-life scenarios cultivates lasting improvements and encourages patients to build upon their own success (Wexler & Bell, 2005).

In contrast, other studies have not shown the same promise for cognitive remediation. One study by Dickinson et al. indicated that improvements seen as a result of cognitive remediation were limited to the training exercises used in the program and that there were no significant benefits for neuropsychological or functional outcome measures. In Dickinson’s study, 69 patients with schizophrenia participated in 36 sessions of computerized cognitive remediation therapy. While there were significant improvements on every training exercise at the end of the study, there was no generalization of training effects to metrics such as social skills, processing speed, and attention (Dickinson et al., 2010). This suggests that practice may not be enough to treat cognitive impairments, that there may be an intrinsic deficit that is unresponsive to training. Great Britain’s National Institute for Health and Clinical Excellence has extensively reviewed studies documenting the efficacy of cognitive remediation. They stated that there is “little consistent advantage of cognitive remediation over standard care and attentional controls” and “no consistent evidence that cognitive remediation alone is effective in improving the critical outcomes, including relapse rates, rehospitalization, mental state, and quality of life” (NICE, 2009). In order to build effective cognitive remediation, we need to identify the active
ingredient. We need to test one strategy at a time to discover the interventions that give consistent results.

**Building Cognitive Remediation:**

Cognitive therapy programs consist of many tasks that exercise specific cognitive faculties. For example, simple auditory reaction time can be exercised by asking a patient to click the mouse as soon as they hear a tone (Bracy, 1995). However, as the tasks become more complex, patients tend to struggle more to improve. Some tasks that require significant sustained attention, such as the Weschler Digit Symbol Coding Task (see figure 1), have been shown to give particular trouble to patients. To improve performance on tasks such as the DST, it is necessary to implement strategies that will guide the patient’s attention towards the relevant information.

In the present study, the DST was modified for computer administration, a modification that has been previously tested and shown to be an adequate, even remediative, adaptation (McLeod, Griffiths, Bigelow, & Yingling, 1982). Since McLeod and colleagues adapted the DST for the computer, many studies have worked with the digital DSTC interface. Of particular interest to the present study is a study by Bachman et al., which modified the DST to a new digital environment. Bachman et al. replaced the blank form of the original DST with a stimulus-response paradigm (see figure 2), which allowed the researchers to "independently manipulate the demands placed on visual scanning efficiency and relational memory while holding decisional and motoric requirements constant. More specifically,
This novel digit symbol coding task includes conditions where the set size and presentation consistency are varied over 60-second blocks of trials. Increasing the number of digit-symbol pairs or set size from 3 to 6 to 9 pairs augments the demands placed upon both scanning efficiency and relational memory. In contrast, presentation consistency, designed to localize relational memory, was assessed by maintaining the digit-symbol pairing throughout the block of trials (Fixed Condition) or by randomly assigning these pairing for each trial in a 60-second block (Random Condition)” (Bachman et al., 2010).

These conditions provided a way to show that the DST was in fact a test of processing speed that included both visual scanning and relational memory components, and that performance worsened as there were more items to process. Both healthy controls and patients performed best on the conditions with the fewer digit-symbol pairs. Furthermore, both controls and patients performed best on the conditions in which the relationship of the digits and symbols in the key remained constant, presumably because the subject learned to associate specific digits and symbols over repeated stimulus presentations via their relational memory (see figure 3). This indicates that healthy controls utilize relational memory to minimize scanning time between presented items, while relational memory impairments minimize this advantage for patients. The Bachman article highlights the severity of working memory and processing speed deficits in patients. A strategy that could improve performance on the DST could lead to the development of more effective treatments of these deficits.

One clever remediatival strategy has tested the role of salient cues in a continuous performance task. Patients had to press the space bar in
response to an X appearing on the screen. However, they were told to respond only if an A preceded the X. Patients had significantly slower reaction times than controls. Of note, though, was that when the A preceding the X was red instead of black, patients answered faster and more accurately (Lee & Park, 2005). By making the relevant stimulus more salient to the subject, he or she was more likely to respond to it appropriately. Lee and Park hypothesized that patients had trouble encoding the relevant stimuli into working memory. Consequently, they sought to improve the efficiency of stimulus encoding by incorporating salient cues to focus the subjects’ attention on the relevant information.

In the present study, we sought to apply the Lee and Park’s findings to the DST. If patients have difficulty encoding the digit symbol relationships into working memory, perhaps a salient cue could prime their attention by guiding them to the pertinent items.

