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Elementary Neurocognition, Learning Potential, and Functional Life Skills: What is the Relationship?

By

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Abstract

Introduction: Elementary neurocognitive measures (e.g., attention, memory, problem-solving) explain 20-60% of the variance in functional life skills for patients with schizophrenia. Learning potential (LP) is a construct that has been hypothesized to explains an additional portion of that variance. LP is unique because it focuses on what the individual is capable of learning rather than what he or she currently knows (Vygotsky, 1978). Learning potential has been a major focus of current neuropsychological research in schizophrenia; studies have compared the characteristics of patients with different levels of learning potential, tested whether LP is related to outcome, and included it into models with elementary cognitive deficits and outcome. The present study will investigate whether LP moderates the relationship between elementary neurocognitive function and outcome. It is hypothesized that for patients with higher LP, the correlation between cognitive deficits and outcome will be weaker than for those with a low LP. **Methods:** 151 clinically stable outpatients with a DSM-IV diagnosis of Schizophrenia or Schizoaffective Disorder were administered a neuropsychological battery including elementary measures of attention, working and verbal memory, problem solving and processing speed. Two measures of learning potential were also used: the CVLT and an adapted version of the WCST. **Results:** Pearson correlations showed elementary neurocognitive function was related to outcome, which replicates previous results. Both learning potential measures were also related to the outcome measure. Analyses revealed that learning potential was a moderator of the relationship between processing speed and everyday life skills, at least in models containing processing speed and working memory. The moderating effect was such that the correlation between neurocognition and functional life skills was stronger for individuals with a high LP versus those with a lower LP. Regression analysis revealed no evidence that measures of LP explained additional variance in everyday life skill beyond that explained by elementary neuropsychological function **Discussion:** LP was not found to be a moderator of the relationship between neurocognition and functional life skills, except in the model containing processing speed. In that case, the direction of the moderating effect was different than initially hypothesized. In hierarchical regression analysis LP did not explain a significant amount of the variance in everyday life skills above and beyond neurocognition.

Introduction

Schizophrenia: A Description of the Disorder

Schizophrenia is a chronic and debilitating mental illness that is of great concern to public health because of its cost to both the affected individuals and to society at large. The disorder is chronic and studies have shown high relapse rates (Robinson, et al., 1999). Schizophrenia is largely a heterogeneous disorder, with patients presenting very differently from each other in terms of their symptomatology, cognitive function, and functional outcome (Grube, Bilder, & Goldman, 1998). Along with the classically recognized symptoms such as hallucinations and delusions, symptoms can also include blunted or inappropriate affect, lack of insight, depressed mood, and reduced speech. (Frangou & Murray, 2000). The disorder is also regularly associated with neurocognitive impairment.

Etiology

The most commonly accepted etiological theory is the stress-diathesis model (Walker & Tessner, 2008). A diathesis is a hereditary vulnerability; therefore this model posits that it is stress, impinging on a predisposed individual, which elicits pathology (Walker & Tessner, 2008). There are a vast number of potential stressors including maternal influenza during pregnancy, birth complications, perinatal brain damage, maternal stress, central nervous system infection, psychosocial events, and drug use. (Jablensky, 2000). There is much evidence that a genetic factors are also involved in the etiology of schizophrenia, as the stress-diathesis model implies. One example, coming from the vast body of twin and family study research is that rates of

schizophrenia in families with an affected member are much higher than expected in the general population (Jablensky, 2000; Frangou & Murray, 2000). The genetic transmission is polygenic; there is no one schizophrenia gene (Walker & Tessner, 2008; Jablensky, 2000; Braff, Freedman, Schork, & Gottesman, 2007).

Current research has identified several candidate genes that might play a role in the etiology of schizophrenia (Craddock, O'Donovan, & Owen, 2006). The COMT gene, which is located on the 22q11.2 chromosome, is one of these candidates. In most people, the gene is involved in the clearance of dopamine. This region of chromosome 22 is the location of a microdeletion, which results in velocardiofacial syndrome. Twenty-five percent of adults with this syndrome meet full criteria for schizophrenia. This, and the fact that the gene has to do with dopamine clearance, make it a possible candidate gene for schizophrenia, and the subject of much current research (Craddock, O'Donovan, & Owen, 2006; Willliam, Owen, & O'Donovan, 2007).

BDNF, located on chromosome 11p13, is another gene that may influence the transmission of schizophrenia. This gene encodes for a brain-derived neurotrophic factor that regulates survival, differentiation, morphology, and the synaptic remodeling of neurons. The evidence surrounding the role of this gene is controversial and further investigation is required (Jönsson, et al., 2006; Craddock, O'Donovan, & Owen, 2006).

Incidence

The reported prevalence rates for schizophrenia vary between reports, but current estimates range between 1.4/1000 and 4.6/1000 (Jablensky, 2000). The disorder is found in similar proportions around the world (Jablensky, 2000). While the disorder is universal, many studies show that it does not affect the genders equally. The median male: female ratio found in a major meta-analysis of epidemiology studies is 4:1 (Messias, Chen, & Eaton, 2007). While the exact ratio varies throughout the literature, most studies show that the disorder is far more common in men than in women (Jablensky, 2000; Wu, Shi, Birnbaum, Hudson, & Kessler, 2006). Some authors have found opposing evidence regarding the gender distribution of schizophrenia however(Häfner, 2003).

Cost to Society

Despite the fact that the proportion of the population suffering from schizophrenia is very low, the disease has a disproportionately high impact on society for two reasons. First, the onset of the disorder usually occurs in early adulthood, and second, schizophrenia tends to have a chronic course despite treatment efforts (Saha, Chant, Joy, & McGrath, 2005). For example, one study showed that 81.9% of schizophrenia patients will relapse and that patients who relapse once have high rates of further relapse despite careful treatment and monitoring (Robinson, et al., 1999). This means that in addition to the costs directly related to the management of schizophrenia (hospital bills, medication, therapeutic efforts, costs of residential living, etc.), there are even greater indirect costs such as a general loss of productivity (Mangalore & Knapp, 2007). In schizophrenic samples, the unemployment rate is around 80% (Gaite, et al., 2008; Marwaha, et al., 2007; Mangalore & Knapp, 2007).

