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2009

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UNIVERSITY OF CALIFORNIA, SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Executive Functions in Schizophrenia: Defining and Refining the Constructs

A Dissertation submitted in partial satisfaction of the
Requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

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ABSTRACT OF THE DISSERTATION

Executive Functions in Schizophrenia: Defining and Refining the Constructs

By

Gauri Nayak Savla

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2009

San Diego State University, 2009

Professor Barton W. Palmer, Chair

Executive functions are among the strongest neurocognitive predictors of functional disability among people with schizophrenia. However, there remains considerable debate about what constitutes executive functions, the extent to which they are uniquely impaired above and beyond other cognitive abilities, and their relationship with clinical and everyday functioning correlates of schizophrenia. The aim of the current study was to simultaneously assess multiple executive functioning abilities, as measured by the Delis-Kaplan Executive Function System (D-KEFS) among people with schizophrenia (SCs) compared to demographically-matched healthy comparison subjects (HCs), to assess for differential impairment among specific multi-level abilities and basic cognitive skills, to clarify the construct of "executive functions" in schizophrenia, and to examine the relationship of specific executive functions to psychopathology and everyday

functioning. In this study, SCs, on average, had consistently worse multi-level executive functions in comparison to HCs. The differences between ipsative performances on multi-level tasks (e.g., switching) and basic cognitive tasks (e.g., motor speed) were greater among SCs than among HCs on some, but not all executive functioning tasks. Although the specific member components varied among SCs and HCs, exploratory factor analyses with the two groups examined separately, both revealed two factor solutions (cognitive flexibility/switching and abstraction/conceptualization). Latent profile analysis of the D-KEFS scores in the SCs indicated three distinct profiles, i.e., mildly impaired, average, and high average-to-superior. The high functioning group was characterized by higher levels of premorbid functioning (as estimated with education and word reading performance). Within-group, ipsative comparisons indicated that those in the mildly impaired group did worse on abstraction tasks and better on switching tasks compared with each subject's own respective mean performance, while those in the high average group had the opposite pattern. Path models indicated intact working memory as necessary for intact cognitive flexibility, and intact abstraction as necessary for intact logical reasoning and sorting abilities. Severity of thought disorder was associated with worse performance in terms of cognitive flexibility/switching and abstraction/conceptualization; there were no other significant relationships found between severity of psychopathology and executive functioning. Both D-KEFS factors were also significantly correlated with functional capacity, but not level of independence in current living situation, or quality of life.

1. Introduction

In their classic texts on schizophrenia, Eugen Bleuler (1911) and Emil Kraeplin (1919/1971), considered to be the pioneers of schizophrenia research, noted that many of their patients with the illness appeared to have cognitive deficits. Based on the research accumulated over the subsequent century, it is now well documented that most (but not all; Palmer, Heaton, Paulsen, Kuck, Braff, et al., 1997) people with the schizophrenia (which includes schizoaffective disorder) have deficits in multiple areas of cognitive functioning, that the pattern and severity of deficits is heterogeneous, and that cognitive deficits compromise the ability of the affected individuals to function well and live independently (Green, 1996; Heinrichs & Zakzanis, 1998; Savla, Moore, & Palmer, 2008).

Suggestions that schizophrenia is characterized by impairment in what today are labeled as "executive functions" were present a century ago in Kraepelin's description of this condition as a "disorder of will" (Zec, 1995). Executive functions remain a key focus in many contemporary neurocognitive models of schizophrenia (reviewed in Palmer & Heaton, 2000, and Velligan & Bow-Thomas, 1999), and are among the strongest neurocognitive predictors of functional disability among people with schizophrenia (Green et al. 2000). Yet, the very concept of executive functions lacks conceptual, psychometric and neurobiological clarity – there is only vague, general consensus among researchers in their definition of executive functions, what they are comprised of, and how they can be effectively measured (Palmer & Heaton, 2000). Much of the existing research describes executive functions as if they were a unitary construct, and the choice of tests selected for the "executive function" domain of test batteries varies widely across research studies. This lack of consistency in executive functioning measures, as well as uncertain psychometric equivalence among neuropsychological tests (including those measuring specific executive functions) makes it difficult to identify differential relationships among the specific functions broadly classified as executive functions (Chapman & Chapman, 1973). Furthermore, all executive functioning tests are multifactorial (Delis, Kaplan, & Kramer, 2001), and the current norm is to examine only one score that denotes success or failure of task completion (referred to

as the "achievement score"), rather than a breakdown of the task into the various skills that are needed for its completion, or the process by which the solution is achieved (typically, number and types of errors; Kaplan, 1988). The practice of examining only achievement scores yields little information about whether there actually exists a deficit in the specific executive functions ostensibly measured *above and beyond* deficits in the more basic skills, e.g., attention, motor speed, etc., that are required for the task.

The recent publication of the Delis-Kaplan Executive Functions Battery (Delis, Kaplan, & Kramer, 2001b) provides an excellent opportunity to measure a variety of skills that fall under the umbrella of executive functions but also to parse out basic, component processes that form the fundamentals of these higher-level skills. The nine D-KEFS tests, and their subcomponents (which range from simple to increasingly complex tasks) are co-normed, which allow for a head-to-head comparison of the tests, that is more psychometrically rigorous than the comparison of individually normed test performances across different studies.

The current study aims to 1) to evaluate the types and levels of impairment among executive functions in adults with schizophrenia relative to demographically matched healthy-comparison subjects; 2) to investigate the degree to which various D-KEFS executive functioning variables have shared versus independent variance among people with schizophrenia (this helps determine whether the D-KEFS measures a single construct or multiple executive functioning constructs in schizophrenia); and 3) to determine whether specific executive functions are differentially associated with severity of psychopathology, functional capacity, and functional status (specifically, level of independent living) among patients with schizophrenia.

The study background includes a review of the historical and contemporary literature on specific executive functions, their measures, and the application of these constructs and measures to the study of schizophrenia. The review of methods of executive function assessment will also include a detailed consideration of the D-KEFS, a review of the several critiques of the battery, and the findings from the few existing studies using the D-KEFS tests with adult clinical populations with dementia, chronic alcoholism, focal frontal lesions, and Asperger's syndrome.

Next, the aims and specific hypotheses are described in detail, followed by the methods and results of the statistical analyses. The dissertation ends with a discussion of the results, strengths and limitations of the study, and its theoretical and clinical implications.

2.   What are Executive Functions?

This section examines the historical and contemporary definitions of executive functions. Section 2.1. details the evolution of the terminology of executive functions since its earliest known documentations, and is followed by a discussion of some popular definitions of the concept in Section 2.2. Section 2.3. comprises a description of the typical constructs that make up executive functions, and commonly used measures of the constructs.

2.1.   Terminology

According to a recently published review (Beatriz Jurado & Rosselli, 2007), the term, "executive functions" was first used by Baddeley and Hitch (1974) when they described their concept of the "central executive" as a part of their model for working memory. However, researchers of human thought and behavior have been talking about executive functions, in some form or the other for at least the past hundred years (Luria, 1966). The history of this construct or term spans multiple traditions, including computer science/artificial intelligence (AI), cognitive psychology, behavioral neurology, biological psychiatry, and neuropsychology (Miller, 2005). In the context of neuropsychology and neuroscience, the term, "executive functions," has been used synonymously with "higher cortical functions," and "frontal lobe functions," and virtually every published study using a comprehensive neuropsychological battery includes an "executive functions" domain, among others (e.g., Levin, 1984, Luria, 1966, Palmer & Heaton, 2000). The use of the term, "frontal lobe functions" was a consequence of the early theory that they were exclusively mediated by the frontal lobes, specifically, the prefrontal cortex, e.g., Levin (1984) Cognitive deficits such as those in abstraction and novel problem solving were also among the most prominent deficits observed in people with frontal lobe lesions, or frontal lobotomies/ leucotomies (Luria, 1966). However, the prefrontal cortex is responsible for a number of different functions besides the executive functions, including volitional eye movements, speech and language, motor reflexes, and motor control (Damasio & Anderson, 2003). On the other hand, as technology such as neuroimaging emerged, it became clear that executive functions were

mediated by *circuits* that involved not only the prefrontal cortex, but also several subcortical structures (Lichter & Cummings, 2001). Therefore, non-frontal or even sub-cortical injuries can cause deficits on "executive tasks," e.g., a recent review of executive functions and the frontal lobes (Alvarez & Emory, 2006) noted that although the majority of studies found the performance of people with frontal lesions on the Wisconsin Card Sorting Test (WCST), compared to those with non-frontal focal lesions, there were a few studies that demonstrated that there was no difference in impairment on the WCST among people with frontal, and diffuse or basal ganglia lesions. People with posterior and thalamic lesions also performed poorly on the WCST relative to neurologically normal controls.

2.2.   Definitions

The Oxford English Dictionary defines the word, "executive" as "to follow out, carry into effect (an intention, plan, instruction, or command)" originating in the late 14th century from Old French (*exécute-r*) or Medieval Latin (*execūtāre*), both meaning "to follow out" (Oxford English Dictionary, retrieved 9/18/07). Although the essence or the basic idea of executive functions is familiar to all neuropsychologists, there is much variability in how they define the concept. Palmer and Heaton (2000) reviewed a range of definitions of "executive functions" and noted that while a clear consensus definition remained elusive, a common theme underlying the various definitions seemed to be that executive functions "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." (p. 53). As exemplified in the preceding comment, there seems to be more consensus regarding the purpose (function) of executive processes or abilities, but much less clarity regarding which specific cognitive abilities are or are not properly conceptualized as being among the executive functions, nor specifically how these abilities are used to fulfill these purposes (although there is some work in the latter types of areas; cf. Baddeley 2007).

Luria (1902-1977), one of the pioneers of modern neuropsychology, is often credited with being the first to directly and comprehensively discuss executive functions and their importance in daily functioning. In his classic text, "*Higher Cortical Functions in Man,*" (Luria, 1966), he not only documented early historical theories of what we now call executive functions, but also his observations of patients with focal frontal lesions, his interpretations of the findings, and based on these findings, his own model of executive functioning. He defined higher mental functions as "complex reflex processes, *social in origin*, mediate in structure, and conscious and voluntary in mode of function." (p. 30, italics added). According to Luria, higher mental processes comprised purposive, goal-directed behavior, planning, decision making, initiation and execution of plans, and self-monitoring. He made particular distinctions between these and other mental processes, also associated with the frontal lobes (which he called the "organ of civilization"), such as movement, gnosis, praxis and speech.

Lezak and colleagues (2004) defined executive functions as "the most complex of behaviors…intrinsic to the ability to respond in an adaptive manner to novel situations…also the basis of many cognitive, emotional, and social skills." (p. 611).

The dictionary of the International Neuropsychological Society (INS) described executive functions as follows:

"Cognitive abilities necessary for complex goal-directed behavior and adaptation to a range of environmental changes and demands. Executive function includes the ability to plan and anticipate outcomes (cognitive flexibility) and to direct attentional resources to meet the demands of nonroutine events. Many conceptualizations of executive function also include self-monitoring and self-awareness since these are necessary for behavioral flexibility and 'appropriateness'." (p.64, Loring, 1999).

In their manual for the Delis-Kaplan Executive Function System (D-KEFS), the test authors write, "(higher-level cognitive functions) are referred to as executive functions because they draw upon the individual's more fundamental or primary cognitive skills, such as attention,

language, and perception, to generate higher levels of creative and abstract thought." (p.1, Delis, Kaplan, & Kramer, 2001c).

Definitions of executive functions that we now know are less accurate also continue to exist; for example, in the glossary of terms on the website of the National Academy of Neuropsychology (NAN), the term "executive" is defined as "referring to the frontal lobes." They go on to describe "executive function disorder" as an "intellectual impairment that results from lesion of the dorsolateral portion of the frontal lobes," and consisting of "impairment of hypothesis-testing and abstract reasoning, memory disorder, attention deficits and difficulty in initiation of cognitive activity." (NAN, 2000). The definition needs both updating in terms of its exclusive neuroanatomical associations, and further honing, given that it includes concepts only loosely related to executive functions.

2.3.   Specific constructs and their commonly used measures

The historical concept of executive functions subsumed certain "psychological" functions, such as volition, social judgment and comprehension the broad category (volition, being one of the earliest documented executive functions, and defined as "the capacity for intentional behavior") (p. 612, Lezak et al., 2004). While this section will only discuss the executive functions relevant to the current proposed study, i.e., the neurocognitive executive functions, a brief mention of the construct of volition is warranted because of the increasing awareness that volitional and motivational deficits appear to be pervasive among patients with severe psychiatric illness, and may be the bridge between neurocognitive capacity and actual functioning (Velligan, Kern, & Gold, 2006).

Volition is the ability to initiate activity directed toward a purposive action, and self-awareness in the context of the current situation/ environment (Lezak et al., 2004). Impairment in volition can be extreme, such as in the case of catatonic or apathetic individuals, or minimal, wherein they can respond to basic physiological needs, but none other. There are no standardized, neuropsychological measures of volition, but clinical interviews typically probe for

signs of impaired motivation and/ or volition. Commonly used methods include asking the individual to describe to the examiner his/ her typical day, hobbies/ leisure activities, and short and long-term life-goals. The individual's behavior is also noted for mood, and emotional response. Volition assessed in this manner, therefore may fall under the general category of "affective" or "negative" symptoms. Nevertheless, it is considered to be a quintessential executive function – without volition, none of the other functions will even be initiated. Measures of volition are NOT commonly included as part of a neuropsychological battery, but are typically included as part of an informal screening of an individual's cognitive status.

Sections 2.3.1 through 2.3.6 discuss the major executive functions, and some common ways in which they are operationalized. As with most neuropsychological tests, the measures discussed under each construct are by no means reflective of a unitary, "pure" cognitive ability, i.e., they often tend to tap into multiple skills. Importantly, measures *within* each construct may also only partially overlap, because they may measure different aspects of the same construct. Also discussed, is a brief summary of neuroanatomical relevance and clinical findings associated with the measures. A review of the literature on the constructs and measures, specifically in regard to schizophrenia will be discussed in Section 4.

2.3.1. Abstract Thinking/ Conceptualization

Abstract thinking is the ability to extract meaningful semantic connections between individual verbal or visual stimuli, or to the ability to simplify concepts at the level of ideas or generalizations (Lezak et al., 2004). Among the simplest tests of verbal abstraction are those in which the examinee is asked to state how two stimuli are alike, e.g., "How are an apple and an orange alike?". Subjects may give concrete responses such as "they both have peels," which although technically correct, is not indicative of the appropriate semantic category. On the other hand, the response, "they are both food," is also partially correct, but not ideal, because it is *overly abstract.* It does not denote the appropriate superordinate category because it is too broad. The *Similarities* subtest of the WAIS-III is one the most widely used verbal abstraction measures,

and has roots in the early Binet-Simon scales from the early 1900s (Tulsky, Saklofske, & Zhu, 2003). One could argue that similarities and interpretation of common problems or sayings may not require active abstraction, if they are familiar. A true verbal abstraction measure may consist of asking the examinee to interpret novel, but plausible proverbs or sayings. The D-KEFS has a standardized proverbs test, which includes both common and uncommon proverbs, and is described in detail in section 3.1.9.

The *Wisconsin Card Sorting Test (WCST)* (Berg, 1948; Heaton, 1981; Heaton, Chelune, Talley, Kay, & Curtiss, 1993) is considered the prototypical measure of abstraction and problem-solving, as well as of cognitive flexibility, and is among the most widely used tests in neuropsychological research and practice today (Rabin, Barr, & Burton, 2005). The original version of the test contained 4 stimulus cards (1st = one red triangle, 2nd = two green stars, 3rd = three yellow crosses, and 4th = 4 blue circles) and 60 response cards (each with 1, 2, 3 or 4 triangles, stars, crosses or circles, of one of four colors, i.e., red, green, yellow or blue). The examinee was asked to match each of the 60 cards to one of the four key cards, with no instructions regarding how to match them, but feedback about whether each match was correct or wrong. The examiner looked for sorts in three predetermined categories, i.e., color, form and number, in that order, and when the examinee got five correct responses in one category, the correct sorting category was implicitly changed by the examiner (as indicated by the continued feedback after each response implying the changed category) (Berg, 1948). Grant and Berg (1948) made some modifications to the original task so that there were 128 response cards, and the examiner waited until the examinee got 10 consecutively correct responses in one category before shifting to the next one. Heaton (1981) standardized the administration procedure so that the four stimulus cards were always presented in the same order, as were the 128 response cards (which he accomplished by numbering them). This version of the WCST is currently used, and a shorter version with 64 response cards is also popular (Heaton et al., 1993; Kongs, Thompson, Iverson, & Heaton, 2000). There are computerized versions of the WCST as well (Artiola i Fortuny & Heaton, 1996), which reduce the "executive" demands on the *examiner*, who

has to be constantly alert when evaluating the examinee's response, mark off all the categories the current card matches with on the scoring response sheet, and make sure that the category is changed after 10 correct matches. Computerized administration and scoring, therefore, can considerably reduce error and ensure standardization. Besides the total number of categories achieved, the WCST yields several process scores, such as number of errors, number of perseverative responses and errors, conceptual level responses, and failure to maintain set. Milner (Milner, 1964) used Grant and Berg's version of the WCST to distinguish between patients with atrophic lesions in the dorsolateral frontal cortex and controls (patients with atrophic lesions elsewhere in the brain, e.g., orbitofrontal, temporal, parietal cortices). Milner reported that the dorsolateral frontal lesion group made significantly more perseverative errors and achieved fewer sorting categories, while the control group, including the subgroup of patients with orbitofrontal cortex lesions, did well. Of note, there were no significant group differences in the number of nonperseverative errors. There have also been some studies suggesting that the WCST is non-specific to frontal impairment. For example, Grafman and colleagues (Grafman, Jonas, & Salazar, 1990) found no differences in impairment on the WCST between patients with focal frontal lesions and those with non-frontal lesions (e.g., anterior temporal lobe lesions). The WCST has also been extensively used with schizophrenia patients (please see section 4.1.1. for a review of the findings).