Using PsyScope, a free program designed for the development and administration of psychological experiments (Cohen, Flatt, MacWhinney, & Provost, 1993), we were able to integrate the DST template into a digital environment. PsyScope provided the advantage of mobile testing on a laptop, which allowed data to be collected in the community. Additionally, PsyScope allowed for complete creative control over the specifications of the test. We were able to design unique symbols and present them in 12 unique conditions. From here, we could incorporate salient cues into the test. We hoped that salient cues could enable patients to behave more like controls on the DST by catalyzing
stimulus-driven attention in the encoding stage of working memory. Any strategy that improves patient performance on the DST paves the way for the amelioration of one of the most intractable deficits in schizophrenia.

Hypotheses:

1) Subjects will perform better on conditions with fewer digit-symbol pairs in the key. In other words, subjects will answer the most items correct in the least amount of time when there are 3 digit-symbol pairs in the key, followed by 6 and then 9.

2) Subjects will perform better on the fixed conditions that include 10 items of salient priming than the fixed conditions that do not include salience. The salience will facilitate encoding of the fixed symbol-digit relationships. However, salience should have no effect on the varying conditions as enhanced encoding of digit-symbol key pairings will not be meaningful as these relationships change from trial to trial.
Methods:
Recruitment

Data were collected from 20 healthy control subjects in the Middletown, CT community. First, we posted the following advertisement on craigslist.org to recruit subjects:

EARN $10 IN
20-30 MINUTES

HEALTHY PARTICIPANTS SOUGHT FOR A WESLEYAN UNIVERSITY STUDY OF PROCESSING SPEED. IF YOU ARE 18 OR OLDER AND WITHOUT HISTORY OF MENTAL ILLNESS YOU MAY QUALIFY. STUDY REQUIRES A BRIEF INTERVIEW FOLLOWED BY A FIFTEEN MINUTE COMPUTER TEST.

Call 860-685-2704 for enrollment and information

After the recruitment effort on craigslist.org failed to spur any interest in the study, subjects were recruited in person. Since the computer program was loaded onto my laptop, I was able to test subjects remotely and immediately upon introducing the study. I recruited subjects in Klekolo World Coffee, a café on Court Street in Middletown, and Russell Library, a public library on Broad Street also in Middletown. Both locations provided quiet spaces with minimal distractions. I collected data on weekend afternoons in these locations.

After completing the study, participants were paid $10 cash compensation for their time. If the potential subject declined to participate I thanked them for their time and moved on. If the subject agreed to participate I led them to an empty table where I gave them the consent forms and administered a brief preliminary interview.
Experiment

The experiment was designed and administered using PsyScope. The virtual environment of the test was designed to resemble the computerized DST utilized by Bachman et al. (see fig. 3). The basic instructions were also derived from Bachman's protocol. Subjects were presented with a key of digit-symbol pairs and a digit-symbol pair below the key. Subjects were asked to press the "1" key on the keyboard if the single digit-symbol pair matched the key or "0" if it did not. PsyScope recorded all responses and their corresponding reaction times in a data file. As soon as subjects answered, a new digit-symbol pair appeared. Subjects were instructed to answer as many correctly as they could in 60 seconds. The 60 seconds began as soon as they responded to the first item. As soon as 60 seconds had expired, PsyScope displayed the words "END OF CONDITION." At this point, subjects had the opportunity to take a break if they wanted, but pressing any key would cause PsyScope to proceed to the next condition. The 60 seconds for the next condition, like all of the conditions, began as soon as the subject responded to the first item.

Conditions had keys with 3, 6, or 9 digit symbol pairs. Like the Bachman study, the relationship between the digits and symbols was either fixed (FR) or varied from trial to trial (VR). Additionally, half of the conditions began with salience (s) priming that consisted of 10 trials. A red arrow appeared over the relevant digit symbol pairing in the key. Therefore, the 12 trials were 1) FR3, 2) FR6, 3) FR9, 4) VR3, 5) VR6, 6) VR9, 7) FR3s, 8) FR6s, 9) FR9s, 10) VR3s, 11) VR6s, 12) VR9s (see figures 4-16). The order of the 12 conditions was
randomized for each subject to account for the effect of practice. No personal information other than the subject’s initials and the test date was recorded. All ordinal condition information was kept in a notepad.