Mangalore et al. (2007) conducted an analysis of both direct and indirect costs associated with schizophrenia in England. The costs included in the computations were: health services, social care, other public expenditures, private expenditures, informal care, as well as costs of loss of productivity, premature mortality, and the criminal justice system. The estimated overall total societal cost of the disorder to England was estimated at 6.7 billion pounds a year (Mangalore & Knapp, 2007).

Symptomatology

There are two main classifications of schizophrenia symptoms: positive and negative (Frangou & Murray, 2000). The classification terminology began with Huglings Jackson in 1869. Positive symptoms were defined as those that were pathological in their presence whereas negative symptoms were defined as a loss of some normal function (Johnstone, Humphreys, Lang, Lawrie, & Sandler, 1999; Sommers, 1985). The ten most commonly reported symptoms are:lack of insight, auditory hallucinations, ideas of reference, suspiciousness, flattened affect, second person hallucinations, delusional mood, delusions of persecutions, thought alienation, and thoughts spoken out loud (Frangou & Murray, 2000). Symptoms tend to vary over the course of the disorder in individual patients as well as from one patient to another; schizophrenia is a heterogeneous disorder (Hughes, et al., 2002).

Positive symptoms are described as being “superimposed on mental status” and are often conceptualized as distortions of reality (Kay, Fiszbein, & Opler, 1987; Klingberg, Wittorf, & Wiedemann, 2006). A study of 6,523 patients, information on whom was collected from their treating physicians, found that positive symptoms

occur in 52% of cases (Lecrubier, Perry, Milligan, Leeuwenkamp, & Morlock, 2007). Positive symptoms consist of hallucinations, delusions and disorganization (Kay, Fiszbein, & Opler, 1987; Salokangas, 1997; Tamminga, Buchanan, & Gold, 1998). A hallucination involves the perception of something that is not actually present (Frangou & Murray, 2000). They can be experienced in any sensory modality; auditory, visual, olfactory and tactile, although auditory hallucinations are most common (Mancevski, et al., 2007). In the Lecrubier sample described above, it was reported that 59% of patients experience hallucinations. Delusions are beliefs that are held despite being contradictory to reality (Frangou & Murray, 2000). Delusions fall into several categories including; persecutory delusions, grandiose delusions, delusions of reference, and delusions of thought withdrawal or insertion (Mancevski, et al., 2007). 73% of the patients in the Lecrubier sample reported having delusions.

Harrow and Jobe conducted a 20-year multi-follow-up study on 200 patients to examine delusional activity. They found that 57% of their subjects had frequently occurring (present at more than 3 of the 6 follow-up sessions) or persistent delusions. 29% of their sample had no delusional activity over the course of the study (Harrow & Jobe, 2008). Hallucinations and delusions tend to co-occur in practice, although they are statistically independent of one another (Harrow & Jobe, 2008; Salokangas, 1997).

A third, newly described dimension of schizophrenia symptomatology is disorganization. It has historically been considered a positive symptom of schizophrenia, but recently it is sometimes listed as its own separate factor (Shean, 2004). The symptoms making up disorganization are inappropriate affect, bizarre

behavior, poverty of content of speech, disturbances in thought, flight of ideas and loose associations (Mancevski, et al., 2007; Klingberg, Wittorf, & Wiedemann, 2006; Shean, 2004). These symptoms were manifested in 59% of the Lecrubier patients.

Positive symptoms are the most commonly reported features of schizophrenia and are more frequent in inpatient and in female populations than in outpatient and male populations respectively (Lecrubier, Perry, Milligan, Leeuwenkamp, & Morlock, 2007; Mancevski, et al., 2007). Positive symptoms are not tightly associated with prognosis or adaptive function (Velligan, Mahurin, Diamond, Hazleton, Eckert, & Miller, 1997; Kay, 1990). In cases of severe positive symptomatology, such as was experienced by the subsample of the Harrow and Jobe study that had full delusional activity, the symptoms influence ability to work, and the employment rates can fall as low as 10% (Harrow & Jobe, 2008). Over the course of the disorder, positive symptom levels tend to decrease (Harrow & Jobe, 2008). One study found that they decreased at a rate of 0.36 symptoms per decade (Mancevski, et al., 2007). It is thought that positive symptoms result from hyperdopaminerga, or excess dopamine (Kay, Fiszbein, & Opler, 1987; Sommers, 1985). As a result this class of symptoms tends to respond well to neuroleptic medications, which lower dopamine levels in the brain. In fact, 40-53% of patients report that their positive symptoms were well controlled through their medications (Lecrubier, Perry, Milligan, Leeuwenkamp, & Morlock, 2007).

In the early 19th century, negative symptoms were identified by Bleuler and Kraeplin, two of the pioneers of schizophrenia research (Kay, 1990). Negative symptoms are defined as an absence of behaviors that people normally exhibit

(Zubin, 1985). These deficits influence cognitive, affective and social functions (Kay, Fiszbein, & Opler, 1987). In Lecrubier's study, physicians identified which negative symptoms they most frequently encounter in practice. The symptoms identified were social withdrawal, impoverished thought, apathy/avolition, anhedonia, and lethargy/fatigue (Lecrubier, Perry, Milligan, Leeuwenkamp, & Morlock, 2007). In Herbener's longitudinal study, 59.6% of his participants experienced negative symptoms during at least one of their follow-up appointments (Herbener & Harrow, 2001). According to the Lecrubier sample, 27% of patients have predominantly negative symptoms. Negative symptoms are more common in men and tend to have an earlier onset than positive symptoms (Tamminga, Buchanan, & Gold, 1998). Outpatient samples have higher rates of negative symptoms than inpatient samples (Lecrubier, Perry, Milligan, Leeuwenkamp, & Morlock, 2007).