Another useful test of conceptualization and problem solving is the *Category Test* (Halstead & Settlage, 1943; Reitan & Wolfson, 1993). Conceptualized by Halstead as a measure of the "ability to discover commonalities among objects," it has gone through several modifications since its inception (reviewed in Choca, Laatsch, Wetzel, & Agresti, 1997). The most psychometrically sound version of this test consists of 208 visual stimuli (presented in booklet form or on the computer), grouped into seven sections, the first six of which require the examinee to deduce the general principle underlying the stimuli in each set, in order to pick the correct response out of four possible choices. The seventh subtest consists of a subset of items from the previous six subtests, and the examinee must remember the rule that yielded the correct

response the first time they saw the item, and select it from four potential response choices (in this sense, this subtest calls on incidental memory rather than abstraction). Similar to the WCST, there are no overt instructions about the idea underlying each subtest, and the examinee is given feedback ("correct" or "incorrect") after each response. Although the test could potentially yield some interesting process scores, e.g., perseveration on an incorrect idea even after repeated feedback, and cognitive flexibility, i.e., abandoning the incorrect rule, and applying different rules until one gets the correct one, the only score that is commonly used is the total number of errors (across the seven subtests).

Studies examining the overlapping variance of the WCST and the Category Test have revealed that the two are not as closely related as one might presume; for example, a study particularly aimed at examining the interrelationships between the two measures among people with mixed brain injuries demonstrated that the two were moderately correlated (rs = .4 to .6) (Golden, Kushner, Lee, & McMorrow, 1998). Furthermore, these correlations substantially diminished when age, education, and Vocabulary and Block Design scores were examined as potential predictors of variance.

Measures that require categorization of objects were popular during the initial period of interest in abstract functioning and conceptualization, right after World War II, but had been less commonly used over the past half century. The interest in such measures has been revived with their inclusion in the D-KEFS (e.g., Sorting, Twenty-Questions Test), which is discussed in section 3. Early versions of such object sorting tests consisted of a series of objects randomly arrayed, with instructions to the examinee to sort them according to specific principles. Hanfmann & Kasanin (Hanfmann & Kasanin, 1942), in their book, "*Conceptual Thinking in Schizophrenia"* described their own sorting task, that involved 22 blocks of various shapes, height, color and size, and labeled as belonging to one of four nonsense categories, unknown to the examinee. The examinee's task was to find and separate the four kinds of blocks.

Other types of abstraction measures are logical visual abstraction tests, and although not as widely used as the verbal measures described earlier (such as Similarities and proverbs), are

appearing more and more frequently in comprehensive neuropsychological batteries. One of the oldest visual abstraction measures is *Progressive Matrices*, originally developed by J.C. Raven (Raven, 1941; Raven, 2000). It consists of multiple items in which an abstract pattern (either colored or black and white) is presented, with a missing segment. Below each pattern is a set of alternatives, one of which completes the pattern. There are various versions of this test, but the items are typically arranged in sets, so that each set becomes increasingly difficult. The latest version of the WAIS (WAIS-III; Wechsler, 1997) includes the *Matrix Reasoning* subtest, which is a modified version of the Raven's Progressive Matrices. As with the original, it consists of abstract patterns, which are arranged in a logical manner, and the missing part must be chosen from five possible alternatives based on inductive reasoning.

The *Picture Arrangement* subtest (Wechsler, 1997) of the various versions of the Wechsler intelligence batteries is also a useful measure of logical sequencing and verbal organization of complex, sequential visual data. The stimuli consist of sets of black and white, or color line drawings, which can be arranged to form coherent stories. Each set of drawings is presented to the examinee in a predetermined random order, with instructions to arrange them in a way that they make a story that makes the most sense. Patients with subscribed frontal lobe lesions demonstrate impaired ability to make hypotheses regarding the sequence of events in the pictures, and therefore do poorly on this test (McFie & Thompson, 1972). The test, however, is not specific to frontal lobe lesions, as logical sequencing is one of the first abilities to become impaired with any kind of diffuse brain injury, as well as focal lesions in the parietal and temporal lobes, as well as subcortical structures (Warrington, James, & Maciejewski, 1986)

There are various other, less commonly used measures of abstraction and problem solving, which are beyond the scope of this report. Tests such as Mazes, or the Tower of London/ Hanoi may also be considered measures of problem solving, but are generally included under the subdomain of Planning. Tests of the D-KEFS such as the Sorting, Proverbs, and Word-Context tests are discussed in more detail in section 3.1.

2.3.2.   *Cognitive Flexibility/ Set Switching*

Cognitive flexibility may overlap with problem solving in that it is required to generate and test different approaches to problem-solving in novel situations. This can be tested with both the WCST and the Category Test, when subjects must think of, and be able to implement different matching strategies after an initially adaptive strategy is no longer resulting in correct responses. The type of cognitive flexibility that will be discussed in this section is *set switching or "shifting set"* which is the ability to alternate between two or more ideas. The most commonly used measure of set switching is the *Trail Making Test*, originally called *"Distributed Attention,"* and later, the *"Partington's Pathways Test"* (Army Alpha Tests, 1944; Partington & Leiter, 1949) was adapted as part of the Halstead Reitan Battery (Reitan & Wolfson, 1993). The Trail Making Test consists of Parts A and B, the former merely requiring the ability to rapidly visually scan and connect the items on a page (numbers from 1 to 16) and sequence them in order, and the latter (Part B), being the set switching component of the test. Part B consists of circles containing either numbers or letters, which must be connected so that the examinee goes from a number to a letter, to the next number, to the next letter and so on (i.e., 1 to A, A to 2, 2 to B, B to 3, and so on). If the examinee goes from one number to the next number, the error is considered a set loss. Both parts of the Trail Making Test are highly vulnerable to brain damage (Spreen & Benton, 1965), while part B is associated with perseverative errors on the WCST, and is a good predictor of everyday functioning activities, such a driving (Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002). While the Trail Making Test has clinical utility because of its short administration time, and sensitivity to even mild brain injury, performance on the test is highly dependent on familiarity with English alphabet. For the same reason, results can be confounded by learning disability. There are various versions of "Color Trails," that have been developed to address this problem; one version consists of numbers and two sets of colored circles (Maj, D'Elia, Satz, & Janssen, 1993).

Several D-KEFS tests, besides the D-KEFS Trail Making Test have a set-switching component, and are discussed in detail in section 3.1 (also see *Table 3.1.*).

2.3.3. *Planning*

Planning may be defined as the ability to identify and organize the steps and elements needed to carry out an intention or achieve a goal (Lezak et al., 2004). Volition is a precondition to planning; as Lezak notes, "(p)atients who are unable to form a realistic intention also cannot plan." (p. 614). One of the most commonly used measures of planning is *Mazes*, in which subjects must find their way through a maze, the most efficient manner, in order to reach a target. In the *Porteus Maze Test* (Porteus, 1959; Porteus, 1965), the examinee must trace mazes, ranging in level of difficulty, without entering any blind alleys in order to demonstrate efficiency. The test yields time to completion scores, and variety of qualitative, error scores, with repeated entries into the same blind alley indicating perseveration. The test also contains basic cognitive components such as sustained attention, working memory and visuospatial function, so impairments in any of those functions can lower performance. The Maze Test is sensitive to the presence, as well as the severity of brain damage (reviewed by Lezak et al., 2004).

The *Tower* Tests, in their various incarnations (the most well-known being the Tower of London, and Tower of Hanoi, and recently, the D-KEFS Tower Test) have been used widely as measures of planning (Shallice, 1982). The test typically consists of a board with three vertical pegs, and a set of disks, that must be moved from one position to a target position in the fewest moves possible. The different versions have different rules, e.g., only one disk must be moved at a time, or only a specified number of disks must be left on each peg at a time. (The D-KEFS Tower Test is described in detail in section 3.1.8.). The Tower Test is especially sensitive to damage to the prefrontal cortex (Lazeron et al., 2000), and also taps into other cognitive functions such as response inhibition, motor speed, and working memory. (There are verbal analogues to the Tower test as well, e.g., the controversial "Missionaries and Cannibal" problem (Jeffries, Polson, & Razran, 1977), or current modifications of similar "river-crossing" problems, such as: "A man has to get a fox, a chicken, and a sack of corn across a river. He has a rowboat, and it can carry him and one other thing. If the fox and the chicken are left together, the fox will eat the

chicken. If the chicken and the corn is left together, the chicken will eat the corn. How does the man do it?")

The Block Design tests (e.g., from the Wechsler intelligence scales) are considered to be primarily visuospatial functioning, specifically, visuospatial construction tasks. However, optimal performance on Block Design relies on planning, appreciation of gestalt (a pattern so integrated with properties that cannot be derived merely from a summation of its parts), and monitoring in that the examinee must compare between his or her own three-dimensional design and the target design (Stuss & Benson, 1986). In their manual on the Wechsler Adult Intelligence Scale – Revised as a Neuropsychological Instrument (WAIS-R NI), Kaplan and colleagues (Kaplan, Fein, Morris, & Delis, 1991) discuss how broken configurations, indicative of an appreciation of an internal pattern, while neglecting to simultaneously maintain the global configuration are typical of patients with right frontal lesions.

2.3.4.   Fluency

There is some debate regarding whether Verbal Fluency tests should be considered executive functions, or simply verbal expression or processing speed measures (e.g., factor analytic studies by Gladsjo, McAdams, Palmer, Moore, Jeste, et al., 2004; Welsh, Pennington, Ozonoff, Rouse, & McCabe, 1990), and the answer is yet unclear. The argument for their inclusion as executive function measures is that optimal performance on the task facilitates an organized search of various phonological and semantic networks in order to generate words (Moore et al., 2006).

The first fluency test was developed in the 1930s, and was later modified to its current version as the Thurstone Word Fluency Test, included as part of the Expanded Halstead Reitan Battery (Heaton, Grant, & Matthews, 1991; L. L. Thurstone, 1938). In the earliest version of the test, invented by Thelma Thurstone, subjects were told to write as many words as they could think of that began with a specific letter, and ended with a specific letter. In the more current version, subjects are asked to write as many words as they can think of that begin with a

specified letter (i.e., S) in a span of five minutes (L. L. Thurstone, 1938). They are then asked to write as many four-letter words as they can, beginning with the letter, C within four minutes. Not surprisingly, the Thurstone Word Fluency Test is heavily influenced by vocabulary, motor function and speed, and intact verbal learning in school.

The Controlled Oral Word Association Test (COWAT; Benton, 1968) is the most widely used verbal fluency task today (Rabin et al., 2005). In the "FAS" version of the task, subjects are asked to say aloud as many words as they can think of that begin with the letter F, in a span of one minute. The same procedure is repeated with the letters A and S. Some response recording methods involve simply writing all the responses, while others involve recording the responses in each 15-second interval for each trial. Total words obtained, and number of errors (set-losses, repetitions, intrusions) are the scores yielded by most versions of the COWAT. The D-KEFS version of the COWAT also has an overt category switching component, and the D-KEFS version yields many more process scores, which are described in section 3.1.2.

The Category Fluency task involves asking subjects to name as many items from a single specified category they can, in a span of a minute (Goodglass & Kaplan, 1983), the most common category being Animals. Any damage to the frontal cortex tends to cause impairments on any fluency measures, but the task is also influenced by cognitive flexibility, anxiety, and poor volition (Lezak et al., 2004).

A nonverbal analogue to the verbal fluency tests are various versions of the figural fluency or design fluency tests. The original Design Fluency Test (Jones-Gotman & Milner, 1977) consisted of a free condition trial, in which the examinee was asked to "invent" non-nameable drawings, followed by a second, fixed condition, in which the examinee had to draw figures that are limited to four curved or straight lines, within four minutes. The test was modified to include more structure, e.g., rows of squares, and five symmetrically placed dots (Regard, Strauss, & Knapp, 1982) to make scoring more accurate, and was subsequently further modified to include distractor stimuli, e.g., Ruff Figural Fluency Test (Evans, Ruff, & Gualtieri, 1985; Ruff, Light, & Evans, 1987). The primary measure is the number of novel or unique drawings the examinee can

draw, while maintaining certain rules, such as use of only a specific number of lines, etc. There is evidence that patients with frontal lesions find this test difficult, making the most errors, especially those involving rule-breaking (Varney, Roberts, Struchen, & Hanson, 1996).

2.3.5. Response Inhibition

Response inhibition, in the context of executive functioning refers to the ability to hold back an immediate, automatic response in favor of a less intuitive alternate response. The Stroop task (Stroop, 1935), in its various incarnations (Delis, Kaplan, & Kramer, 2001b; Dodrill, 1978; Golden, 1978) is a frequently used measure of response inhibition. The Stroop can be difficult for even neurologically normal individuals, and a popular interpretation, since the time of James McKeen Cattell in the 1886, emphasizes the notion of response competition (reviewed by MacLeod, 1991). On an overly simplified level, the Stroop can be viewed as requiring active inhibition of automatic processes to read words, in favor of less automatic color naming. This need for effortful response inhibition, and a deliberate allocation of attentional resources (selective attention) is characteristic of an executive task. Visual competence, including ability to see colors is an obvious precondition for the test. In the Color Word Interference trial of the Stroop, subjects are presented with color names printed in colored ink that is discordant with the color the word denotes, e.g., the word blue will be printed in red ink, green in blue ink, and so on. Subjects are instructed to ignore the word, which is the more automatic response, and name the dissonant ink color instead, which is the more difficult response. Lezak and colleagues (2004) note that the task is based on findings that naming colors is more difficult than reading words, and naming the color of the ink in which the word is printed not only requires conscious effort, but also freedom from distractibility. Other Stroop trials, besides the Color Word Interference trial, include simply reading aloud as fast as possible, words denoting color names, that are printed in black, and naming patches of color. The D-KEFS version of the Stroop, simply called the Color-Word Interference Test has an even more cognitively demanding trial, which is a combination of a

traditional color-word interference trial and a working memory task, and has been described in section 3.1.4.

Intact performance on the Stroop has been connected to both cortical and subcortical structures in the brain, including the frontal lobes, anterior cingulate, and basal ganglia (Posner & Raichle, 1994). The test can be highly sensitive to even mild forms of brain injury, as well as closed head injuries with purported "good recovery" (reviewed in Lezak et al., 2004). Likewise, it can also be affected by emotional distress, even mild attentional problems, and fatigue.

2.3.6. Working Memory

Baddeley and Hitch (1974) conceptualized the model of the working memory as a dynamic system, consisting of an attentional control system ("the central executive"), and two subsidiary storage systems, the articulatory/ phonological loop and visuospatial sketchpad. Norman and Shallice (1980) subsequently proposed their model of willed and automatic controlled behavior, in which they introduced the "supervisory attentional system" (SAS). In response to criticism and self-recognition that the original model of working memory had only a vague specification of how the central executive actually worked, Baddeley (1986) adopted the notion of SAS as a reasonable explanation of the process (described in Baddeley (1986, 2007). While the phonological loop and visuospatial sketchpad are typically classified under the larger domain of attention, the SAS, which selects and operates strategies for maintaining and switching attention is closely related to executive functioning (Grafman, 1989).