**Analysis**

After the completion of the experiment, raw data from the PsyScope data file was exported to an Excel file that contained the answer key for each condition. Since only the order of the conditions was randomized, the correct responses for each condition remained constant between subjects. Using the ordinal condition information to identify each condition, the raw scores were pasted into the Excel file, which determined the total number of correct responses for each condition. The answer key also determined the average reaction time for each condition. The scores, reaction times, and subject information such as age, gender, test date, and education were then imported into a Statistical Package for the Social Sciences (SPSS) file.

To determine the effect of the relationship (fixed or varying), the number of digit-symbol pairs in the key, and salience, a two-factor, within subject, repeated measures ANOVA was performed. No between-subject factors were examined.

**Results:**

A Greenhouse-Geisser test of significance was applied to the repeated measures ANOVA. The Greenhouse-Geisser test adjusts for possible violation of the assumption of homogeneity across repeated measures. A series of within-
subject ANOVAs were run to assess the effects of key length (3, 6, or 9) and salience (present or absent) on the dependent measures (total correct and reaction time). These analyses were run separately for trials in which the digit-symbol relationships in the key were fixed and then again when the digit symbol relationships in the key varied from trial to trial. In summary, four separate ANOVAs were run to determine the following: 1) the effect of salience on score within the fixed relationship conditions, 2) the effect of salience on score within the varying relationship conditions, 3) the effect of salience on reaction time within the fixed relationship conditions, 4) the effect of salience on reaction time within the varying relationship conditions.
1) *Effect of salience on score in fixed relationship conditions.*

Salience was significantly related to number correct $F(1, 19) = 11.84$, $p < .01$ in FR trials. The number of symbols alone $F(2, 18) = 5.27$, $p < .01$, affected the total correct as well. Finally, the interaction of the effect of salience and number of symbols was non-significant ($p > .05$).
2) **Effect of salience on score within the varying relationship conditions.**

Salience $F(1, 19) = 4.92, p < .04$ had a significant effect on total score in the varying relationship conditions. However, this was the only significant finding. The number of digit-symbol pairs and the interaction of salience and number of symbols was non-significant ($p > .05$).
3) *The effect of salience on reaction time within the fixed relationship conditions.*

Salience did not affect reaction time (p > .05) in the fixed relationship conditions. Conversely, more digit-symbol pairs in the key significantly slowed reaction time, showing an F(2, 18) = 6.97, p < .01. The interaction effect was insignificant (p > .05).
4) *Effect of salience on reaction time within the varying relationship conditions.*

Salience and the number of pairings had no impact on reaction time in the varying relationship conditions. The effect of salience alone, the effect of the number of digit-symbol pairs alone, and the interaction effect all showed $p > .05$. Because all of these p-values are greater than .05, all of these factors are considered insignificant.
Discussion:

This study sought to test 2 hypotheses. 1) Subjects will perform better on conditions with fewer digit-symbol pairs in the key. In other words, subjects will answer the most items correct in the least amount of time when there are 3 digit-symbol pairs in the key, followed by 6 and then 9. And 2) Subjects will perform better on the fixed conditions that include 10 items of salient priming than the fixed conditions that do not include salience because salience will facilitate encoding of the fixed symbol-digit relationships into relational memory. However, salience should have no effect on the varying conditions as enhanced encoding of digit-symbol key pairings will not be meaningful as these relationships change from trial to trial.

Neither of the hypotheses proved to be correct across all of the conditions. From the four ANOVAs analyzed, it was evident that some of the factors contributed statistically significant effects to some of the conditions. However, there was no real pattern that predicted significant effects from any of the factors.

In terms of hypothesis 1, there was a negative correlation between the number of digit-symbol pairs in the key and total score in the fixed relationship conditions; as the key grew larger, subjects’ scores decreased. This effect was most dramatic from 3 to 6 symbols and was not as significant from 6 to 9 symbols. Likewise, there was a positive correlation between the number of digit-symbol pairs in the key and reaction time in the fixed relationship conditions; as the key grew larger, subjects took longer to respond to each trial. The link
between number of symbols and score was an important finding because it reproduced Bachman’s finding from his computerized DST, while the link between reaction time and score substantiated that link. Reproducing Bachman’s results was the first step in demonstrating that our computerized DST was a legitimate template for experimentation. Unfortunately, these correlations did not extend beyond the fixed relationship conditions. Interestingly, in terms of hypothesis 2, adding the 10 trials of salient priming with red arrows produced a significant effect on score but not on reaction time. This is counterintuitive. One would hypothesize that any effects on score would be mirrored in reaction time because a higher score is dependent upon a lower reaction time. However, reaction times for incorrect responses were considered along with reaction times for correct responses. This means that subjects could have responded fast and incorrectly many times to achieve a low score and a low reaction time. Conversely, answering slowly with 100% accuracy could achieve a high score and high reaction time.