Negative symptoms are pharmacologically resistant and may increase over the lifespan (Tamminga, Buchanan, & Gold, 1998; Lecrubier, Perry, Milligan, Leeuwenkamp, & Morlock, 2007; Zubin, 1985; Mancevski, et al., 2007). One study found that negative symptoms increase at a rate of .16 symptoms per decade (Mancevski, et al., 2007). In the subsample that presented with primarily negative symptoms in the Lecrubier study, only 23-29% felt that their symptoms were well controlled by medication (Lecrubier, Perry, Milligan, Leeuwenkamp, & Morlock, 2007). Most studies show that negative symptoms are associated with poor prognosis. For example, these symptoms are correlated with having limited social networks, poor occupational function and problems with community outcome (Tamminga, Buchanan, & Gold, 1998).

Neurocognition

In addition to symptoms, many patients with schizophrenia also present with neurocognitive deficits (Green, Kern, Braff, & Mintz, 2000). These deficits were even noticed by some of the first scholars of schizophrenia (Frangou & Murray, 2000; Tyson, Laws, Flowers, Mortimer, & Schulz, 2008). The previous name for the disorder, dementia praecox, coined by Kraeplin, reflects that he believed cognitive decline was central to the disorder (Frangou & Murray, 2000). As Kraeplin suggested, cognitive deficits have come to be seen as a central facet of the disorder. Cognitive deficits represent an independent factor in schizophrenia; they are not reliably correlated with positive or negative symptoms (Lewis, 2004). These features are often evident before the onset of illness and are also found in unaffected first degree relatives(Lewis, 2004; Tamminga, Buchanan, & Gold, 1998).

Longitudinal studies of cognitive function in schizophrenia patients have suggested that cognitive decline occurs early; often by adolescence. It is believed that this might be due to a halt in normal neurodevelopment rather than an actual decline (Rund, 1998). While cognitive deficits are a very common feature of schizophrenia, not all patients experience them. In his literature review, Rund concluded that up to 30% of patients maintain normal cognitive function (Rund, 1998).

A variety of neurocognitive deficits are consistently associated with the diagnosis of schizophrenia (Heinrichs & Zakzanis, 1998; Lewis, 2004). First, persons with schizophrenia have a generalized deficit, in which full scale IQ declines when comparing postmorbid to premorbid scores (Lewis, 2004; Tyson, Laws,

Flowers, Mortimer, & Schulz, 2008). One review found that on average IQ drops by 33 points (Sharma & Harvey, 2000). In addition to the generalized deficit, there are specific cognitive areas that decline over and above what might be expected by IQ loss, including attention, processing speed, memory, and executive function.

With respect to attention, patients with schizophrenia traditionally show deficits in three areas; selective, sustained and divided attention (Tyson, Laws, Flowers, Mortimer, & Schulz, 2008; Lewis, 2004). Selective attention is the ability to focus on pertinent stimuli and screen out irrelevant stimuli, and sustained attention is the ability to maintain this skill over a period of time (Tyson, Laws, Flowers, Mortimer, & Schulz, 2008; Green, Kern, Braff, & Mintz, 2000). Divided attention is the ability to attend to multiple stimuli such as the several elements that make up a task or even to multiple tasks (Tyson, Laws, Flowers, Mortimer, & Schulz, 2008).

Memory is another neurocognitive area that is consistently implicated in schizophrenia (Lewis, 2004; Green, Kern, Braff, & Mintz, 2000; Sharma & Harvey, 2000). Deficits are evident in several subcomponents of memory. One is working memory, which is the ability to hold small amount of information in the mind for a few seconds. Secondary memory, the ability to store information over a longer period of time; typically from minutes to a couple of hours, is also affected (Green, Kern, Braff, & Mintz, 2000). Other memory deficits include difficulties in applying overarching organizational strategies to learned material and trouble with recognition and retrieval (Sharma & Harvey, 2000).

Another area of cognition that is compromised is executive function, a set of skills that underpin volition, planning, purposive action, and the self-monitoring of behavior (Lewis, 2004; Sharma & Harvey, 2000; Green, Kern, Braff, & Mintz, 2000). These skills "permit an adaptive balance of maintenance and shifting of cognitive or behavioral responses to environmental demands permitting longer term goal-directed behavior rather than reflexive or automated action" (Sharma & Harvey, 2000, p. 53).

The final neurocognitive construct that is consistently implicated in schizophrenia is processing speed. Processing speed is rate at which different cognitive operations can be executed. A deficit in processing speed serves as a constraint on general performance because other cognitive operations are speed dependent. This construct is highly related to functional disability, independent living, community functioning and other important outcome measures, even relative to impairment in other cognitive domains (Dickinson, Ramsey, & Gold, 2007; Salthouse, 1996).

Neurocognitive dysfunction has been increasingly studied in regards to schizophrenia. One reason it is of particular interest is that unlike symptoms, cognitive deficits are relatively stable (Lewis, 2004; Hughes, et al., 2002; Rund, 1998) and also may represent a genetic endophenotype of the disorder (Tamminga, Buchanan, & Gold, 1998). The main reason that neurocognition has come under study is that it is significantly related to outcome (Green, Kern, Braff, & Mintz, 2000; Rempfer, Hamera, Brown, & Bothwell, 2006; Tamminga, Buchanan, & Gold, 1998). A meta-analysis by Green et al. found that these deficits explain 20-60% of the variation in outcome (Green, Kern, Braff, & Mintz, 2000). This correlation is over

and above that found between symptoms and outcome (Christensen, 2007; Velligan, Mahurin, Diamond, Hazleton, Eckert, & Miller, 1997).

The areas of cognition most strongly associated with outcome are secondary verbal memory, executive function, working memory, and vigilance/attention (Christensen, 2007). The presence of cognitive impairment is related to a more severe course of the disorder and a higher rate of use of psychiatric services (Sharma & Harvey, 2000). Cognitive deficits are especially related to specific areas of outcome. For instance, there is ample evidence linking cognitive function to social functioning (Sharma & Harvey, 2000; Velligan, Mahurin, Diamond, Hazleton, Eckert, & Miller, 1997; Sergi, Kern, Mintz, & Green, 2005). Cognitive dysfunction is also related to employment. A study by Christensen et al. found that unemployed patients tend to have worse scores on neurocognitive tests than their employed counterparts (Christensen, 2007).