The Tower tasks (described in section 2.3.3.) are considered especially good measures of the SAS, in that the task requires that subjects keep the target arrangement on their "mental workbench" while initiating the various steps toward the goal, and at the same time, deciding whether the steps are proceeding toward the desired goal (Shallice, 1982). The SAS may also be effectively operationalized with dual task paradigms, in which subjects are engaged in one task, while being exposed to a number of interfering secondary tasks. The Letter-Number Sequencing (LNS) task of the Wechsler scales may also be considered to be a measure of SAS; it consists of

presenting subjects with strings of jumbled numbers and letters, which they have to unscramble, and first say the numbers, in ascending order, and then the letters, in alphabetical order. The SAS appears to be mediated by the ventral and dorsolateral prefrontal cortex (Grafman, 1989; Fletcher et al., 1998)

3.   The Delis-Kaplan Executive Function System (D-KEFS)

The D-KEFS (Delis, Kaplan, & Kramer, 2001b) is a battery of tests exclusively designed to measure multiple aspects of executive functions, and the fundamental skills that mediate them. It is the first battery of executive functioning tests that was co-normed on a large sample of healthy (non-clinical) children and adults demographically representative of the U.S. population. The tests of the D-KEFS include Trail Making Test, Verbal Fluency Test, Design Fluency Test, Color-Word Interference Test, Sorting Test, Twenty Questions Test, Word-Context Test, Tower Test, and the Proverb Test. While many of these tests are modifications of existing tests, two are relatively new, i.e., the Word-Context Test and the Sorting Test, developed by one or more of the D-KEFS authors. The tests are relatively easy to administer, and are presented in a game-like format, and the scoring is broken down to identify the individual's performance on higher order skills, as well as the basic skills that form their foundation. The tests can also be administered as stand-alone tests, and all, except the Proverb Test can be given to individuals between the ages of 8-89 (the latter can be given to individuals aged 16-89).   Each test yields a primary, or achievement score, which is usually the examinee's final solution to the task. It also provides norms for the process scores, which can shed light on the way the examinee approaches the task. These process scores (which include types of errors, and contrast measures [how the examinee did on one versus other conditions of a task]) are optional. Section 3.1. is an overview of the nine D-KEFS tests, the conditions within each, scores obtained, and the executive and related fundamental skills they ostensibly measure are depicted in Table 3.1. Section 3.2. is a brief review of the literature on D-KEFS-related findings among various clinical populations.

Table 3.1. D-KEFS Tests and their Components, and Constructs Measured (Executive Functioning Components of Measures are in Bold Font)

Test	Primary Measures	Optional (Process) Measures	Constructs Measured
Trail Making	Completion Times: Visual Scanning Number Sequencing Letter Sequencing **Number-Letter Switching** Motor Speed	Contrast measures (completion times) Error analysis (sequencing, set-loss and time-discontinue errors)	Attention and scanning Visuomotor sequencing **Cognitive flexibility** **Working memory** Motor Speed
Verbal Fluency	Total Correct: Letter Fluency Category Fluency **Category Switching** Total Switching Accuracy	Interval total correct Set-loss errors Repetition errors	Initiation Psychomotor Speed Fluency **Cognitive flexibility** **Working memory**
Design Fluency	Total Correct: Filled Dots Empty Dots Only **Switching**	Set-loss designs Total repeated designs Total attempted designs	Fluency **Cognitive flexibility** **Working memory**
Color-Word Interference	Completion Times: Color Naming Word Reading **Inhibition** **Inhibition/ Switching**	Contrast measures (completion times) Error analysis (corrected errors, uncorrected errors, total errors)	Attention Psychomotor Speed **Response Inhibition** **Cognitive Flexibility** **Working Memory**
Sorting	**Free Sorting: Confirmed Correct Sorts, Free** Sorting Description Score Sort Recognition: Sort Recognition Description Score	Word reading errors, word comprehension errors Confirmed correct verbal sorts, perceptual sorts Confirmed/ unconfirmed target sorts Repeated sorts, set-loss sorts, nontarget even sorts, attempted sorts	**Abstraction Sorting**
Twenty Questions	Initial abstraction score Total questions asked **Total weighted achievement score**	Spatial questions Repeated questions Set-loss questions	**Abstraction Deductive Reasoning**
Word-Context Test	**Total consecutively correct**	Consistently correct ratio Repeated incorrect responses, no/ don't know responses, total correct-to-incorrect errors	**Verbal Abstraction Working Memory**
Tower	**Total achievement score**	Mean first-move time Time-per-move ratio Move accuracy ratio Total rule violations Rule-violations-per-item ratio	**Planning** Sequencing **Working Memory**
Proverb	**Total achievement score: free inquiry**, multiple choice	Free Inquiry: Common proverb achievement score Uncommon proverb achievement score Accuracy only Abstraction only No/ don't know responses Repeated responses	**Verbal Abstraction**

3.1. D-KEFS Tests

3.1.1. D-KEFS Trail Making Test

As discussed in section 2.3.2., the Trail Making Test has undergone relatively minor modifications over the years. The D-KEFS version of this test retains the two traditional parts of the test (number sequencing and number-letter switching), with some modifications, and has three novel additions, i.e., letter sequencing, visual scanning and motor speed in drawing lines. The stimuli are also arranged in a manner a few "capture" the attention of the examinee so as to tempt him or her to make an error, e.g., in the Switching condition, two consecutive numbers may be placed close to one another, so the examinee has to consciously inhibit the impulse to connect to the next number, but must go on to the next letter instead. (The need to inhibit the "capture" response seems to explicitly require input from the SAS [see Section 2.3.6.].) While letter-number switching may be considered the true "executive," particularly, cognitive flexibility task, the other four conditions are useful to parse out basic abilities, such as sequencing numbers and letters (both of which are overlearned tasks), line drawing speed, and visual scanning and attention, all of which contribute to this higher order, more difficult task. Deficient switching scores can therefore be examined with relation to the scores on the underlying component scores. Achievement scores for this test include the completion-time scores for each condition, and process scores include error types (set-losses, sequencing errors, and time-discontinue errors, i.e., number of connection the examinee failed to make before the maximum time limit), and contrast measures comparing the examinee's performance on each of the conditions.

3.1.2. D-KEFS Verbal Fluency Test

This test is also a modified version of the long existing Thurstone Written Fluency test, and the currently, widely used spoken-response form, the COWAT (see section 2.3.4.). The D-KEFS Verbal Fluency Test comprises the two traditional conditions, i.e., letter fluency and category fluency. The Category Fluency condition of this test uses the traditional semantic category of animals, and additionally, uses boys' names as an additional category in the standard

form. Alternate forms of the Letter and Category Fluency conditions use B, H, and R, and items of clothing and girls' names, respectively. The novel addition is that of the Category Switching condition, which requires the examinee to switch between two semantic categories, i.e., fruits and furniture in the standard form, or vegetables and musical instruments in the alternate form. The test aims to measure the ability to generate words fluently in a speeded manner within a 60-second time limit, in different formats, i.e., phonemic (Letter Fluency condition), overlearned semantic category (Category Fluency condition), and alternating between two overlearned semantic categories (Category-Switching condition). Achievement scores for which age-corrected normative data-based conversions are available include total number of correct responses in each condition, and process scores with normative conversions include total number of correct responses in each 15-second interval for each condition, error types (set-losses and repetitions), and contrast measures comparing performances across conditions.

3.1.3. D-KEFS Design Fluency Test

The examinee's task on the D-KEFS Design Fluency Test is to rapidly generate as many different designs as he or she can within a set time limit. In addition to the time limit, response constraints are that the designs must be drawn by connecting dots with straight lines within a series of boxes, and that each design must be composed from exactly four lines (no fewer, no more). The first two conditions are based on earlier versions of the test, i.e., the Filled Dots condition presents the examinee with boxes containing five filled dots, and requires him/ her to draw as many different designs using four lines as he/ she can within 60 seconds, and the Empty Dots Only condition requires the examinee to draw designs using the five empty dots in each box, while ignoring the five filled dots, which serve as distractor stimuli. The novel addition is the Switching condition, in which the examinee is presented with boxes containing five filled and five empty dots (identical to the Empty Dots Only condition), but this time, he/ she is asked to make designs with four lines, while switching between the empty and filled dots. While the Filled Dots condition is purely a measure of design fluency, the Empty Dots Only condition measures both

design fluency and response inhibition, and the Switching condition measures design fluency and cognitive flexibility. Age-corrected scaled scores are available for both achievement scores (total number of correct designs in each condition), and process measures (contrast measures, and set-losses errors, and repeated designs).

3.1.4. D-KEFS Color-Word Interference Test

The classic form of this test is credited to Stroop (1935; see section 2.3.5.), which underwent several revisions, and even today, exists in multiple forms. The primary underlying mechanism measured by all versions of the original Stroop Test is the ability of the examinee to inhibit an automatic verbal response, i.e., word reading, while correctly generating a conflicting response involving naming the *dissonant* color of the ink the word is printed in. The D-KEFS version of the Stroop Test involves three traditional conditions, i.e., naming patches of color, reading words (color names) printed in black on a white background, and naming the ink that color names are printed in, while inhibiting the more automatic response of the word denoting a dissonant color. A novel interesting condition in the D-KEFS Color-Word Interference Test requires the examinee to switch back and forth between naming the color of the ink versus reading the actual word based on whether the stimulus is inside a box or not (thus making further demands on the pool of available, conscious processing resources). This condition measures both response inhibition and cognitive flexibility. Primary, achievement scores include time to complete each condition and combined time to complete the naming and reading condition. Process measures include contrasts between performances on the individual conditions, and number of uncorrected and self-corrected errors for each condition.

3.1.5. D-KEFS Sorting Test

The Sorting Test is one of the relatively new tests in the D-KEFS, originally developed by Delis (the senior author of the D-KEFS), and first published as the California Card Sorting Test (Delis, Squire, Bihrle, & Massman, 1992). Delis based this test on the informal, non-standardized

sorting procedures used by Vygotsky, and Kurt Goldstein in their clinical exams, which typically consisted of asking subjects to sort objects, blocks or tokens based on their visual features (Delis, Kaplan, & Kramer, 2001c). The D-KEFS sorting test uses an innovative approach, in which six cards may be sorted in groups of three each, based on both verbal-semantic stimuli (e.g., three of the cards have animal names, while the other three have means of travel), and visual-spatial stimuli (e.g., three of the cards are blue, while the other three are yellow). The test has Free Sorting and a Sort Recognition conditions, the first requiring subjects to sort the first, and then the second set of six cards into two sets of three as many times as they can, while describing how they sorted the cards. The recognition paradigm procedure involves the examiner sorting the cards, and the examinee having to identify the categorization rule by which they were sorted. Achievement is measured by the accuracy of the sort, as well as the verbalization of the rule by which the examinee categorized the cards, in order to examine his or her concept-formation and reasoning skills. The test authors' goal was also to measure the examinees' ability to initiate modality-specific (verbal and nonverbal) problem-solving behavior, and to measure flexibility of thinking (Delis, Kaplan, & Kramer, 2001c). Other achievement scores are the sort recognition description score for the Sort Recognition condition, and the Sort Recognition versus Free Sorting Description score. There are numerous process measures normed in this task, including confirmed correct sorts, confirmed correct verbal and perceptual sorts, confirmed/ unconfirmed target sorts, repeated sorts, set-loss sorts (e.g., sorting four versus 2 cards), nontarget even sorts, attempted sorts, percent scoring accuracy, time-per-sort ratio, free sorting description for each set, incorrect/ repeated descriptions, percent description accuracy for the Free Sorting condition. For the Sort Recognition, process measures include sort recognition description score, and verbal and perceptual sorting rules, no/ don't know responses, noncredit responses (which may be technically correct, but not one of the target sorts or could apply to more than one card set), overly abstract descriptions (e.g., "I sorted them by color," but lack of specific description, such as "These are blue, and these are yellow), and incorrect or repeated descriptions can be calculated for both conditions combined.

3.1.6. D-KEFS Twenty Questions Test

"Twenty Questions," a popular children's game, was adapted as an experimental task by Mosher and Hornsby (1966) for the study of concept-formation skills in healthy children, and later modified for use with child as well as adult clinical populations. The D-KEFS Twenty Questions Test is adapted from this game, and involves carefully selected and standardized stimuli (30 pictures of common objects), arranged in a manner so as to elicit concrete questions. The objects were selected to represent varying numbers of categories and subcategories (e.g., "nonliving things" = 15 objects, "kitchen items" = 8, "silverware" = 3 OR "living things" = 15, "animals" =8, "fish" = 2).   The examinee is required to ask the fewest number of questions that can be answered as yes or no by the examiner, so that the best questions eliminate the most number of objects. Achievement scores normed include initial abstraction score (i.e., for each item, the number of items eliminated by the examinee's first question), total questions asked, total weighted achievement score (bonus points awarded if the target object is identified with the optimal number of questions, e.g., identifying the object after asking 4 or 5 questions for each item constitutes the maximum number of points, i.e., 5). This last score is an especially useful measure of executive functions because it reflects the examinee's actual abstraction process, i.e., arriving at the correct response by means of careful elimination, rather than guesswork. The other goals of the test are to measure the ability to perceive the various categories and subcategories represented by the objects, and the ability to use the examiner's yes/ no feedback to formulate more effective questions. Process measures normed for this test include spatial questions (the number of questions asked that eliminate objects based on their location on the stimulus page, e.g., "Is it on the left half of the page?"), and repeated and set-loss questions.

3.1.7. D-KEFS Word-Context Test

The original Word-Context test was developed by Heinz Werner and Edith Kaplan in 1952 as a means of studying the way in which children acquired the meanings of words. The D-

KEFS Word-Context Test is adapted for use with children as well as adults, and is an excellent means of assessing verbal deductive reasoning, integration of gradually acquired information, hypothesis testing and cognitive flexibility. The examinee is asked to pretend that he or she is confronted with words in an unfamiliar language, and has to decode the meaning of each word, based on how it fits within five descriptive sentences. The words themselves are made-up (e.g., "*sev*,") and do not depict an actual language; each is provided with a phonological guide to keep the pronunciations standardized. The primary achievement measure is the total consecutively correct variable, i.e., the first correct response to a clue sentence that is maintained for all the remaining clue sentences for that item. Process scores include consistently correct ratio (total consecutively correct raw score: first sentence correct raw score), repeated incorrect responses, no/ don't know responses, and correct-to-incorrect errors.

3.1.8.   D-KEFS Tower Test

The Tower Test, like some of the others in the D-KEFS also has a long history, and exists in several incarnations today, the most popular being the Tower of London and Tower of Hanoi (see section 2.3.3.). While earlier versions of the Tower Test were criticized for having poor psychometric properties, such as poor internal reliability, floor or ceiling effects, the D-KEFS Tower Test was specifically designed to address these problems. The test includes a board with 3 vertical pegs, and five disks of varying size. The examiner places 2 to 5 disks on the pegs in a standardized starting position, and the examinee is asked to move the disks across the three pegs in the fewest possible moves to build a target tower as displayed in a picture presented to the examinee. The examinee is instructed to work according to certain rules: he/ she can only move only one disk at a time, and can never place a larger disk atop a smaller one. This test, unlike its predecessors, has a wider range of difficulty, so that easier and more difficult items have been included, in order to minimize both floor and ceiling effects. The test measures spatial planning, rule learning, inhibition of impulsive and perseverative responding, and ability to establish and maintain the instructional set. Besides the achievement score (sum of achievement

scores, including bonus points for all items administered), several process measures are also normed, including first-move completion time, total number of moves, item-completion time, final achievement (correct or incorrect tower), and number of rule violations.

3.1.9. D-KEFS Proverb Test

As discussed in section 2.3.1., asking subjects to interpret common proverbs is one of the quickest, and most commonly used, informal screening measures of concrete thinking in the clinical setting. One of the earliest versions of a formal test of interpreting proverbs is credited to Gorham (1956), in which subjects were asked to write their interpretations of proverbs, and then selecting an interpretation of the proverb in a multiple-choice recognition format. Delis et al. developed a version of the current D-KEFS Proverb Test in 1988, which consists of eight proverbs (5 common, and 3 relatively uncommon), that are first presented in a Free Inquiry condition, requiring subjects to elicit a spontaneous response, and then, in a Multiple-Choice paradigm, in which four alternative interpretations are selected, from which the examinee chooses his response. To the extent that the Proverb Test is culture-bound (which may include the familiar, common proverbs), it may be more a measure of semantic memory, and basic verbal skills, than of verbal abstraction. The unfamiliar proverbs, however, may be an effective measure of verbal abstraction skills. An interesting scoring procedure in this test involves scoring responses for accuracy, independent of the level of abstraction, and vice versa for the Free Inquiry condition. The achievement score for this condition is the combination or accuracy and abstraction scores for each proverb interpretation, and the sum of the examinee's achievement scores on each of the eight items for the Multiple-Choice condition. Optional, process scores include separate achievement scores for the common and uncommon proverbs, accuracy only, and abstraction only scores, and no/don't know and repeated responses for the Free Inquiry condition, and common and uncommon proverb achievement scores, and the number of times the examinee endorses each type of alternate response (i.e., correct abstract, correct concrete, incorrect phonemic, or incorrect related) for the Multiple-Choice condition.