Even more puzzling was the fact that the effect of the 10 trials of salient priming with red arrows was significantly negative. In both the fixed and the varying relationship conditions, subjects performed worse on the conditions with salience than on the conditions without it. This was completely unexpected. The mean scores for the fixed relationship conditions were significantly higher in the conditions without salience. This was a paradoxical finding. The effect of salience caused dramatic differences in score between the varying conditions with 3 and 9 symbols but almost no difference between the 6-symbol conditions.
This finding contradicts hypothesis 2, which predicted that salience would have no effect on the varying relationship conditions because enhanced encoding of digit-symbol key pairings would not be meaningful as these relationships changed from trial to trial.

The red arrows at the beginning of these salience conditions may not be entirely responsible for this finding. Four unique sets of symbols were used in an attempt to keep subjects interested in the experiment. There was one set for each of the fixed relationship conditions (with salience and without salience) and one set for each of the varying relationship conditions (with salience and without salience). Perhaps the symbol sets themselves were responsible for the differences in score. One set of symbols could have been inherently easier to process because of visual simplicity or because no two symbols in the set looked alike. There is no way to measure the effect of this confounding variable on the data. This element of error could be removed by remaking the experiment using only one set of symbols for every condition. With one set of symbols, we could eliminate an unaccountable covariant, isolating the effects of salience and number of digit-symbol pairs on score and reaction time.

It goes without saying that much more work needs to be done with the test before it is ready for patient experimentation. The first step will be to use incorporate homogenous set of symbols to eliminate the interference caused by four separate sets of symbols.

This experiment was a great opportunity to devise and test a new strategy for remediation. While only healthy controls were tested, this study served as a
pilot for future investigation on schizophrenia patients. Furthermore, even though we obtained statistically significantly paradoxical results, the experiment was by no means a waste. There is no way to predict how salience will affect the performance of patients. Likewise, tinkering with the test itself and testing a larger sample of controls could reveal more promising findings.


schizophrenia following prenatal exposure to an influenza epidemic. *Archives of General Psychiatry, 45*(2), 189-192.


Appendix

Digit Symbol—Coding

Sample Items

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Figure 1:
The Weschler Digit Symbol Test
with first three items answered

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Figure 1. Schematic Illustration of the Parametric Digit Symbol Coding Task

In this illustration of a trial of the computerized digit symbol coding task, the single digit-symbol pair in the middle of the figure represents the target pair, which the participant must check against the reference set, represented by the row of digit-symbol pairings along the top of the figure. For publication, bright blue features of symbols were transformed to gray scale. Reference set size was varied parametrically (3, 6, or 9 pairs) between blocks of trials. Additionally, blocks included either a fixed reference set, in which the digit-symbol pairings remained constant from trial to trial, or a random reference set, in which digits were randomly reassigned to the symbols at the beginning of each new trial. Performance during the fixed condition is enhanced by memory of the reference set. Conversely, performance during the random condition is particularly dependent upon visual scanning, because the target pair must be compared to the reconfigured reference set on each trial. In all trials, subjects indicate via button press, if the target pair was identical to one the digit-symbol pairs in the reference set. The arrows reminding the subject which button to press to indicate that the target is the same as or different than a pairing in the reference set remained visible throughout task performance.

Figure 2:
Screenshot from Bachman’s computerized stimulus-response modification to the original Digit Symbol Coding Task.
Figure 2: Digit Symbol Coding Performance
Performance is plotted in number of correct responses provided within a 60 second block of trials, separately for each set size and condition. Patient (N=85) averages are depicted as filled circles and control (N=30) averages are filled squares. Main effects of Condition, Set Size, and Diagnostic Group are apparent, whereby performance was better in the fixed condition, and at lower set sizes. Controls also performed better than patients, a difference that was greater in the fixed condition than in the random condition.

Figure 3: Bachman's plot showing the number of correct responses in 60 seconds on his computerized DST. Performance declined linearly as number of items increased. Controls improved much more from the random to fixed condition than patients did.
Figures 4-16: Screenshots showing the 12 unique conditions in the present study

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