Traditionally, researchers have utilized static measures of neurocognition to examine the relationship between cognitive deficits and outcome in schizophrenia. Static measures are administered a single time to obtain a score. A study by Velligen et al. exemplifies this study design. In the study, a sample of 41 inpatients aged 18-50 were given a test battery including the Brief Psychiatric Rating Scale, the Negative Symptom Assessment, and tests of attention, memory, visual-spatial organization and executive function. These variables were entered into a regression model to explain the variance in outcome measured by the Functional Needs Assessment. The authors found that only the cognitive function score explained a significant amount (42%) of

variance in the dependent variable (Velligan, Mahurin, Diamond, Hazleton, Eckert, & Miller, 1997).

A study by Harvey et al. employed a similar methodology. This study involved a sample of geriatric individuals with a DSM-III-R diagnosis of schizophrenia to compare chronically hospitalized patients, acute admissions patients who had been living in the community, and nursing home residents on symptomatology, neurocognition, treatment history, and adaptive functioning. In the regression analyses for all three groups, cognitive function explained 50-62% of the variance in function, which is more than was explained by the symptoms (Harvey, et al., 1998).

Learning Potential

Static tests of cognition measure abilities that have already been developed. Recently, it has been suggested that a new methodology might better capture those aspects of cognitive skill crucial to outcome. This new method is dynamic testing, which seeks to measure an individual's learning ability over a series of testing trials (Green, Kern, Braff, & Mintz, 2000). Learning potential focuses on latent capacity rather than on the performance of already acquired skills. As the name indicates, the construct basically reflects an individual's ability to learn, given the opportunity (Green, Kern, Braff, & Mintz, 2000).

As early as 1922, Thorndike stated that the ability to learn should be measured and included in the definition of intelligence (Grigorenko & Sternberg, 1998). Assessment of LP requires a dynamic testing protocol, which would assess how well

subjects change in response to instruction (Grigorenko & Sternberg, 1998). Lev Vygotsky then compiled the first complete theory of dynamic testing. He once said, "The psychologist must not limit his analysis to functions that have matured" and his accompanying theory followed that logic (Grigorenko & Sternberg, 1998). In his book, *The Mind in Society*, Vygotsky defined the Zone of Proximal Development as "the distance between the actual developmental level as determined by independent problem solving and the level of potential development as determined through problem solving under adult guidance or in collaboration with more capable peers" (Vygotsky L. S., 1978). Feuerstein developed a similar theory in the 1980's; the mediated learning experience. She defined this as an interaction-based process in which the adult modifies both the task and the child to help the child solve the task (Grigorenko & Sternberg, 1998). Dynamic testing in general assumes that if subjects are given the opportunity to learn how to solve a problem, then at least some of them will improve their performance beyond that predicted by the traditional static tests (Grigorenko & Sternberg, 1998).

Some studies have shown that dynamic measures of neurocognition have better predictive validity than traditional static measures. Fiszdon et al. conducted a study on learning potential as a predictor of rehabilitation readiness. They compared the predictive validity of a measure of learning potential versus performance on static subtests of the WAIS-III for a measure of rehabilitation readiness. The researchers found that the dynamic measure accounted for 8.6% of variation over and above the static one. Furthermore, the static measure did not account for any variation over and above that of the dynamic measure, suggesting that measures of learning potential

explain variance in outcome distinct from static measures (Fiszdon, McClough, Silverstein, Bell, Jaramillo, & Smith, 2006). A study by Sergi et al. had similar results. In this study, a single administration of the Wisconsin Card Sorting Task (WCST) was used as a static measure of cognition. The subjects were also administered two subsequent trials of the test, with the first one including a training protocol. Using a gain score formula, the learning that occurred over the trials was used as the dynamic measure of cognition. The study found that 13% of the variance in outcome was explained by the static administration of the WCST, but that the dynamic protocol explained an additional 15% (Sergi, Kern, Mintz, & Green, 2005).

One of the common paradigms used in learning potential research is classifying patients into three learning groups. This method was originated by Schottke in 1993 and is still common today. Schottke classified patients as learners (those who test poorly initially and then improve), non-learners (those who test poorly initially and do not improve), and high scorers (those who score high initially) (Green, Kern, Braff, & Mintz, 2000). Using these groupings, researchers have compared subjects based on their learning potential. A study by Kurtz and Wexler, for example, sought to characterize the cognitive profiles of the different learning groups. They found that learners perform better on measures of verbal learning and divided attention than non-learners(Kurtz & Wexler, 2006). This, and other evidence, suggests that there may be two distinct cognitive profiles in schizophrenia that vary along the lines of learning potential.

A study by Rempfer et al. (2006) also supported this theory. This study looked at learning potential in 60 subjects with serious mental illness. The subjects

were administered a static neuropsychological test battery along with the WCST to assess learning potential using the test-train-test paradigm. Using the learning potential scores, the subjects were divided into three learning groups according to the Schottke method. There were differences between non-learners and high scorers on measures of sustained attention, auditory attention and working memory. In these areas, the learners scored in between the non-learners and high scorers, but their scores were not significantly different from either group. On tests of verbal working memory, the learners scored closely to the high achievers and both of those groups scored significantly higher than the non-learners (Rempfer, Hamera, Brown, & Bothwell, 2006).

Some researchers have proposed that LP may influence the relationship between static neurocognitive function and outcome. Green's paper was so influential in part because it implied that learning potential was something that could be targeted by an intervention to influence outcome (Green, Kern, Braff, & Mintz, 2000). Two studies (Vaskinn, et al., 2008; Watzke, Brieger, Kuss, Schoettke, & Wiedl, 2008) have investigated this possibility.