3.2. Review of the D-KEFS

The technical manual of the D-KEFS reports reliability and validity estimates, which are generally satisfactory for use with individuals over the age of 16. However, the psychometric properties of the various test components vary widely (Delis, Kaplan, & Kramer, 2001a). See Table 3.2. for split-half and test-retest reliability estimates. Given the relative newness of the D-KEFS, there are only a handful of published studies that have used some of the tests, most with child clinical population. The few studies with adult clinical populations are reviewed here.

Table 3.2. Reliability Estimates of the D-KEFS Tests (D. C. Delis, Kaplan, & Kramer, 2001a)

Test	Internal Consistency *(Spearman-Brown formula; ranges across age groups, ages 16-89)*	Test-Retest Reliability *(All ages)*
Trail Making	Combined Number + Letter Sequencing composite score = .60 (ages 70-79) - .81 (ages 50-59)	Visual Scanning = .56 Number Sequencing = .59 Letter Sequencing = .59 Switching = .38 Motor Speed = .77
Verbal Fluency	Fluency total = .77 (ages 40-49) - .90 (ages 30-39) Category fluency = .60 (ages 16-19) - .76 (ages 80-89) Switching correct = .43 (ages 20-29) - .62 (ages 11-13) Switching accuracy = .51 (ages 60-69) - .72 (ages 30-39)	Fluency total = .80 Category fluency = .79 Switching correct= .52 Switching Accuracy = .36
Design Fluency	Not available	Filled Dots Only = .58 Empty Dots Only = .57 Switching = .32
Color-Word Interference	Combined Color Naming + Word Reading composite score = .72 (ages 40-49) - .86 (ages 50-59)	Color Naming = .76 Word Reading = .62 Inhibition = .75 Inhibition/ Switching = .65
Sorting	Free Sorting Confirmed = .72 (ages 16-19) - .86 (ages 50-59) Free Sorting Description = .73 (ages 16-19) - .84 (ages 60-69) Sort Recognition total = .74 (ages 16-19) - .81 (ages 70-79)	Free Sorting Confirmed = .51 Free Sorting Description = .50) Sort Recognition total = .60
Twenty Questions	Initial Abstraction = .74 (ages 16-19) - .87 (ages 70-79) Total Weighted Achievement = .10 (ages 16-19) - .48 (ages 80-89)	Initial Abstraction = .24 Total Weighted Achievement = .43
Word Context	Total Consecutively Correct = .51 (ages 16-19) - .74 (ages 70-74)	Total Consecutively Correct = .70
Tower	Total Achievement = .60 (ages 16-19) - .78 (ages 70-74)	Total Achievement = .44
Proverb	Total Achievement: Free Inquiry = .68 (ages 16-19) - .81 (ages 60-69)	Total Achievement: Free Inquiry =.76

Specific tests and their component measures have also demonstrated good sensitivity in distinguishing certain clinical populations, such as fetal alcohol syndrome, chronic alcoholism, Parkinson's disease, or focal frontal lesions, from healthy subjects. In one of the earliest reports

demonstrating the clinical utility of the D-KEFS, Cato and colleagues (Cato, Delis, Abildskov, &
Bigler, 2004) discussed the case of a man with long-standing penetrating injuries to the bilateral
ventromedial prefrontal cortex, who despite having everyday functioning difficulties throughout
life, continued to scoring well within normal to above normal limits on all neuropsychological tests,
including traditional executive functioning measures such as the WCST. However, when the
patient's errors on tests that placed simultaneous demands on multiple executive functions, such
as those requiring switching were examined, his performances were in the moderately to severely
impaired range, indicating that such tests may have particular utility in tapping functions that are
mediated by the ventromedial prefrontal cortex, that was previously considered cognitively
"silent." Error analysis was also used in a recent study to demonstrate the use of the D-KEFS
Tower test in distinguishing between frontotemporal dementia (FTD) and Alzheimer's disease
(AD; Carey, Woods, Damon, Halabi, Dean, et al., 2008). The study demonstrated that while the
two samples did not differ on the overall achievement score of the Tower test, the FTD patients
committed many more rule violation errors than did the AD patients. Another recent study
comparing the D-KEFS Verbal and Design Fluency performance in individuals with focal lesions
in the frontal lobe showed that they did poorly on both tests compared to demographically
matched controls (Baldo, Shimamura, Delis, Kramer, & Kaplan, 2001). Comparison between
individuals with left versus right frontal lesions indicated that the former do more poorly on the
Verbal Fluency test, but that there is no difference in performance in the groups on the Design
Fluency test. Performance on the two fluency measures were examined in another study
comparing the performance of older adults at risk for AD (with apolipoprotein E ε4 [APOE ε4]
genotype) versus those without this risk (Houston et al., 2005). The authors reported distinct
asymmetrical profile, i.e., "high verbal" (better Verbal Fluency) versus "high spatial" (better Design
Fluency) on the switching components of the tasks. Studies among adults with autism or
Asperger's disorder indicate lower-than normal scores on a composite measure derived from the
Color-Word Interference Test, Trail Making Test, and Verbal and Design Fluency tests
(Kleinhans, Akshoomoff, & Delis, 2005). Authors also reported that their participants had

difficulties with the switching components of the verbal task, but demonstrated intact performance on the inhibition component of the Stroop.   There are currently no published studies of the D-KEFS among people schizophrenia, but a review of the available literature on prior versions of the tests with this population is included in Section 4.1.

4. Executive Functions in Schizophrenia

There is unequivocal evidence that schizophrenia is a neurodevelopmental, neurocognitive disorder (Bilder et al., 2006; Green, 1996), characterized by mild to moderate deficits in multiple domains of neuropsychological functioning (Heinrichs & Zakzanis, 1998) (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Savla, Moore, Palmer, in press). There is a great deal of importance placed on executive dysfunction in schizophrenia, partly due to its status as one of the first cognitive deficits documented in patients with the illness, and due to its relevance to everyday functioning (e.g., driving, work attainment and maintenance, level of independent living, etc.; Green, 1996, Velligan & Bow-Thomas, 1999). A few studies have reported that executive functions are predominantly impaired in schizophrenia (Kremen, Seidman, Faraone, & Tsuang, 2001); however, it remains unclear whether they are uniquely impaired, i.e., more than other cognitive functions in schizophrenia, or even that they are consistently impaired in all schizophrenia patients (Braff et al., 1991; Palmer et al., 1997). Like with most characteristics among individuals with schizophrenia, executive dysfunction varies greatly among individual patients (Braff et al., 1991). Some of this variance can be explained by the types of specific constructs included in the domain and which were not, and the tests used to measure those constructs.

Early reports on executive functions included observations and studies of volition (e.g., Kraepelin, 1919/ 1971), conceptual thinking (Vigotsky, 1934), problem-solving (Cameron, 1939), abstraction (Goldstein & Scheerer, 1941), and so on, while the majority of the contemporary literature talks about executive functions in general. In this section, the literature on specific executive functions in schizophrenia will be reviewed, followed by a summary of neuroanatomical correlates of executive functions in schizophrenia. The section will conclude with a discussion of the practical implications of executive functions in schizophrenia. Relevant findings are summarized in Table 4.1. Also summarized (Table 4.2.) is a list of existing tests of executive functions that are widely used clinically, and in research and the D-KEFS tasks that are related to them.

4.1. *Review of Literature*

4.1.1. *Abstraction/ Conceptualization*

Concrete thinking, referring to the inability to make generalizations, or simply, the inability to think abstractly (Lezak et al., 2004) is often associated with formal thought disorder in schizophrenia (Andreasen, 1986), and has been documented since the time of Bleuler (1911). Muncie (1937) noted that patients with schizophrenia often used metaphors in the literal sense, which he interpreted as a "loss of social value and the resort to autistic gratification" (reviewed in Cameron, 1939). To my knowledge, there is only one contemporary published study that formally assessed concrete thinking among schizophrenia patients (Subotnik et al., 2006); the study authors used the Abstract/ Concrete Rating System (Marengo, Harrow, Lanin-Kettering, & Wilson, 1986) based on the Gorham Proverbs (Gorham, 1956); three sets of 12 proverbs each) as part of a larger battery of tests, and reported that impairments in verbal learning and immediate auditory memory, and intrusion errors were associated with concrete responses, while patients with intact verbal learning and memory were correlated with abstract responses. The study did not have a healthy comparison group, and only the mean raw score on the Abstract/ Concrete Rating System was reported, so there was no way to assess the level of impairment in the schizophrenia sample with relation to expected norms.

One of the earliest documented theories of thought processes related to novel concept formation in schizophrenia was put forth by Vygotsky in the late 1920s (translated by Kasanin, 1934). Vygotsky's model was based on his extensive work in the area of development of thought process in children, and he compared the thought processes of individuals with schizophrenia to those of children, which he termed as "complex." (His definition of "complex" is counterintuitive: he defined it as "simple elementary generalization.") He posited that his way of thinking transitioned to a more mature, conceptual way of thinking in adolescence in normal development, but that it was disrupted in individuals with schizophrenia, noting that "the most important

deterioration of thought occurring in schizophrenia is a disturbance, an impairment, in the function of formation of concept." (p. 1065).

There have been numerous attempts at measuring abstract thinking and concept formation in schizophrenia since the early 1920s. Cameron (1938, 1939) used the block categorization task developed by Hanfmann and Kasanin (1942; described in section 2.3.1.), with a minor modification, i.e., he asked subjects to verbalize their thought process while forming the categories. He published several reports on studies using this method to characterize the nature of problem solving patients with schizophrenia (Cameron, 1939), and concluded that thought processes in schizophrenia were distinct from those in healthy children, as well as those with dementia. He reported that schizophrenia patients were unable to block out peripheral characteristics ("fringe-elements") of the stimuli to be categorized, and demarcate boundaries between properties of objects, and therefore tended to form loosely organized, over-inclusive categories with essential links between the objects missing.

Fey (1951) published the first study using the WCST with schizophrenia patients, but it was the relatively recent publication of the study by Weinberger and colleagues (Weinberger, Berman, & Zec, 1986) demonstrating that performance on the WCST activated the dorsolateral prefrontal cortex in healthy comparison subjects, but not in patients with schizophrenia that triggered an overwhelming interest in the use of the test. There are several hundred recent reports of studies that have examined WCST performance in schizophrenia (a PubMed search done on 8/8/07 revealed 172 articles in just the past 5 years), including several meta-analytic reviews. Heinrichs and Zakzanis (1998) reported a moderately large effect size (d = .95) of the WCST, but significant correlation with performance on IQ tests [r (33) = -.54, p<.01], suggested that poor performance on the test may be a reflection of low general intellectual abilities. [Of note, many other ability areas/ tests had higher effect sizes, the highest being Global Verbal Ability (d = 1.53), followed by Performance IQ (d = 1.46), and Bilateral Motor Functions and Nonverbal Ability (both ds = 1.42).]   The association between the WCST and IQ has been echoed by Laws (1999), who further broke down effect size analyses to processes on the WCST; he reported moderate to

moderately high effect sized for categories achieved (*d* = 0.91), and total perseverative

responses (*d* = 0.53) but small effects for perseverative errors (*d* = 0.18). He also reported that

the effect size of the WAIS far exceeded in strength than any of the WCST variables, i.e., *d* =

1.23, therefore concluding that executive functioning in schizophrenia in fact is not

disproportionately impaired compared to I.Q., and may reflect a generalized deficit.

There are also some studies that report contradictory findings in regard to WCST

impairment above and beyond a generalized deficit; for example, Goldberg and colleagues

(Goldberg, Weinberger, Berman, & Pliskin, 1987) demonstrated that even patients with

schizophrenia who received step-by-step, explicit instructions, did not learn how to do the WCST,

but were able to learn word-lists on the Selective Reminding memory test. The authors concluded

that neurocognitive deficits mediated by the prefrontal cortex, such as novel problem solving,

tended to be more impaired in schizophrenia than other domains. Another meta-analysis

indicated that patients with schizophrenia on average had a greater frequency of both

perseverative and random errors, and that both schizophrenia patients and normal comparison

subjects tended to make more perseverative errors than random errors (Li, 2004). The author

cautioned against attributing to poor WCST performance of schizophrenia patients to impairment

in set-shifting or response inhibition, instead, suggesting that it may be a function of attention and

working memory deficits associated with schizophrenia. Goldman-Rakic (1994) and others have

also suggested that working memory deficits may underlie impaired WCST performance in

schizophrenia. Gold and colleagues (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997)

further broke down the WCST variables, and found that performance on Letter-Number

Sequencing predicted the number of categories achieved on the WCST, while performance on

measures of set-shifting, verbal fluency, and attention were good predictors of perseveration.

The Category Test (described in section 2.3.1.) yields consistently poor performance (i.e.,

higher frequency of errors) among patients with schizophrenia compared to healthy comparison

subjects, which is sometimes on par with the performance of persons with chronic brain damage

(reviewed in Choca et al., 1997). Difficulties with this test have been attributed to the impairments

in sustained attention and mental control (needed to utilize the examiner's feedback in order to maintain or change the examinee's strategy on an item in a particular set of items), but given that the current scoring system does not include process measures similar to the WCST (particularly, perseverative responses, and set failures), it is difficult to determine the precise nature of the deficits.

The California Card Sorting Test (CCST), the original version of the current D-KEFS Sorting Test (described in section 2.3.1.) was recently used in a study to characterize the nature of abstraction and concept formation in patients with schizophrenia or schizoaffective disorder (Beatty, Jocic, Monson, & Katzung, 1994). Authors reported that the patient group did not differ from the healthy comparison group on the total number of sorts, and non-perseverative errors, but that they did significantly worse on the proportion of correct sorts, and perseverative errors. Patients also did poorly on verbal explanations of how they sorted the cards, which also tended to be more perseverative, as compared to the controls.

4.1.2. *Cognitive Flexibility*

Part B of the Trail Making Task is generally thought to represent cognitive flexibility, and patients with schizophrenia tend to do poorly when compared to healthy comparison subjects on this task (Braff et al., 1991; Saykin, Gur, Gur, & Mozley, 1991). Trails B has long been considered to be highly sensitive to frontal lobe lesions (Stuss & Benson, 1986), but given its dependence on several other functions, e.g., motor speed, and sequencing, besides switching, the processes underlying the impairment are unclear. Heaton and colleagues (Heaton, Nelson, Thompson, Burks, & Franklin, 1985) suggested examining the differential performance between Trails A and B in order to control the motor and sequencing components, and while this method has hardly been used in current neuropsychological research, the D-KEFS version of the Trail Making Test has several components that help parse out the various contributory processes (see section 3.1.1., *Table 3.1.*).

4.1.3. Planning

The various versions of the Tower task are especially popular ways in which planning is operationalized, and as described in section 2.3.3., besides planning, tap into response inhibition, working memory, and motor speed. Compared to the other subdomains of executive functioning, there has been little research on planning in schizophrenia, but there is some evidence that it may be impaired compared to healthy comparison subjects in all parameters of the task, i.e., many more moves, including disallowed moves, and fewer perfect trials (Goldberg, Saint-Cyr, & Weinberger, 1990). However, they improved to near-perfect levels with repeated exposures to the Tower, suggesting the ability to learn a procedure, which in turn points toward relative sparing of the basal ganglia compared with the prefrontal cortex in schizophrenia. (Of note, one could argue that this procedure changes the nature of the test by removing its novelty, and hence does not measure an executive function at all.)

Mazes have typically been used to study planning in children (largely owing to its inclusion in the Wechsler Intelligence Scale for Children), but one study that used mazes of varying levels of difficulty with a unique group of first-episode patients with schizophrenia, some of whom were neuroleptic-naïve, while others were on medication for five weeks (Krieger, Lis, & Gallhofer, 2001). The authors reported considerable impairments, characterized by repeated encounters with dead-ends, and longer routes to the goal in their schizophrenia sample, compared with healthy subjects. They, however, reported improvements with repeated exposure to the mazes in the neuroleptic-naïve group, with relatively smaller improvements in the medicated group of patients.