In a longitudinal study by Watzke et al. (2008), 41 patients with clinically stable schizophrenia or schizoaffective disorder were entered into a vocational rehab program. Participants were divided into three groups: high scorers who were intact on the LP test, learners who were impaired on the test but improved with training, and non-learners who showed no real improvement in LP test scores. The results revealed that learning potential was significantly related to gains in outcome over time. High scorers were found to have better outcome than all other groups at all follow-up

stages. Learners and non-learners started at a similar point, but learners benefitted more from rehabilitation efforts. These findings added support to Green's idea that learning potential is indeed a possible mediator of the relationship between outcome and cognition (Watzke, Brieger, Kuss, Schoettke, & Wiedl, 2008).

The study by Vaskinn used the California Verbal Learning Test (CVLT) to measure learning potential in place of the WCST. This procedure is different in that it does not involve an active training phase per se. Instead a list of 16 words is read to the subjects five times and after each trial the participant recalls as many of the listed words as they can (Delis, Kramer, Kaplan, & Ober, 2000). As in the Watzke design, the study looked at how the relationship between learning potential and outcome varied for different levels of learning potential – something that would indicate the possibility that it is a mediator in that relationship. The results showed that while learners and non-learners were similar on the first trial of the test, by the fifth trial, learners' scores were more similar to those of the high scorers (Vaskinn, et al., 2008).

Relation between learning potential and outcome has not been a consistant finding in the literature. For example, a study by Woonings et al. (2002) failed to find a relationship between learning potential and outcome. This study was unique in that it examined three different types of learning at baseline to outcome at the end of an 8-month rehabilitation program. Learning potential, as assessed in a modified WCST procedure, was only related to baseline social functioning and not to longitudinal improvement in functioning (Woonings, Appelo, Kluiter, Slooff, & van den Bosch, 2002).

Present Study

While much progress has been made toward understanding the relationship between learning potential, elementary static measures of cognition, and outcome in schizophrenia some methodological concerns remain. Due to the low base rate of schizophrenia in society, most studies have been limited by small sample sizes. The majority of the studies reviewed had from 40 to 60 subjects (Watzke, Brieger, Kuss, Schoettke, & Wiedl, 2008; Woonings, Appelo, Kluiter, Slooff, & van den Bosch, 2002; Rempfer, Hamera, Brown, & Bothwell, 2006; Kurtz & Wexler, 2006; Fiszdon, McClough, Silverstein, Bell, Jaramillo, & Smith, 2006; Sergi, Kern, Mintz, & Green, 2005). Only one study examined had over 100 subjects (Vaskinn, et al., 2008). It is critical that future studies include large samples so that they have enough statistical significance to address relevant research questions.

Another area of concern is division of participants and the consistency in how subjects are divided into learning groups, which makes comparison across studies difficult. For example, some use the Schottke method of dividing subjects into high scorers, learners, and non-learners (Green, Kern, Braff, & Mintz, 2000; Rempfer, Hamera, Brown, & Bothwell, 2006; Fiszdon, McClough, Silverstein, Bell, Jaramillo, & Smith, 2006). Among these studies, there were different methods for deciding which participants belonged in each group. In the Rempfer study, cut scores were used. Subjects scoring over 43 on the 64-card version of the WCST were considered high scorers and a gain of 15 points or more constituted learning (Rempfer, Hamera, Brown, & Bothwell, 2006). In the Fiszdon study, high scorers were those who scored 1.5 SD above the group mean. Learners were those whose second score was

significantly different from their first score according to the confidence interval (Fiszdon, McClough, Silverstein, Bell, Jaramillo, & Smith, 2006). Other studies created gain score formulas to conceptualize learning potential on a continuum, but have still separated patients into intact, learner, and non-learner sub-groups (Sergi, Kern, Mintz, & Green, 2005; Vaskinn, et al., 2008).

Researchers varied on how they have analyzed their data. Many of these studies divided patients into learner and non-learner groups. In one study, subjects were divided into high/low learning potential groups using a median split of the gain scores (Sergi, Kern, Mintz, & Green, 2005). In another study, the gain score reflected the slope of the learning process. Learners were defined as those who had a slope of zero or above (Vaskinn, et al., 2008). With so much variation in methodology, it is difficult to compare different studies. Furthermore, the division of subjects into categories is somewhat arbitrary. There is not necessarily much difference between the non-learner who learned the most and the learner who learned the least. Treating the construct of learning potential as a continuous variable will allow comparison across studies and ensure that information in the data is not lost through the treating of LP as a dimensional construct.

Another area in which there is little consistency within the body of the research is what test should be used for the dynamic assessment of learning potential. For the most part, studies have used either the Wisconsin Card Sorting Task (WCST) or the California Verbal Learning Task (CVLT). The WCST uses a direct training sequence in which the examiner trains the subject on the test and gives them feedback. The CVLT does not have a training round; instead the test is repeated over

so many trials that learning occurs without concrete assistance. These two measures have yet to be compared directly with regard to how effectively they predict outcome in schizophrenia. Understanding which test better captures the construct will allow for more consistent methodologies and therefore more comparable results. This study will be the first to directly examine two commonly used learning potential assessment measures to determine which is a better predictor of outcome.

To date, learning potential has been examined as a predictor of outcome (Watzke, Brieger, Kuss, Schoettke, & Wiedl, 2008; Woonings, Appelo, Kluiter, Slooff, & van den Bosch, 2002; Sergi, Kern, Mintz, & Green, 2005; Fiszdon, McClough, Silverstein, Bell, Jaramillo, & Smith, 2006) and as a mediator of the relationship between neurocognition and outcome (Green, Kern, Braff, & Mintz, 2000; Vaskinn, et al., 2008). There are other possibilities that have yet to be considered. One such possibility is that learning potential is a moderator of the relationship between neurocognition and a measure of life skills. We hypothesized that consistent with pervious research that static neuropsychological measures and dynamic LP assessments would be related to outcome. We also hypothesized that learning potential moderate the relationship between elementary neurocognition and outcome such that the greater the learning potential, the weaker the correlation will be between neurocognitive test scores and the outcome measure. Another study goal was to compare the explanatory value of the two classic methods of measuring learning potential, the WCST and the CVLT, with respect to functional life skills.