4.1.4. Fluency

Patients with schizophrenia tend to do poorly on word production tasks, such as the Thurstone Word Fluency Test, COWAT and Category (Animals) fluency compared to healthy comparison subjects (Bokat & Goldberg, 2003; Heinrichs & Zakzanis, 1998), which is generally attributed to the retrieval difficulties in schizophrenia In a meta-analysis of studies measuring both

phonemic and semantic fluency deficits in schizophrenia, Henry and Crawford (Henry & Crawford, 2005) found that both had moderate effect sizes, with significantly larger effects for semantic fluency (mean effects = .43 and .49, respectively). Bokat and Goldberg also found this difference between semantic and phonemic fluency, although their overall effects were higher (1.27 and 0.99, respectively). Authors of both meta-analyses have inferred that the greater semantic fluency deficit is a result of the disruption of the semantic store in addition to general retrieval deficits in schizophrenia.

Moore and colleagues (Moore, Savla, Woods, Jeste, & Palmer, 2006) examined the clustering and switching mechanisms underlying verbal fluency in schizophrenia, and found that while patients tended to have intact clustering (defined as the successive generation of words that begin with the same first two letters, differ by a vowel sound, or are homonyms in phonemic fluency tasks, and those belong to the same subcategory in the semantic fluency task), they demonstrated considerable impairments in switching between clusters compared with healthy comparison subjects.

4.1.5. *Response Inhibition*

One of the most common measures of response inhibition is the Stroop task, particularly the color-word interference trial. The first published study of the Stroop in schizophrenia was done in 1960 by Wapner and Krus, in which they demonstrated that patients with schizophrenia did worse than healthy comparison subjects on the word reading, color naming and color-word interference trials. Subsequent research since then has shown that patients with schizophrenia, on average, tend to have a greater number of errors and a slower speed on the interference task, not only compared to healthy subjects, but also compared to their own performance on the other two trials (Perlstein, Carter, Barch, & Baird, 1998). This finding has been attributed to increased attentional demands (therefore implicating the SAS, described in the following section), as well as inability to self-monitor in order to inhibit the more automatic response. An interesting finding from studies using the Stroop is that schizophrenia patients show

augmented facilitation, i.e., faster-than-normal responding the color-congruent, color naming trial when compared to the neutral, word reading trial (Henik & Salo, 2004; Perlstein et al., 1998).

4.1.6. *Working Memory*

As discussed in section 2.3.6., the SAS system of working memory is considered to be a part of executive functions, and while tests measuring the phonological loop and visuospatial sketchpad systems are often included under the executive functioning domain, they may be better conceptualized as measures of working memory. Nonetheless, patients with schizophrenia tend to do poorly on measures of SAS as well as the phonological loop. (reviewed by Oram, Geffen, Geffen, Kavanagh, & McGrath, 2005). Studies have also demonstrated that visuospatial working memory in patients with schizophrenia, examined by means of a delayed response task is severely impaired (Park & Holzman, 1992).

Table 4.1. Summary of Literature on Executive Functions in Schizophrenia

Measures	*Types/ Level of Impairment in Schizophrenia*
Gorham Proverbs (1 study)	Impaired verbal learning and immediate auditory memory, intrusion errors = concrete responses
WCST (meta-analyses)	d = .95; significantly related to I.Q. tests [r(33) = -.54, p<.01] (Heinrichs & Zakzanis, 1998) d = .91 (categories achieved), d = .53 (perseverative responses), d = .18 (perseverative errors) (Laws, 1999)
Category Test (review)	Higher number of errors than HC
California Card Sorting Test (1 study)	Relatively poor verbal explanations of sorts, perseverative compared with HC. No difference on number of sorts, non-perseverative errors
Trail Making Test Part B (multiple studies)	Longer time to complete relative to HC
Fluency (meta-analyses, study)	d = .43 (letter fluency), d = .49 (semantic fluency) (Henry & Crawford, 2005) d = 1.27 (letter fluency), d = .99 (semantic fluency) (Bokat & Goldberg, 2003) intact clustering, impaired switching
Stroop (multiple studies)	Greater number of errors, slower speed on interference task relative to HC Faster reading speed on color-congruent trial than HCs

Table 4.2. *Commonly Used Measures of Executive Functions and Related D-KEFS Tests*

Test	Constructs Measured		Related D-KEFS Test
	Executive Functioning	Others	
Proverbs	Abstraction	Verbal Expression, Vocabulary	Proverb Test Word-Context Test
Wisconsin Card Sorting Test	Problem-Solving Novel Concept Formation Set-Shifting/ Cognitive Flexibility Working Memory	Attention	Sorting
Category Test	Problem-Solving Concept Formation Cognitive Flexibility	Sustained Attention	Sorting
Matrix Reasoning	Abstraction Logical Reasoning	Visuospatial Functioning	None
Picture Arrangement	Sequencing Logical Reasoning	Verbal Expression	None
Trail Making Test	Part A = Sequencing Part B = Sequencing, Working Memory, Set Switching	Motor Speed, Visual Attention and Scanning	Trail Making Test
Mazes	Planning Working Memory		None
Tower of London/ Hanoi	Planning		Tower Test
COWAT	Fluency Set Maintenance	Initiation, Vocabulary, Intact Verbal Learning	Verbal Fluency
Category Fluency	Fluency Set Maintenance	Initiation, Vocabulary, Semantic Memory	Verbal Fluency
Ruff Figural Fluency	Fluency Cognitive Flexibility Working Memory	Motor Speed, Attention	Design Fluency
Stroop tasks	Response Inhibition, Working Memory	Attention, Reading, Intact Visual Acuity, Color Perception	Color-Word Interference Test
Digit Span Backward	Working Memory	Attention	None
Letter-Number Sequencing	Working Memory, Sequencing	Intact Verbal Learning	None

4.2.   Relationship of executive functions to everyday functioning

Schizophrenia causes disability in the majority of people affected by the illness (Velligan, Bow-Thomas, Mahurin, Miller, & Halgunseth, 2000), and one of the strongest predictors of poor everyday functioning is cognitive impairment (Green, 1996). Retrospective studies of people with schizophrenia have suggested that subnormal functioning may precede onset of active illness; for example, children who go on to develop the illness often do less well in school than those who do not, and may have difficulties forming social relationships (e.g., Bilder et al., 2006; Kremen et al., 1998). There is little known about the unique effects of impairment in specific executive functions to adaptive functioning in schizophrenia, especially because of the complex nature of the illness, concomitant deficits in other cognitive domains, and emotional/ psychiatric symptoms. However, studies with more homogeneous clinical populations, such as people with focal brain lesion studies, have demonstrated that intact executive functions are indispensable to optimal adaptive everyday functioning (Lezak et al., 2004; Luria, 1966).

Of the few studies that have attempted to relate specific executive functions to aspects of everyday functioning, the WCST emerges as a useful predictor of illness awareness, medication compliance, quality of occupational functioning, and independence in performing instrumental activities of daily living (Green, 1998; reviewed by Velligan & Bow-Thomas, 1999). Impaired performances by schizophrenia patients on the Stroop and COWAT appear to be related to the level of independent living, but not to quality of work or social functioning (Brekke, Raine, Ansel, & Lencz, 1997). Also, there are some assertions that working memory and other executive functions are particularly important to decisional capacity, but a recent review of cognitive correlated of decision-making capacity indicated that while cognitive deficits have a more deleterious effect on decisional capacity than do the primary psychiatric symptoms, no particular cognitive abilities, including executive functions, stood out clearly as consistently unique predictors of overall decisional capacity (Palmer & Savla, in press). Studies examining predictors of success in cognitive and/ or vocational rehabilitation have also highlighted the importance of executive functions in general, in terms of skill acquisition, and attaining and maintaining

employment (Evans et al., 2004; McGurk, Mueser, Walling, Harvey, & Meltzer, 2004; McGurk &

Mueser, 2006).

5. Current Study

5.1. Aims and Hypotheses

<u>Aim 1:</u> To evaluate the types and levels of impairment in executive functions among individuals with schizophrenia.

<u>Rationale:</u> Schizophrenia is widely recognized as a neurocognitive disorder, and executive function deficits are among the strongest predictors of functional disability in people with the illness. However, given that "executive functions" potentially refer to a number of more distinct processes, it is important to examine the level and severity of these processes among patients with schizophrenia, and the relationship of these processes with other basic cognitive functions.

<u>Hypothesis 1.1.</u> People with schizophrenia, on average, have lower executive functioning abilities than do demographically comparable neuropsychiatrically healthy individuals.

<u>Hypothesis 1.2.</u> Relative to the pattern among neuropsychiatrically healthy individuals, people with schizophrenia show greater discrepancy between basic/component skills and multi-level executive skills, i.e., relative to their own basic abilities, schizophrenia patients have more marked impairment in executive functions.

<u>Exploratory Corollary Analysis for Aim 1:</u> We will use Latent Profile Analysis to examine possible patterns of performance on the different executive functioning components of the D-KEFS tests among individuals with schizophrenia.

<u>Aim 2:</u> To investigate the degree to which the executive functions, as measured by the D-KEFS, have shared versus independent components in schizophrenia.

Rationale: While it is generally acknowledged that schizophrenia is associated with impairments in multiple neurocognitive domains, it has been difficult to parse out ability areas that might be differentially impaired from a generalized cognitive deficit.

Hypothesis 2.1. By means of an Exploratory Factor Analysis (EFA), we expect to find that cognitive flexibility, abstraction, planning, and response inhibition are independent constructs in schizophrenia.

Hypothesis 2.2. Among people with schizophrenia, intact cognitive flexibility is contingent upon intact working memory. Also, intact sorting ability, and verbal reasoning is contingent upon intact simple abstraction.

Aim 3: To determine whether specific executive functions are associated with psychopathology, functional capacity, and everyday functioning among patients with schizophrenia

Rationale: Given the relationship of neurocognitive abilities to disease burden and functional disability in schizophrenia, the current study will also examine the unique relationships (if any) of the specific executive functions with psychopathology, and daily functioning.

Hypothesis 3.1. Executive functions are strongly associated with thought disorder, and negative clinical symptoms, but not with positive symptoms in schizophrenia.

Hypothesis 3.2. Executive functions have moderate to strong relationships with functional capacity. Cognitive flexibility is the strongest predictor of quality of life, and the level of independence in living situation.

5.2.   Method

5.2.1.   Study Design and Participants

The current study was based on a case-control design (Shadish, Cook & Campbell, 2002), and examined data from 81 community-dwelling outpatients with schizophrenia or schizoaffective disorder (SC), age 18 and over, and demographically-matched healthy comparison subjects. We decided to include patients with schizoaffective disorder, because of the existing evidence that there are minimal clinical and neurocognitive differences between schizophrenia and schizoaffective disorder, and because schizoaffective disorder is a subtype of schizophrenia (Evans, Heaton, Palusen, McAdams, Heaton, et al., 1999; Palmer & Savla, in press).

The neuropsychiatrically healthy controls (HC) were matched on an individual basis with the schizophrenia sample, first on age (+/- 2 years), then education (+/- 1 year), ethnicity, and finally, gender, in that order of priority. The author remained blind to any neuropsychological test scores during the matching process.

This study was partly based on a secondary analysis of existing data from individuals with schizophrenia or schizoaffective disorder who have participated in several ongoing studies at the University of California, San Diego (UCSD). Inclusion criteria for the parent studies were: (1) Presence of a schizophrenia-spectrum or primary psychotic disorder; (2) age 18 or older at the time of enrollment; and (3) the ability to give written, informed consent to participate in the studies. Exclusion criteria for the parent and current studies were (1) a concurrent DSM-IV diagnosis of dementia at the time of enrollment; (2) a diagnosis of delirium at the time of enrollment; or (3) report of substance use within 3 months prior to enrollment.

For the current study, data from only those participants from the parent studies with a DSM-IV Diagnosis of schizophrenia or schizoaffective disorder were used; Diagnoses are determined by the patients' treating psychiatrists clinically and/or by means of a SCID, and confirmed via chart reviews by trained research associates.

Data from 64 participants were available at the time the study was proposed, and data from 17 more participants became available between December 2007 and March 2008 (total N = 81). Participants in the schizophrenia sample were primarily recruited from the UCSD Outpatient Psychiatry Clinic, or the VA San Diego Healthcare System. The comparison sample (HC) was obtained from the D-KEFS standardization sample database, which consists of 916 neuropsychiatrically healthy adults (age 18 and over), recruited as part of a nationwide, multisite study for the standardization of the D-KEFS.

5.2.2. Assessment

5.2.2.1   Demographic and Diagnostic Information

All participants' age, highest level of education, gender, ethnicity, and living situation (each patient's community residential setting on a scale from 1 to 4, with 4 representing the highest independence in living; alone in an apartment =4, alone in a house = 4, with other(s) in an apartment = 3, with other(s) in a house = 3, board and care facility = 2, other assisted living facility = 2, and homeless = 1 were recorded. For the patient sample, diagnoses were determined by patients' treating psychiatrists, and were confirmed via chart reviews. For the patient sample, age of onset of illness, duration of illness, medication information (current medication type, i.e., conventional, atypical, or both), and past or current psychosocial interventions (if administered), were recorded.

5.2.2.2   Measurement of Psychopathology

Severity of positive symptoms (e.g., hallucinations, delusions) and negative symptoms (e.g. blunted affect, alogia, apathy) were assessed using the Positive and Negative Syndrome Scale (Kay, Opler, & Fiszbien, 1987). The PANSS includes 30 items, each rated from 1 (for "absent") to 7 (for "extremely severe"), and is designed to evaluate severity of positive and negative symptoms and general psychopathology. The positive and negative syndrome

subscales were analyzed separately. The PANSS has been extensively used in schizophrenia samples, and has shown good interrater reliability (upward of >.80) and has good construct, and criterion-related validity (Kay, Opler, & Lindenmayer, 1988). We also examined four items from the PANSS (conceptual disorganization, difficulty in abstract thinking, disorientation, poor attention), whose content relates to thought disorder, as defined by Andreasen (1979). (These items also loaded on a single factor in a PCA done by Higashima and colleagues [1998], albeit on Japanese patients with schizophrenia.) The 17-item Hamilton Depression Rating Scale (HAM-D) was utilized to evaluate the severity of depressive symptoms. Interrater reliability for both instruments, checked every six months is >.90 for individuals administering the questionnaires at the Advanced Center for Innovations and Services in Intervention Research at UCSD, where all the data were collected.

5.2.2.3   Neuropsychological Variables

Data from all nine tests of the D-KEFS were used for this study; these include the Trail making Test, Verbal Fluency Test, Design Fluency Test, Color-Word Interference Test, Sorting Test, Twenty Questions, Word Context Test, Tower Test, and Proverb Test. The D-KEFS is widely recognized as a significant advance in the assessment of executive functions, and has proven to have excellent reliability and other psychometric properties (for a detailed description of the D-KEFS and its tests, please refer to section 3.1.). Table 3.1. (p. 19) lists the tests, the available measures from each test.

The American National Adult Reading Test (ANART) scores of the SCs were converted to WAIS-R estimated premorbid VIQ scores (Grober & Sliwinski, 1991). The ANART was not administered to the HCs, instead, their current VIQ was derived from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

SCs also had data for the WAIS-III Digit Span and Letter Number Sequencing Tests (WAIS-III; Wechsler, 1994), and the UCSD Performance-Based Skills Assessment (Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001), a performance-based measure that uses role-play

scenarios to evaluate everyday functioning in five areas: Shopping, Communication, Finance, Transportation, and Planning Recreational Activities.

5.2.2.4 Adaptive Functioning

The Quality of Life Interview (QOLI; Lehman, 1988) was administered to the SCs to measure their objective and subjective QOL. Two domains of objective QOL were examined based on their relevance to activities of everyday functioning in schizophrenia: daily activities and social relations. Subjective QOL was measured as the mean of two identical general life satisfaction questions (asked at the beginning, and then at the end of the interview), "How do you feel about life in general?," rated on a 1-7 scaled, 1 being "terrible" and 7 being "delighted."

5.2.3. Data Analyses

Hypothesis 1.1. SCs on average, have lower executive functioning abilities, than do HCs.

Dependent Variables: (Raw scores)

Cognitive flexibility:

- Trail Making Test number-letter switching total (time to completion)
- Verbal Fluency category switching total correct (number of responses)
- Design Fluency switching total correct (number of responses)
- Color-Word Interference inhibition/switching total (time to completion)

Verbal abstraction

- Twenty Question Test total achievement
- Word-Context Test total achievement
- Proverb Test total achievement score on free inquiry

Conceptualization and sorting

- Sorting Test confirmed correct sorts on free sorting

Response inhibition

- Color-Word Interference inhibition (time to completion)

Independent Variables:

- Diagnostic Group (SC vs. HC).

Statistical Methods: A between-subjects (1 factor [diagnostic status], 2-level [SC vs. HC]) Multivariate Analysis of Variance (MANOVA) using SPSS (version 16.0) was conducted (given that all dependent variables were correlated with at least one other variable at $r = |.4|$ or higher. Given the interrelatedness of the multiple DVs, a MANOVA was more appropriate than separate ANOVAs in order to protect against Type I error.

Post-hoc Analysis: A MANOVA between participants with schizophrenia and those with schizoaffective disorder within the SC sample as conducted to explore possible differences on the 10 D-KEFS tests.

Hypothesis 1.2. Relative to the pattern among HCs, SCs show greater discrepancy between basic/component skills and multi-level executive skills, i.e., relative to their own basic abilities, SC have more marked impairment in executive functions.

Dependent Variables:

Difference Scores, i.e., scaled score on multilevel task – scaled score on each basic component task for each test.

Trail Making Test

- Multilevel skills: Completion times for Number-Letter Switching
- Basic components: Completion times for Visual Scanning, Number Sequencing, Letter Sequencing, Motor Speed

Verbal Fluency Test

- Multilevel skills: Total correct for Category Switching
- Basic components: Total correct for Letter and Category Fluency

Design Fluency Test

- Multilevel skills: Total correct for Switching
- Basic components: Total correct Filled Dots and Empty Dots Only

Color-Word Interference

- Multilevel skills: Completion times for Inhibition and Switching

- Basic components: Completion times for Color Naming, Word Reading, Inhibition
  (Switching)

Independent Variables:

- Diagnostic Group (SC vs. HC).

Statistical Methods: A between-subjects (1 factor [diagnostic status], 2-level [SC vs. HC])

Multivariate Analysis of Variance (MANOVA) was conducted, given expected inter-relatedness of

the dependent variables.

Exploratory Corollary Analysis for Aim 1: We will use Latent Profile Analysis (LPA) to examine

possible patterns of performance on the different executive functioning components of the D-

KEFS tests among SCs.

Variables to be used in LPA:

- Scaled scores of all executive functioning components of D-KEFS tests (See list of DVs
  for Hypothesis 1.1.).

Statistical Analysis: Latent profile analysis (LPA) using Mplus (version 5.0; Muthén & Muthén,

2007) was used to examine the patterns of performance on the D-KEFS executive functioning

components, as it allows for both the measurement of specific functions, while simultaneously

creating patterns or typologies of executive functioning performance.

LPA utilizes all observations that are associated with the dependent variables, and

performs maximum likelihood estimation (Little & Rubin, 1987). It also allows for the probability of

an individual's membership in an executive functioning profile to be estimated in the same model

as the estimation of that profile (Hill, Degnan, Calkins, & Keane, 2006). The flexibility of LPA

accounts for the likelihood that there is uncertainty in class membership and allows for both

prediction of the probability of membership in a particular group while simultaneously estimating

the executive functioning classes. Consequently, each individual's probability of class

membership can be estimated so the person may be classified into the most appropriate class (Hill, Degnan, Calkins, & Keane, 2006). Although the points of the distribution are occupied by individuals in different latent classes, it is up to the analysis interpretations, in light of possible covariates and substantive theory, to decide if these classes can be seen as substantively different categories or simply representing a single, non-normal distribution (Muthén, 2006).

Post-hoc Analyses: ANOVAs were conducted to examine the demographic and clinical differences between the groups of people classified into different patterns of performance by the LPA. We also conducted ipsative, within group (descriptive) comparisons of the subjects' performances on the individual D-KEFS tasks with each subject's respective mean score.

Hypothesis 2.1. By means of an Exploratory Factor Analysis (EFA) we expect to find that cognitive flexibility, abstraction, planning, and response inhibition are independent constructs in schizophrenia.

Variables to be entered in EFA:

- Normal scores (z-scores) of ten executive functioning components of D-KEFS tests (See list of DVs for Hypothesis 1.1.)

Statistical Methods: Exploratory factor analyses using principal axis factoring with direct oblimin rotation in SPSS (version 16.0) were conducted to explore the dimensionality of the ten D-KEFS multi-level skills. The variance accounted for by the solution, the variance accounted for by each individual factor, and the interpretability of the factors were all evaluated to determine the initial plausibility of the factor structure. A parallel analysis was used to further confirm the factor structure.

Post-hoc Analysis: An EFA was also conducted on the performances on the ten D-KEFS tasks among the healthy comparison sample in order to compare the factor structures between the two samples.

Hypothesis 2.2. Among people with schizophrenia, intact cognitive flexibility is contingent upon intact working memory. Also, intact sorting ability, and verbal reasoning is contingent upon intact simple abstraction.

Independent variables (exogenous variables):

- Schizophrenia diagnosis

Mediator variables:

Working Memory

- WAIS-III Digits Span
- WAIS-III Letter-Number Sequencing

Verbal abstraction

- Proverb Test total achievement score (scaled score)

Dependent variables (ultimate endogenous variables):

Cognitive flexibility

- Switching components of Trail Making Test, Verbal Fluency, Design Fluency, and Color-Word Interference Test (mean scaled score)

Sorting

- Sorting Test confirmed correct sorts on free sorting (scaled score)

Logical reasoning

- Twenty Question Test total achievement weighted score, and Word-Context Test total achievement (mean scaled scores)

Statistical Methods: Path analytic models using Mplus were used to examine the relationships specified in Hypothesis 2.2. Hypothesized path diagrams are as follows:
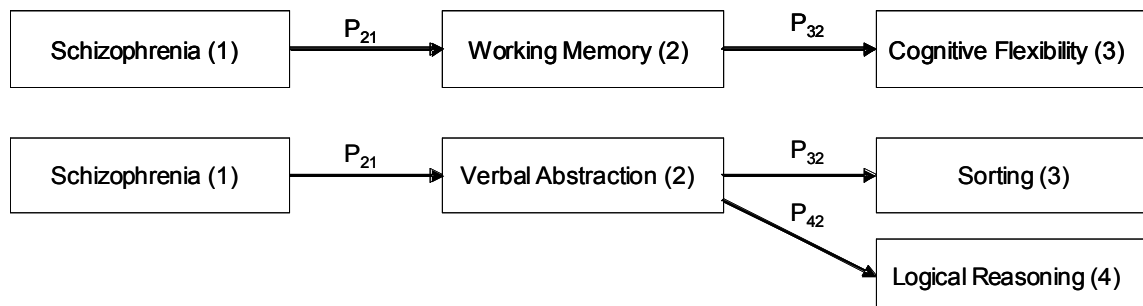
Figure 5.1. Path Diagram for Hypothesis 2.2.

<u>Hypothesis 3.1.</u> Executive functions are strongly associated with thought disorder, and negative clinical symptoms, but not with positive symptoms in schizophrenia.

<u>Independent variable (exogenous variable):</u>

- Schizophrenia diagnosis

<u>Mediator variables:</u>

Positive and Negative Symptoms

- PANSS positive symptom total, PANSS negative symptom total

Thought Disorder

- Four items on PANSS: conceptual disorganization, difficulty in abstract thinking, disorientation, poor attention (see section 5.2.2.2., p. 45)

<u>Dependent variables (ultimate endogenous variable):</u>

- All executive functioning *components* of D-KEFS as determined by EFA. Performance on each component determined by averaging the scaled scores of individual executive functioning measures of the D-KEFS (see section 5.2.2.3.).

Statistical Analysis: Path analytic models using Mplus were used to examine the unique relationships between the variables, as specified in Hypothesis 3.1. Hypothesized path diagrams are as follows:
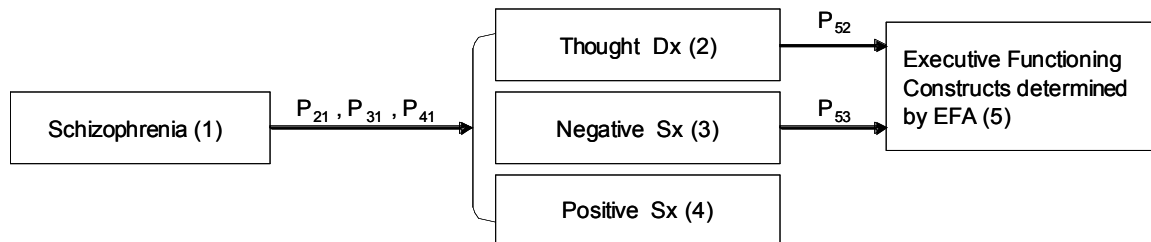
Figure 5.2. Path Diagram for Hypothesis 3.1.

Hypothesis 3.2. Executive functions will have moderate to strong relationships with functional capacity. Cognitive flexibility is the strongest predictor of quality of life, and level of independence in living situation.

Variables to be correlated:

Executive Functioning Components

- All executive functioning components of D-KEFS as determined by EFA. Performance on each component determined by averaging the scaled scores of individual executive functioning measures of the D-KEFS (see section 5.2.2.3.).

Functional Capacity

- UPSA Total score (out of 100)
- UPSA subscale scores: Recreational Planning, Shopping, Financial Skills, Communication, Transportation (each out of 20)

Quality of Life

- Quality of Life Questionnaire
    - Subjective QOL (mean of "general life satisfaction" rating)
    - Objective QOL: Daily Activities and Social Relations (z-scores within each domain)

Level of Independent Living

- See section 5.2.2.1.

Statistical Analyses: Correlational analyses were used to test Hypothesis 3.2.The hypothesis that cognitive flexibility is the strongest predictor of quality of life, and level of independent living was tested using general linear models.

Supplementary Post-hoc Analyses:

      To further explore the results found on the post-hoc analysis of the LPA, separate MANOVAs for the HC and SC samples were conducted to examine whether there were any differences between Caucasian and non-Caucasian subjects on the ten D-KEFS tests (see Hypothesis 1.1.).

6.   Results

Description of the samples:

Baseline demographic, clinical, and neurocognitive characteristics are provided in Table 6.1. The majority of the combined sample had completed a high school education (43.2 % of SCs and 45.7% of HCs). The mean scores on the PANSS positive and negative symptoms (evaluated in the SC sample only) indicated mild severity of psychopathology at the time of testing. Estimates of premorbid verbal IQ (or for HCs, actual current verbal IQ) indicated that premorbid verbal functioning of the SC sample was on the average range, and similar to the current level of verbal functioning in the HCs.

A little over 50% of our schizophrenia sample consisted of patients with schizoaffective disorder. We did not expect to find any demographic or clinical differences between participants with schizophrenia and those with schizoaffective disorder, and our assumption was statistically supported by t-tests conducted on relevant demographic and clinical variables, as well as on ANART-estimated VIQ.

The distributions of all variables were checked for the presence of significant skewness or kurtosis, and none of the variables required transformation to meet assumptions for parametric analyses.

Table 6.1. Description of the Schizophrenia and Neuropsychiatrically Healthy Comparison Samples

		Schizophrenia (N = 81)	Healthy Comparison (N = 81)
		Mean (SD) or %	Mean (SD) or %
Age at testing (years)		48.5 (10.3)	48.4 (10.3)
Education level (years)	≤8 9-11 12 13-15 ≥16	1.9 12.3 43.2 22.8 19.8	2.5 9.9 45.7 21.0 21.0
Gender (%)	Women Men	38.3 61.7	51.9 48.1
Ethnicity (%)	Caucasian African American Latino Other	66.7 14.8 12.3 6.2	80.2 9.9 6.2 3.7
Living Situation (%; Patients Only)	Alone in Apartment Alone in House In Apartment with Someone In House with Someone Board and Care Other Assisted Living Homeless	28.8 1.3 20.0 26.3 16.0 4.0 2.5	Not Available
Verbal IQ	ANART Estimated for Patients WASI VIQ for Controls	108.4 (9.7)	 101.23 (15.6)
Diagnosis (%)	Schizophrenia Schizoaffective Disorder	47.0 53.0	
Age of Onset of Illness (years)		24.5 (10.2)	
Duration of Illness (years)		23.4 (12.3)	
PANSS Positive Symptom Score	(7 items; Min: 7) Range of Scores: 1 (Absent) – 7 (Severe)	15.6 (5.7)	
PANSS Negative Symptom Score	(7 items; Min: 7) Range of Scores: 1 (Absent) – 7 (Severe)	15.4 (5.6)	
PANSS-Derived Thought Disorder Score	(4 items; Min: 4) Range of Scores: 1 (Absent) – 7 (Severe)	7.8 (3.0)	
Hamilton Depression Rating Scale (17-item total)	(17 items; Min: 0)	11.4 (6.8)	
Type of Antipsychotic Medication	Conventional Atypical Both None	3.7 86.4 3.7 6.2	

6.1. *Aim 1: Characterization of executive functioning impairment in schizophrenia*

<u>Comparison between the SC and HC samples on the D-KEFS executive functioning measures</u>
<u>(See Hypothesis 1.1., p. 41):</u>

Bivariate correlations among the ten D-KEFS executive functioning measures were
moderate-to-high in the expected direction (ranging from .404 for Proverb total achievement raw
score and Color-Word Inhibition raw score to -.721 for Color-Word Switching and Color-Word
Inhibition), with all correlations being significant at the .<001 level. Given that all variables were
correlated at $r \geq |.4|$, a MANOVA was conducted to examine the differences in performance on
the executive functioning measures between the patients and healthy comparison subjects. Using
an alpha level of .001 to evaluate homogeneity assumptions, Box's M test of homogeneity of
covariance for the was statistically significant (p <.001). (However, given the equal sample sizes,
robustness of significance tests is expected, and the result of the Box's M test may be
disregarded; Tabachnick & Fidell, 2001). Furthermore, Levene's homogeneity of variance test
was statistically significant for Trails Switching and Twenty Questions only (both ps <.001).Using
Wilks' λ as the omnibus test statistic, the combined DVs resulted in a significant main effect for
diagnostic group (SC *vs.* HC), $F(10, 151) = 5.86$, p <.001, partial η^2 = .280, indicating that the
effect size of diagnostic category on performance was in the range traditionally considered to be
"large" (Cohen, 1988). To determine which specific variables underlay the statistically significant
multivariate effect, follow-up univariate ANOVAs were conducted on each individual DV (see
Table 6.2., Figure 6.1.). As hypothesized (Hypothesis 1.1.), there were significant differences
between the SC and HC groups on all ten DVs, with patients consistently performing worse than
HC subjects. Effect sizes for the individual DVs ranged from small (for Twenty Questions and
Sorting) to large (for Trails Switching).

Given the large proportion of patients with schizoaffective disorder within the SC sample,
we conducted a post-hoc, exploratory MANOVA to examine whether there were any differences
on the D-KEFS tasks between the two subgroups. The Wilks' λ omnibus test statistic indicated

that there were no significant differences between the two groups on the combined DVs: $F(10,$

$70) = 1.13$, $p = .351$, partial $\eta^2 = .139$.

Table 6.2. Differences between the SC and HC Samples on D-KEFS tasks (Raw Scores)

DVs	Mean (SD)		Between-Subjects Effects		
	HC	SC	F (1,160)	p	Partial η^2
Trails N-L Switching[#]	85.3 (29.9)	129.4 (54.7)	40.5	<.001	.202
Verbal Fluency Switching Correct	13.3 (2.7)	11.5 (2.9)	16.4	<.001	.093
Design Fluency Switching Correct	7.5 (3.1)	5.6 (2.4)	19.3	<.001	.107
C-W Inhibition[#]	60.4 (17.1)	74.0 (22.1)	19.1	<.001	.106
C-W Switching[#]	67.7 (21.3)	79.9 (24.9)	11.2	.001	.065
Sorting Confirmed Correct	8.6 (3.3)	7.3 (2.8)	7.1	.008	.043
Twenty Questions	28.7 (13.8)	24.9 (14.4)	5.9	.016	.036
Word Context	24.3 (6.2)	19.0 (7.9)	22.3	<.001	.123
Tower	16.2 (4.5)	13.2 (5.0)	16.0	<.001	.091
Proverb	23.4 (6.7)	19.5 (6.3)	14.3	<.001	.082

[#]Lower numbers indicate better performance (measured in time to complete task)
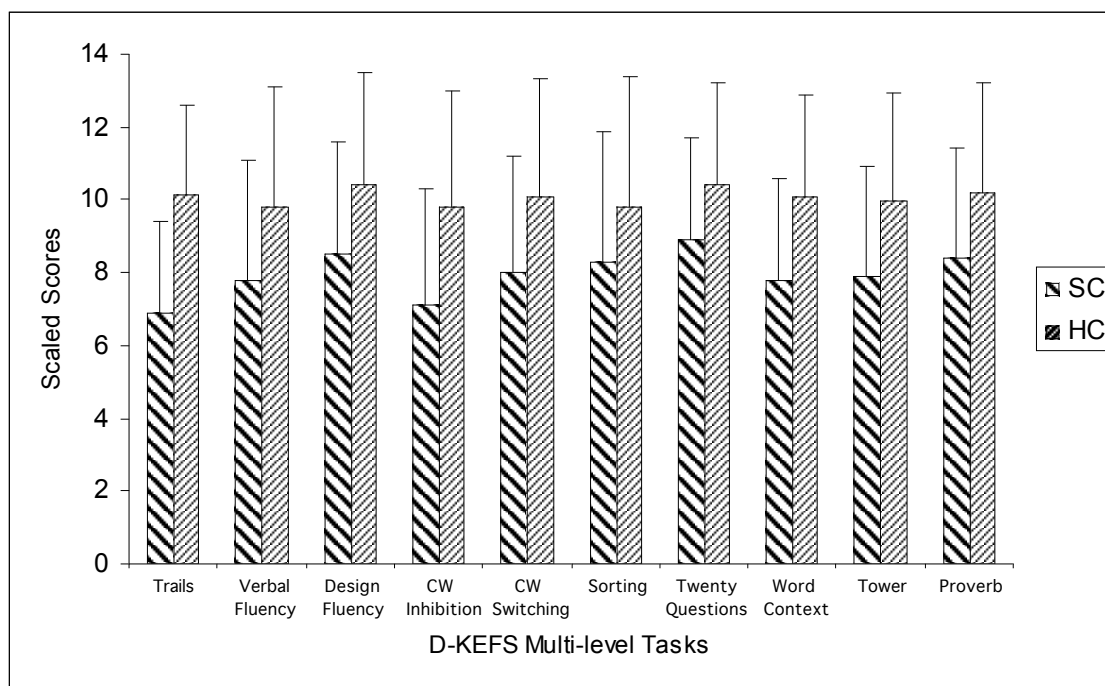
Figure 6.1. Differences between SCs and HCs on D-KEFS Tasks (Scaled Scores)

Comparison between the SC and HC samples on the differences between multi-level and basic

skills on the D-KEFS (see Hypothesis 1.2., p. 41):

As shown in Table 6.3., ipsative differences between the multi-level and basic skills for four D-KEFS tasks were calculated by subtracting the scaled scores of the basic skills from each multi-level skill. Bivariate correlations among the 13 difference scores were moderate-to-high, ranging from .418 to .756 and in the expected direction (all ps < .001). A MANOVA was therefore conducted to test the hypothesis (1.2) that the differences between the multi-level skills and basic skills are greater among the SCs than among the HCs.