Methods

Participants

151 clinically stable outpatients with schizophrenia or schizoaffective disorder participated in the study. Diagnosis was confirmed by the patient form of the Structured Clinical Interview for DSM-IV (Spitzer, Williams, & Gibbon, 1996) which was performed by a trained administrator. Exclusion criteria were: (a) known neurological disease, (b) developmental disability, (c) substance abuse in the past month, or (d) mental retardation as evidenced by a history of services. All patients gave written informed consent. The relevant internal review boards approved all procedures. Data for this study was collected for a study on the effects of cognitive remediation on cognitive and social dysfunction in people with schizophrenia (Kurtz et al. 2007).

A subset was formed based on performance on the Wisconsin Card Sorting Task (WCST). Those that achieved less than 5 categories on the 128-card paper-and-pencil version of the test (10th percentile or below for healthy participants between 20 and 39 years of age) were classified as impaired and thereby selected for further training and testing on the WCST. Table 1 describes the demographic and clinical characteristics of the entire sample and then of the subsample receiving the WCST intervention.

Assessment Measures

Symptom Assessment

The Positive and Negative Syndrome Scale was used to assess the subjects' symptomatology. This is a 30-item clinical interview that examines positive/negative

symptom content over the past week and also tests for general psychopathology. Each item is scored from 1-7, with one being absent and seven being extreme (Kay, Fiszbein, & Opler, 1987)

Neuropsychological Assessment

The patients were administered a neuropsychological test battery including the working memory and processing speed indexes (WMI and PSI respectively) from the Wechsler Adult Intelligence Scale, the Logical Memory subtest of the Wechsler Memory Scale III (LM) which assesses verbal prose recall, Penn Continuous Performance Test (PCPT) of sustained visual vigilance and the Penn Conditional Exclusion Test (PCET) of problem solving. For the PCPT, an efficiency score was used throughout the statistical analyses. This was calculated for each subject by dividing the total positives by the average reaction time. Since this variable is a proportion and the data was not normally distributed, an arcsine transformation was performed. For the PCET, the error score was selected for use during analysis.

Functional Skills Assessment

The UCSD Performance-Based Skills Assessment (UPSA) was used to assess the subjects' functional capacity. This test requires the subjects to demonstrate skills through role-play in the laboratory that are intrinsic to functional success in the outside world. The assessment examines skills in five categories of functioning: household chores, communication, finance, transportation, and planning recreational activities. The raw scores on each subsection are scaled such that the maximum score for each section is 10. The subscale scores are then multiplied by two and summed to

make a total score that ranged from 0-100 (Patterson, Goldman, McKibben, Hughs, & Jeste, 2001).

Learning Potential Assessment

In addition to the static measures of neuropsychological and functional abilities, two dynamic measures were utilized to access the subjects' learning potentials. As described earlier, learning potential is the ability to improve at a task given instruction and guidance.

The California Verbal Learning Task (CVLT) is a test of list learning. The subject is presented with a list of 16 items from four semantic categories and is then asked to recall the items. This procedure is repeated five times using the same list of words. Since the test involves 5 trials, there is ample opportunity for learning to occur (Delis, Kramer, Kaplan, & Ober, 2000).

The subgroup that fell into the impaired range on the Wisconsin Card Sorting Task (WCST) underwent the test-train-test protocol, which has commonly been used to assess learning potential in schizophrenia (Kurtz, Ragland, Bilker, Gur, & Gur, 2001; Rempfer, Hamera, Brown, & Bothwell, 2006; Watzke, Brieger, Kuss, Schoettke, & Wiedl, 2008; Wiedl K. H., Wienobst, Schottke, Green, & Nuechterlein, 2001; Woonings, Appelo, Kluiter, Slooff, & van den Bosch, 2002). The WCST is a test of executive functioning that requires the subject to respond to rule changes and use feedback to guide future answers. The test involves matching a card to one of four target cards on either shape, number, or color. After each 10 consecutive correct responses, the rule switches without the subjects knowing and then they must sort

according to a different attribute (Heaton, 1993). When this test is used to assess learning potential, its procedure is repeated three times. On the first and third trials, the standard protocol is used. On the second trial however, the subject is trained on the task. This involves modeling correct responses, providing practice, and giving corrective feedback. The progress that is made in response to the intervention is seen as a measure of learning (Rempfer, Hamera, Brown, & Bothwell, 2006).

Calculating Learning Potential

Learning potential was calculated by a gain-score formula as was used by Vaskinn et. al (2008). This allowed learning potential to be used as a continuous measure. For the CVLT, which was the measure of learning potential for the whole sample, the formula is as follows:

(Trial 5 score – Trial 1 Score)/(16 – Trial 1 score)

This formula was adapted to be applicable for the error score on the Wisconsin Card Sorting Task. In the denominator, pre errors were subtracted from 6 because six errors represent the best score possible. This is analogous to the sixteen in Vaskinn's formula, which also represents a perfect score. The adaptation is as follows:

(Post errors – Pre Errors)/(6-Pre Errors)

In interpreting numbers yielded by the formula, a positive number indicates that the subject improved from trial one to the final testing trial. The closer the

positive fraction number is to one, the more the subject learned. A negative number would indicate that the subject's score declined in between trials.

Data Analysis

The Statistical Package for the Social Sciences (SPSS for Macs, version 17.0) was used for statistical analyses. Raw scores for each of the measures were converted to age-corrected z-scores using published normative data. For the learning potential assessment, for which no normative data is available, the data was converted to z-scores according to the mean and standard deviation from the current sample. Pearson's correlations were calculated between each of the neurocognitive variables and functional capacity outcome variable.

A hierarchical linear regression model was used to examine learning potential as a moderator of the relationship between neurocognition and functional capacity in the overall sample. In the first step, a neurocognitive variable and learning potential were entered as main effects. In the second step, the interaction between these two variables was added to the model.