Levene's homogeneity of variance test was statistically significant only for the scaled score difference between Design Fluency Switching and Empty Dots Only (p <.001), indicating that the variances between the SC and HC groups for that task were different. Using Wilks' λ as the omnibus test statistic, the combined DVs resulted in a significant main effect for diagnostic group (SC *vs.* HC), $F(11, 150) = 3.52$, p <.001, partial $\eta^2 = .205$, which is considered to be within the range of a large effect size (Cohen, 1988).Follow-up univariate ANOVAs indicated that some, but not all individual DVs were statistically significant; SC patients showed greater disparities than the HC subjects between each of the basic skills for the Trail Making Test and the switching (i.e., multi-level) task (all ps <.05). This was also true for the scaled score difference between the Color-Word Inhibition task and the Words only task (p = .012). Effect sizes for all DVs ranged from nil to .134.

Table 6.3. Ipsative difference scores between multi-level skills and basic skills for Trails, Verbal and Design Fluency, and Color-Word Interference between SC and HC samples

DVs	Mean (SD)		Between-Subjects Effects		
	HC	SC	$F(1,160)$	p	Partial η^2
Trails Switching – Scanning	**.4(3.3)**	**-1.5 (4.1)**	**10.3**	**.002**	**.060**
Trails Switching – Number Sequencing	**.1 (2.9)**	**-1.9 (3.6)**	**15.4**	**<.001**	**.088**
Trails Switching – Letter Sequencing	**-.1 (2.5)**	**-1.0 (3.1)**	**4.2**	**.041**	**.026**
Trails Switching – Motor Speed	**.3 (3.2)**	**-2.4 (3.8)**	**24.7**	**<.001**	**.134**
Verbal Fluency Switching## – Letter	-.2 (4.1)	-1.0 (3.6)	1.8	.177	.011
Verbal Fluency Switching## – Category	.0 (3.5)	.3 (3.1)	.3	.568	.002
Design Fluency Switching## – Filled Dots	.1 (3.6)	-.1 (2.4)	.3	.621	.002
Design Fluency Switching## – Empty Dots	0 (3.7)	.1 (2.2)	.1	.816	.000
C-W Inhibition – Color Naming	0 (3.1)	-.1 (2.4)	.1	.819	.000
C-W Inhibition – Word Reading	**-.1 (3.0)**	**-1.3 (3.2)**	**6.4**	**.012**	**.039**
C-W Switching – Color Naming	.2 (3.0)	.8 (3.0)	1.5	.227	.009
C-W Switching – Word Reading	.2 (2.7)	-.4 (3.3)	1.3	.252	.008
C-W Switching – Inhibition	.3 (2.5)	.9 (3.3)	2.2	.138	.014

All DVs are difference scores between scaled scores of multi-level skills and basic skills
##Switching Correct

Patterns of performance on D-KEFS multi-level tasks (Exploratory corollary for Aim 1):

Three separate patterns of performance on the ten multi-level executive functioning variables of interest emerged among the schizophrenia patients (see Figure 6.2.). Two and 3 class models were separately examined, and then compared to determine the best fit for the data. Model comparison statistics for the 2 and 3 class solutions were as follows: Akaike's Information Criterion (AIC) = 4121.224 and4097.600, respectively and sample-adjusted Bayesian Information Criterion (BIC) = 4097.689 and 4065.715, respectively, the best model being the one minimizing AIC and BIC. The entropy index (ranging from 0 to 1) denotes the quality of the resulting classification, and how possible it is to predict class membership from the observed

indicators. The entropy for both 2 and 3-classmodels was excellent at .933 and .922, respectively,

indicating that the latent classes are highly discriminative. Given the results of the model

comparison statistics, we considered the 3-class model to be the best fit for our data. Of the 81

participants with schizophrenia, 31 had Class 1 profiles, 42 had Class 2 profiles and 8 had Class

3 profiles (Table 6.4.).

Table 6.4. Mean Scaled Scores on the D-KEFS tasks for 3 Classes identified by the Latent Profile Analysis

	Class 1 (N = 31)	Class 2 (N = 42)	Class 3 (N = 8)
Trails N-L Switching	3.3	8.53	11.5
Verbal Fluency Switching Correct	6.07	7.83	14.06
Design Fluency Switching Correct	6.53	9.24	11.44
C-W Inhibition	3.98	8.19	12.56
C-W Switching	4.99	9.40	11.68
Sorting Confirmed Correct	5.90	9.41	11.30
Twenty Questions	7.00	9.69	12.45
Word Context	4.91	9.21	11.31
Tower	6.72	8.18	10.89
Proverb	6.92	9.16	9.93

As seen in Figure 6.2., the overall performance of the individuals with Class 1 profiles (N

= 31) on average, performed within the mildly impaired range across all ten multi-level tasks

(mean 5.7, SD = 1.3); their strongest performance was on Twenty Questions (mean scaled score

= 7.0, SD = 4.6), which is within the low average range of performance, while their weakest was

on Trails Number-Letter Switching (mean scaled score = 3.4, SD = 2.7), which is within the

mildly-to-moderately impaired range of performance.

Individuals with Class 2 profiles (N = 42) performed within the average range of

performance (mean scaled score = 8.9, SD = 0.9). Their strongest average performance was on

Twenty Questions (mean scaled score = 9.7, SD = 3.7) and their weakest performance as on

Verbal Fluency Switching (mean scaled score = 7.8, SD = 2.7), which lie within the average and

low average ranges of performance, respectively.

The eight individuals with Class 3 profiles across all ten D-KEFS multi-level tasks fell

within the high average range (mean scaled score = 11.7, SD = .98). Their strongest performance

was on the Verbal Fluency Switching task (mean scaled score = 14.1, SD = 1.3), which falls

within the superior range of performance, while relatively, their weakest performance was on the

Proverb test (mean scaled score = 9.9, SD = 2.8), which was average.
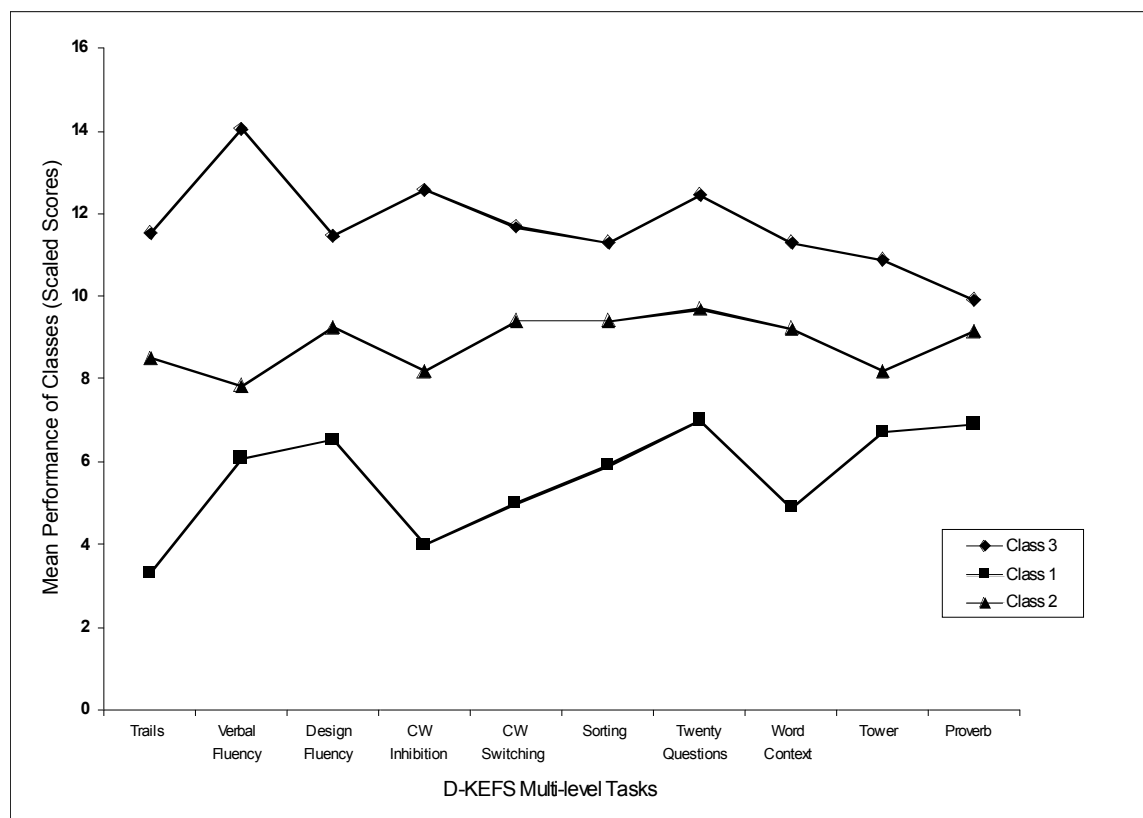
Figure 6.2. Profiles of Performance on D-KEFS Tests in Classes Determined by LPA (SC Only)

Post-hoc examination of results of LPA:

To further examine the potential differences between demographic and clinical

characteristics between the three classes, one-way ANOVAs were used to for the post-hoc

examination of the descriptive characteristics of the patients in each class (see Table 6.5.).

Patients with Class 1 profiles (overall high-average) had higher levels of education than patients

in Class 2 (mildly impaired) and Class 3 (average) profiles. Patients with Class 1 or Class 3

profiles appeared to have fewer/less severe symptoms of thought disorder than patients with

Class 2 profiles. Finally, patients with Class 1 and Class 3 profiles had higher ANART-estimated

Verbal IQ scores (considered to be a measure of premorbid IQ) than those with Class 2 profiles. There was no difference between Class 1 and Class 3 patients on these latter two variables (Table 6.5.).

We also found that there were significantly more Caucasian subjects who were classified into the average and high average classes, while more non-Caucasians, particularly, African Americans were classified as mildly impaired. To determine whether similar differences existed within the SC and HC groups on the ten D-KEFS tasks (see Hypothesis 1.1., p. 41), we also conducted post-hoc, within-group analyses of the effect of ethnic group membership (Caucasian versus non-Caucasian) on subjects' performances on the ten D-KEFS tests. In the schizophrenia sample, a comparison of the performances among Caucasian (N = 54) and non-Caucasian (N = 27) subjects indicated that the non-Caucasians had lower scores on all ten tests, but this difference was significant only on Trails Switching, Category Switching, Color-Word Inhibition, and Tower (all ps <.05), but not on Design Fluency Switching, Color-Word Switching, Sorting, Word Context, Twenty Questions, or Proverbs (ps ranged from .06 to .18). We found similar results in the healthy comparison sample; the non-Caucasians (N = 16) had lower scores than the Caucasians (N = 65) on all ten tests, but significant differences were found only on Trails Switching, Category Switching, Color-Word Inhibition, Word Context, and Proverb (all ps <.05).

Table 6.5. Descriptive Characteristics of Samples in each of 3 Classes as defined by the LPA

	Class 1 (overall mildly impaired; N = 31)	Class 2 (overall average; N = 42)	Class 3 (overall high average; N = 8)	Between-Class Differences (ANOVA or Chi-Square)
	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %	
Age (years)	50.5 (10.2)	46.6 (10.5)	50.6 (8.3)	
Education (years)	12.7 (2.1)	12.8 (2.2)	14.9 (1.6)	3 > 1, 2*
Ethnicity Caucasian	48.4%	73.8%	100%	*++
African American	32.3%	4.8%	0%	
Latino	16.1%	11.9%	0%	
Gender (Male)	61.3%	66.7%	37.5%	
Age of onset of Illness (years)	23.6 (12.1)	22.6 (12.7)	24.4 (12.2)	
Duration of illness (years)	26.9 (10.9)	22.9 (9.8)	25.4 (9.7)	
Antipsychotic Medication None	6.5%	7.1%	0%	
Atypical	87.1%	87.7%	87.5%	
Conventional	0%	7.1%	0%	
Both	6.5%	0%	12.5%	
PANSS Thought Disorder	9.1 (3.1)	7.1 (2.7)	6.0 (2.3)	3 < 1* 1 > 2*
PANSS Positive Symptoms	17.2 (6.2)	14.5 (5.4)	15.3 (4.3)	
PANSS Negative Symptoms	16.7 (5.4)	14.7 (5.4)	14.5 (6.4)	
ANART estimated VIQ	103.8 (9.5)	110.0 (8.2)	117.0 (6.2)	3 > 1* 1 < 2*

All figures are mean (SD)
*significant at the $p < .05$ level++ A chi-square was conducted to examine whether there were differences in proportions of the Caucasian versus Non-Caucasian subjects
PANSS scores are negatively scored, i.e., lower score indicates fewer/less severe symptoms

Ipsative Performance of Patients in Each Class (Overall D-KEFS performance – Performance on

Individual D-KEFS tasks):

We also conducted a post-hoc, descriptive, within-group analysis of ipsative comparisons of performances on individual tasks with each subject's own respective mean performance in order to determine the relative strengths and weaknesses of each group (see Figure 6.3.). Individuals in the mildly impaired group, on average, performed better than their mean performance on Trails Switching, Color Word Inhibition, Color-Word Switching, and Word Context, while they performed relatively worse on all other tasks; however, the magnitude of their relative weaknesses varied from less than 1 scaled score lower than the mean scaled score (e.g., Sorting, Design Fluency Switching, and Verbal Fluency Switching), to 1 to 2 scaled scores lower

(e.g., Twenty Questions, Tower, and Proverb). The pattern of relative strengths and weaknesses in the average performing group was generally similar to that in the mildly impaired group, except that they did better on Verbal Fluency Switching, Tower, and relatively worse on Color-Word Switching. Individuals in the high average group generally the opposite pattern on relative strengths and weaknesses compared to the mildly impaired group; They did better on Proverb, Tower, Word Context, Design Fluency, and Trails, and worse on the rest, relative to their own mean.
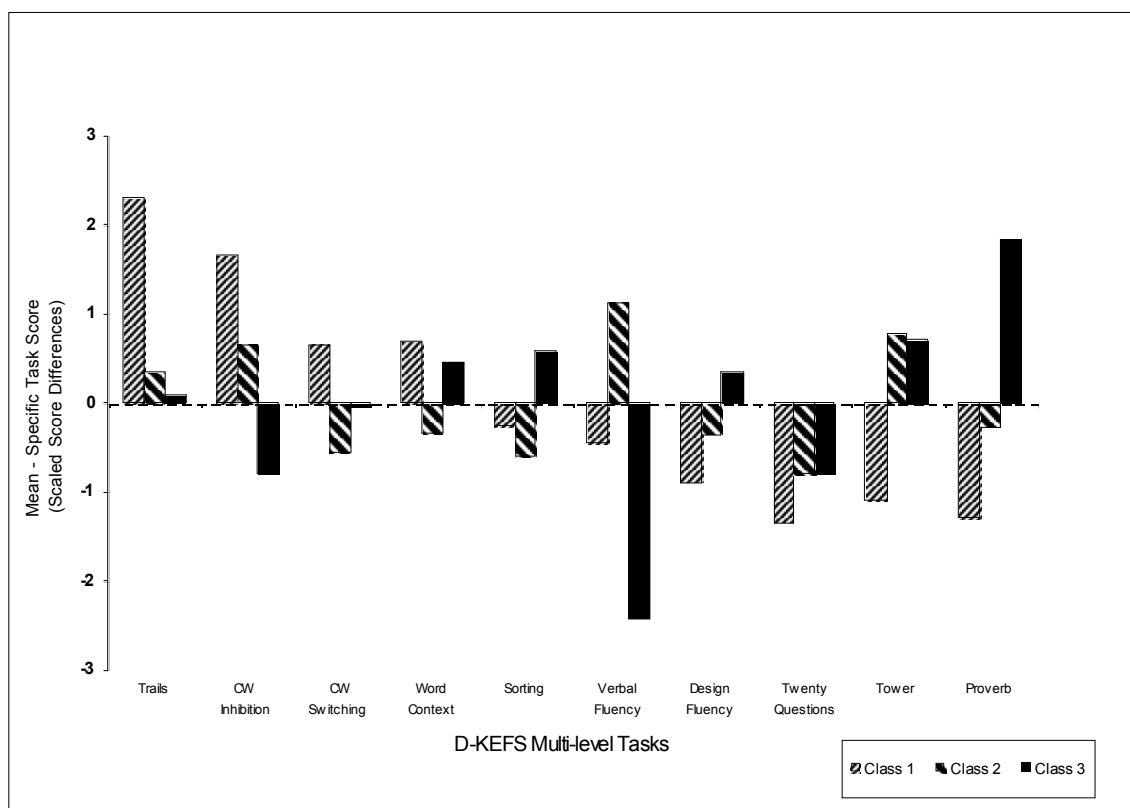
Figure 6.3. Within-Class Ipsative Comparisons of Performance on Individual Tasks vs. Mean Performance

We also examined the ipsative performances of people within each of the three groups on the difference executive functioning *constructs* after we determined what they were in the exploratory factor analysis (the results of the factor analysis are described next, and the relative strengths and weaknesses on the constructs are described on p. 66).