Significant interactions were interpreted using methods outlined by Aiken and West (1991). Simple slope coefficients were calculated for the relation of neuropsychological functioning to functional capacity at low (- 1 SD), medium (mean) and high (+1 SD) levels of learning potential (Aiken & West, 1991).

Next, another hierarchical regression model was tested in the subset trained on the WCST using two measures of learning potential (CVLT and WCST) to identify their unique contribution. This model was run on the subset that got the test-train-test

protocol of the Wisconsin Card Sorting Task. In the first step of the analysis, the elementary, static neuropsychological constructs were added. In the second step, the CVLT score was entered into the model. Finally, the WCST score was entered. The change in R-squared was used to evaluate the relative contributions of each of these measures of learning potential in predicting functional capacity.

Results

Descriptive statistics were calculated for all of the neuropsychological test scores. These are reported in normed format in Table 2. As the literature predicts, the schizophrenic participants performed below the norm on all tests.

Descriptive statistics were also calculated for the two measures of learning potential, and are presented in Table 3. Since there was no standardization data available for these tests, the table reports the raw scores that were calculated using the gain score formula. Our subjects, on average, showed gains in learning potential during the dynamic testing protocol.

Using Pearson correlations, the relationship between neuropsychological test scores and learning potential to a measure of everyday life skills (as measured by the UPSA) was analyzed. WMI ($r=0.57$, $p < .000$), PSI ($r=0.41$, $p < .000$), PCET ($r=.42$, $p < .000$), LM ($r= 0.43$ $p < .000$) and PCPT ($r=0.26$, $p <.004$) were all significantly related to the UPSA. Learning potential, as measured by the CVLT, was also significantly related to the UPSA ($r= .028$, $p < .001$). Using the subset receiving the dynamic testing protocol on the WCST, it was confirmed that learning potential was also significantly related to UPSA performance ($r= 0.29$, $p < .039$) when measured using the WCST.

Results from the hierarchical regression analyses testing the moderating effects of learning potential in the relationship between neurocognition and functional life skills indicated that the regression coefficients for the neuropsychological test scores were significant in each of these models ($p < .032$). This confirmed the results of the correlation analysis. The regression coefficient for learning potential was

significant in the models including PCPT (B=0.25, $p < .005$) and PCET (B = .028, $p < .001$). For the other models, the regression coefficients for learning potential were not significant. The interaction term was only significant in the model including PSI (B = -0.32, $p < .023$).

The interactions in the PSI model was plotted in Figures 1 using the simple slopes method described by Aiken and West (Aiken & West, 1991). At all levels of learning potential, WMI and PSI were significantly related to the UPSA. For both models, high learning potential was more strongly related to UPSA than low learning potential.

To compare the relationship of the two learning potential measure to the UPSA, a correlation was calculated to determine if the two tests were actually measuring similar constructs. The measures were not related ($r= 0.2$, $p < .157$). In addition, we conducted several hierarchical regression analyses on the subset of participants who received both learning potential testing protocols. In the first analysis, CVLT was entered in one block and WCST in another. Results indicated that the WCST uniquely accounted for 4.4% of the variance in outcome. The CVLT uniquely accounted for 6.6% of the variance. Neither score was a significant factor in explaining the variance in outcome ($p < .136$).

Next, a model was tested that included each of the neuropsychological variables independently. The neuropsychological test score was used in the first block, the second block included the CVLT, and the final block was for the WCST. Table 4 shows the R-squared values and significance levels for the

neuropsychological test, WCST, and CVLT scores for each of these models. Depending on which neuropsychological test is used in the model, the variance explained by each measure of learning potential was different (see Table 4). However, across the models, both LP measures failed to be significant predictors of UPSA when neuropsychological measures were controlled.

Finally, a regression model was tested including all of the neuropsychological tests in one block, the CVLT in a second block, and the WCST in the last block. The combined neuropsychological measures accounted for 37.8% of the variance in UPSA ($p < .000$). Neither measure of learning potential was a significant predictor of UPSA when the other neuropsychological measures were controlled for. The effect sizes for both learning potential measures were small and not significant, however it was greater for the CVLT ($R^2=0.026$, $p < .184$) compared to the WCST ($R^2=0.005$, $p < .544$).

Discussion

Consistent with hypotheses, in the present investigation both static measures neurocognition and measures of learning potential were related to functional life skills, as measured by the UPSA. These results are consistent with previous reports Fiszdon, McClough, Silverstein, Bell, Jaramillo, & Smith, 2006). Contrary to hypotheses, learning potential was not found to be a moderator of the relationship between functional life skills and working memory, verbal prose recall, vigilance, or problem solving. This is the first study to acknowledge learning potential as a possible moderator of the relationship of elementary neuropsychological function and functional life skills. Learning potential was found to be a moderator of the relationship between processing speed and functional outcome.

The interaction between processing speed and learning potential explained an additional 3.3% of the variance in UPSA scores. This indicates a small effect size, however it does serve to explain a bit more of the variation in outcome than just learning potential and neurocognition alone. There has been recent research suggestion that processing speed may have a privileged role, relative to other static neuropsych measures, in predicting outcome in schizophrenia ((Dickinson, Ramsey, & Gold, 2007)). Dickinson's meta-analysis of 1961 schizophrenia patients showed that processing speed was the largest deficit out of all of the neuropsychological constructs (Dickinson, Ramsey, & Gold, 2007). In our study as well, processing speed was the neurocognitive variable with the largest degree of impairment. Subjects on average scored 1.2 standard deviations below the mean.

The direction of the moderating relationship was not as we hypothesized. It was predicted that as learning potential increased, that the relationship between

neurocognition and functional life skills would decrease. It was assumed that patients with higher learning potential would be better at compensatory learning, which would leave them less dependent on their elementary neurocognitive function. The data revealed an opposite pattern: for those with high learning potential, there was a stronger relationship between neurocognition and functional life skills. A speculative hypothesis is that individuals with high learning potential may be able to utilize their elementary neurocognitive skills to greater effect in acquiring everyday life skills. This would explain why there would be a stronger relationship between cognition and outcome for those with higher learning potential.

In the hierarchical models, the neurocognitive variables consistently explained more of the variance in UPSA scores than did the learning potential variables. Furthermore, learning potential wasn't significantly related to outcome after controlling for neurocognition. This finding was surprising as it counters the results of previous studies (Green, Kern, Braff, & Mintz, 2000). There is, however; at least one other study that failed to find a significant relationship between learning potential and outcome (Woonings).

The two measures of learning potential were not significantly related, which indicated that they are not measuring the same construct. This was not surprising, given the various methodological differences between these two measures. The results also do not show that one measure consistently explained more variance in functional skills than the other; the results of this analysis were inconclusive.

Several components of our study design should be considered in interpreting the results. The UPSA is a test of functional life skills only. Other studies have

looked at outcome measures that target a variety of skills, including; employment, readiness for rehab, life satisfaction, and social skills, among others. It is possible that learning potential is a better predictor of these other types of outcome than of functional life skills. Of the studies that have found a relationship between outcome and learning potential, only one other uses the UPSA (Kurtz).

Another methodological difference between our study and the previous research was that learning potential was treated as a continuous measure. Most previous studies have grouped subjects and then compared between group differences. One final limitation is that the study used a cross-sectional design. It doesn't assess the utility of learning potential for predicting change after an intervention. There is still a possibility that learning potential would provide more information in a longitudinal setting.

The lack of a moderating relationship between neurocognition and functional outcome is relevant to clinical practice because it indicates that neurocognitive deficits should be interpreted the same across all levels of LP in terms of determining prognosis. As more is learned about the role of learning potential in schizophrenia, rehabilitation efforts can become more tailored.

In summary, while two commonly used LP measures were linked to a measure of everyday life skills, there was little evidence (with one exception) that either measure of LP moderated the relationship of elementary, static neurocognitive function and everyday life skill. Future research should be targeted at determining whether measures of LP play a more important role in predicting the ability to benefit from targeted treatment.

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Table 1.

Demographic and clinical characteristics of subjects

Characteristic	Total Sample (n=151) *mean*	*SD*	Subsample (n=55) *mean*	*SD*
Age	33.2	11.3	34.6	11.9
Education	13.0	2.1	12.2	2.0
# of Hospitalizations	4.5	3.6	5.1	3.4
Illness Duration	10.4	10	12.3	10.6
Vocabulary (scaled)	9.7	3.9	7.6	3.3
PANSS positive	18.4	5.5	18.7	5.2
PANSS negative	20.1	5.1	20.6	4.8

The total sample had 38 females (25.2%) and 113 males (74.8%) and the subsample had 15 females (27.3%) and 40 males (72.7%)

Table 2.

Descriptive Statistics for Normed Scores

	Total Sample		Subset	
	Mean	*SD*	*Mean*	*SD*
LM	-1.12	1.01	-1.55	1.01
PCET	-0.71	1.3	-1.51	1.20
PCPT	-0.28	1.06	-0.51	1.34
PSI	-1.20	0.84	-1.50	.74
WMI	-0.59	1.0	-1.13	.93

Table 3.

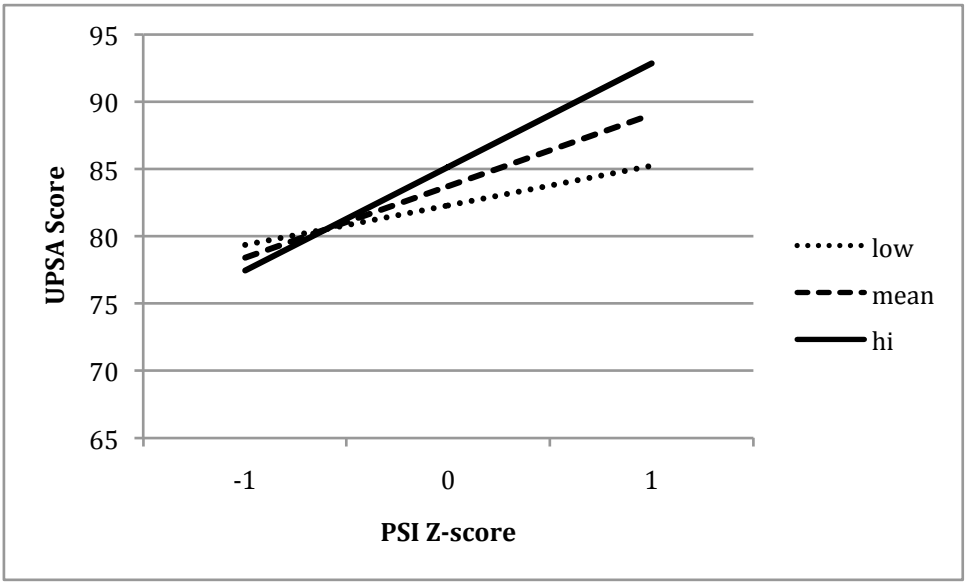
Descriptive Statistics for Learning Potential Gains from Pre to Post Test

	Total Samples		Subset	
	Mean	*SD*	*Mean*	*SD*
CVLTgain z-score	0.45	0.25	0.38	0.27
WCSTgain z-score			0.58	0.44

Table 4.

Hierarchical regression models predicting the variance in UPSA scores.

Neuropsychological Variable Included In Model	Neuropsych		WCST		CVLT	
	R^2	*Sig*	R^2	*Sig*	R^2	*Sig*
WMI	.223	**.001**	.003	.682	.024	.223
LM	.188	**.002**	.038	.138	.004	.645
PSI	.174	**.003**	.041	.125	.009	.471
PCPT	.029	.256	.063	.084	.048	.136
PCET	.025	.297	.056	.110	.061	.100

Figure1.

The moderating effect of learning potential on the relationship between UPSA scores and processing speed.