6.2.   Aim 2: Shared versus independent variance of D-KEFS tests

Exploratory Factor Analyses of 10 D-KEFS multi-level skills (Hypothesis 2.1):

Separate exploratory factor analyses were conducted for the schizophrenia and healthy comparison samples. The raw scores of the ten D-KEFS variables were converted to normal (z-scores) and these z-scores were then used for the factor analyses.

Schizophrenia Sample:

For the schizophrenia sample, an initial exploratory factor analysis of the ten D-KEFS multi-level scores suggested that a 2-factor solution best explained the data. The variance explained by the solution was 58.2% and the two factors individually accounted for 44.3% and 13.7% of the variance. The parallel analysis confirmed this 2-factor solution as the best fit for the data. The eigenvalues from this exploratory factor analysis were compared to the eigenvalues from the randomly generated factors: (a) Factor 1: 4.4 *vs.* 1.6 and (b) 1.4 *vs.* 1.4.

As per the standard procedure following a parallel analysis, we then specified 2 factors and reran the analysis. The variances accounted by this solution were the same as the initial EFA; the total variance was 58.2%, and the variance accounted for by each individual factor was 44.3% and 13.7%, respectively. All ten pattern coefficients were generally high (absolute value loadings ranged from .35 to .89). Nine of these did not contain any secondary loadings, however, Sorting had a high and positive loading on both factors, albeit slightly greater on one factor than the other (pattern coefficients = .45 *vs.* .44). Factor 1 was comprised of 5 items and may be conceptualized as "Switching/Cognitive Flexibility." Factor 2 was also comprised of 5 items and may be considered to be "Abstraction/Conceptualization." The two factors were moderately and positively correlated (r = .47), which indicates that individuals with good abstraction/conceptualization abilities are also likely to have good switching/cognitive flexibility skills.

Table 6.6. Principal Axis Factoring with 2 factors: Pattern Matrix (SCs Only)

	Switching/Cognitive Flexibility	Abstraction/Conceptualization
C-W Inhibition	**-.89**	.06
C-W Switching	**-.89**	.19
Design Fluency Switching	**.66**	.08
Trails N-L Switching	**-.66**	-.23
Verbal Fluency Switching Correct	**.39**	.21
Word Context	.18	**.67**
Twenty Questions	-.10	**.61**
Proverb	-.02	**.54**
Sorting Confirmed Correct	*.44*	***.45***
Tower	.20	**.35**

Pattern coefficients > |.3 | are considered to denote significant loading on a factor

Healthy Comparison Sample:

  The initial EFA conducted on the ten D-KEFS tests for the healthy sample initially suggested a 3-factor solution for the data, the total variance explained being 61.3%, and the three factors accounting for 37.9%, 13.4%, and 10.0% of the variance, respectively. However, Verbal Fluency Switching did not load on any of the factors, so the EFA was rerun on the remaining nine variables. This second EFA yielded a 2-factor solution, which explained 55.1% of the variance, and the two factors accounted for 40.3% and 14.8%, respectively. The parallel analysis confirmed this 2-factor solution as the best fit for the data. The eigenvalues from this exploratory factor analysis were compared to the eigenvalues from the randomly generated factors: (a) Factor 1: 3.6 *vs.* 1.5 and (b) 1.3 *vs.* 1.3.

  We then specified 2 factors and reran the analysis. The total variance accounted by this solution was 555.1%, and the variance accounted for by each individual factor was 40.3% and 14.8%, respectively. All nine pattern coefficients were generally high (absolute value loadings ranged from .35 to .91). Like in the schizophrenia sample, Sorting loaded on both factors, but more on Factor 1 than Factor 2 (pattern coefficients = .35 *vs.* .31). Factor 1 was comprised of 6 items and may be conceptualized as "Cognitive Flexibility and Planning Tasks," while Factor 2, comprised of 3 items may be considered to be "Abstraction and Reasoning Tasks." The two

factors were moderately and positively correlated (r = .43), indicating that individuals with good

cognitive flexibility abilities are also likely to have good abstraction skills and vice versa.

**Table 6.7. Principal Axis Factoring with 2 factors: Pattern Matrix (HCs Only)**

	Cognitive Flexibility/Planning	Abstraction/Reasoning
C-W Switching	**-.80**	-.10
C-W Inhibition	**-.76**	-.18
Trails N-L Switching	**-.58**	-.22
Design Fluency Switching	**.48**	-.06
Tower	**.40**	-.08
Sorting Confirmed Correct	***.35***	*.31*
Word Context	-.11	**.91**
Proverb	.07	**.63**
Twenty Questions	.04	**.47**

Pattern coefficients > |.3 | are considered to denote significant loading on a factor
Note: Verbal Fluency was dropped after the initial EFA because it did not load on either factor.

Follow-up to Post-hoc Analysis of Ipsative Performance of Patients in Each Class Determined by

LPA (see pp. 63, 64): (Overall Executive Functioning – Performance on Specific Constructs):

We also conducted a post-hoc, descriptive, within-group analysis of ipsative comparisons

of performances on the two executive functioning constructs determined by the EFA, i.e.,

Switching/Cognitive Flexibility and Abstraction with each subject's own respective mean

performance to examine the relative strengths and weaknesses of each group (see Figure 6.4).

Individuals within the mildly impaired class performed better on tasks of switching/cognitive

flexibility and worse on tasks of abstraction relative to their mean performance across all tasks.

The high average/superior group showed the opposite pattern of performance, i.e., a relative

weakness on switching, and a relative strength on abstraction tasks. Performances of the

Individuals in the average group varied across all ten tasks, although their general profile was

similar to that of the mildly impaired group, i.e., better on switching tasks and worse on

abstraction tasks, relative to their own mean.
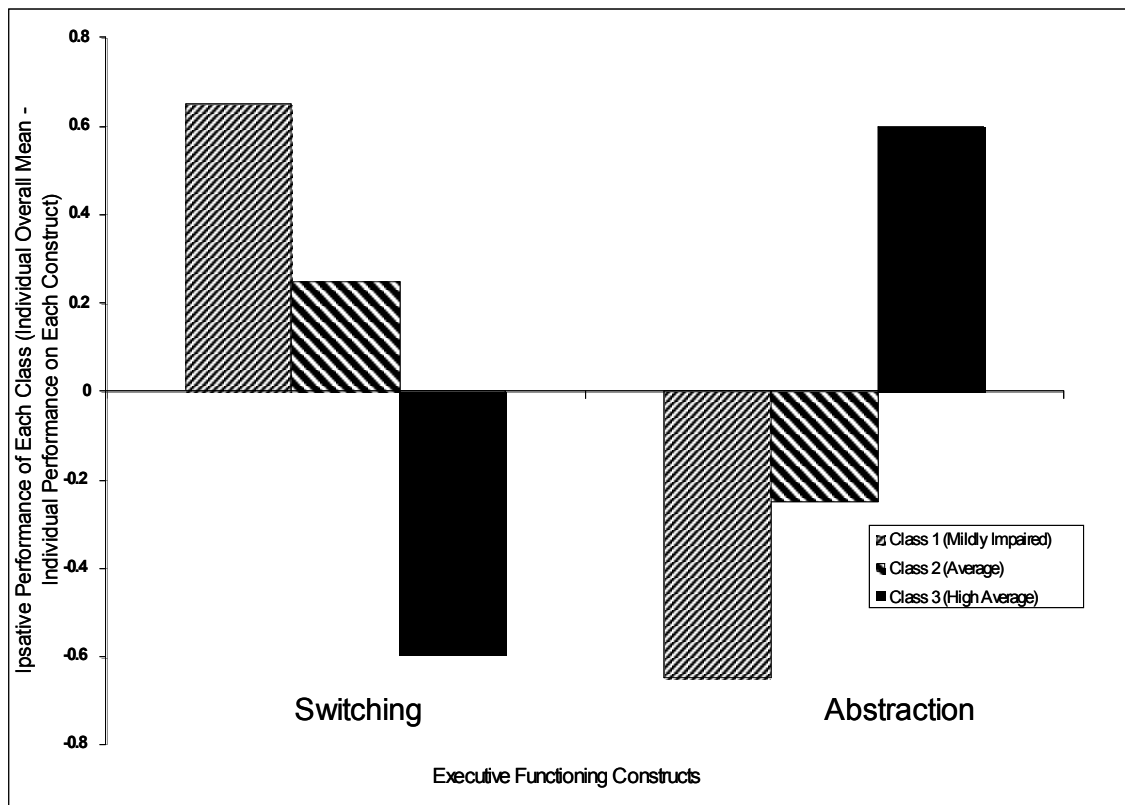
Figure 6.4. Within-Class Comparisons of Executive Functioning Constructs with General Executive Functioning Ability

Relationships among executive functioning constructs in the schizophrenia sample:

Working memory and set switching (Hypothesis 2.2): A path-analytic model was tested to explore the relationships between working memory and set switching (mean scaled score of the five switching tasks on the D-KEFS (determined by the EFA) in the schizophrenia sample only. The target model specified a direct relationship between working memory and set switching in schizophrenia, which was tested using the Mplus statistical program. This direct effect of working memory on set switching was statistically significant (β = .554, p <.001), indicating intact working memory may be essential in order for switching abilities to be intact.

Abstraction, sorting, and reasoning (Hypothesis 2.2): The target model specifying a direct effect of simple abstraction on sorting and reasoning with schizophrenia was also a good fit; the direct

effect of abstraction abilities on both abilities was statistically significant (β = .375 and β = .447, respectively; ps <.001). These results support the hypothesis that good abstraction abilities are necessary for good sorting as well as reasoning skills.

6.3.   Aim 3: Relationships of executive functions with psychopathology and everyday living tasks

Symptoms of psychopathology and executive functioning abilities (Hypothesis 3.1):

The target model specified compound relationships between schizophrenia and the executive functioning abilities (here comprised of the two factors derived from the EFA: Switching/Cognitive Flexibility and Abstraction/Conceptualization; each variable in this model is the mean scaled score of five of the relevant executive functioning tasks within each of the two factors (See Table 6.6.). The hypothesis that thought disorder and negative symptoms would have a direct effect on executive functions, whereas positive symptoms would have no effect was only partly supported. Thought disorder had a statistically significant direct and negative effect on both switching and abstraction (β = -.331 and β = -.497, respectively, ps <.001), indicating that the presence of thought disorder symptoms resulted in poorer performance on switching as well as abstraction. However, negative symptoms were not significantly related to either switching or abstraction (β = -.064, p = .546 and β = -.097, p = .345, respectively). As hypothesized, positive symptoms had no effect on either executive functioning construct (β = -.100, p = .403 and β = -.182, p = .114, respectively).

Relationships between executive functioning abilities and independent living (See Hypothesis 3.2., p. 42):

Switching/Cognitive Flexibility was significantly correlated with UPSA total score (r = .413, p <.001), as well as the Financial Skills and Transportation subscales (rs = .321 and .373. respectively, both ps <.001). Abstraction/Concept Formation was significantly correlated with the UPSA total and all but the Shopping and Communication subscales of the UPSA (rs ranged from .278 - .365, ps <.05). Neither subjective nor objective measures of the Quality of Life scale were

significantly correlated with switching or abstraction. Independence in living was also not

significantly correlated with switching or abstraction (see Table 6.8.).

A general linear regression analysis was conducted to explore if either switching or

abstraction predicted performance on the UPSA total score. The full model explained 16.7%

[$F(2,70)$ = 8.2, p = .001)] of the total variance and the unique variance explained by switching and

abstraction was 5.7% and 2%, respectively. Switching was a significant predictor of UPSA total (β

= 1.051, p = .029), indicating that for every 1 increase in mean scaled score of the switching tasks

of the D-KEFS, UPSA totals increased by 1.051 points. Performance on abstraction was not a

significant predictor of UPSA total (β = .629, p = .194). The full models for each of the UPSA

subscales were also significant: the combined executive functioning constructs predicted 7.4% of

the variance in Recreational Planning [$F(2,70)$ = 8.2, p = .001)] , 10.5% of the variance in

Financial Skills [$F(2,72)$ = 3.9 (p = .023)], 7.2% of the variance in Transportation [$F(2,71)$ = 3.8 (p

= .026)], 6.3% of variance in Shopping [$F(2,72)$ = 3.5 (p = .036)], and 11.9% of the variance in

Communication [$F(2,72)$ = 3.5 (p = .036)]. The individual contributions of the switching and

abstraction constructs varied for the UPSA subscales (See Table 6.9.). Ratings on the Global Life

Satisfaction, Daily Activities, and Social Relations subscales of the Quality of Life scale were not

significantly predicted by these executive functioning constructs. See Table 6.9. for the variance

explained by switching and abstraction on the UPSA subscales.

***Table 6.8. Correlations between Switching/Cognitive Flexibility and
Abstraction/Conceptualization and some measures of everyday functioning***

	Switching	Abstraction
UPSA Total	413**	.365**
UPSA Recreational Planning	.092	.296**
UPSA Financial Skills	.321**	.322**
UPSA Transportation	.373**	.278*
UPSA Shopping	.044	-.218
UPSA Communication	.107	-.156
QOL Global Life Satisfaction (Subjective)	-.122	-.179
QOL Daily Activities (Objective)	.002	.076
QOL Social Relations (Objective)	.086	-.031
Independence in Living [+]	.049	.096
p > .05, **p* < .005 [+]Spearman's rho (Rest are Pearson's *r*)		

Table 6.9. Executive Functioning Ability as Predictors of Everyday Functioning

	Full Model		Coefficients, Unique Predictive Value of **Switching**		Coefficients, Unique Predictive Value of **Abstraction**	
	F (df)	R^2	β	r^2	β	r^2
UPSA						
Total	**F(2,70) = 8.2 (p = .001)**	16.7%	**β = 1.05 (p = .029)**	5.7%	β = .63 (p = .194)	2.0%
Recreational Planning	**F(2,72) = 4.0 (p = .023)**	7.4%	β = -.13 (p = .339)	1.2%	**β = -.38 (p = . 009)**	9.1%
Financial Skills	**F(2,72) = 5.4 (p = .007)**	10.5%	β = .24 (p = .151)	2.6%	β = .25 (p = .147)	2.6%
Transportation	**F(2,71) = 3.8 (p = .026)**	7.2%	β = .36 (p = .051)	5.0%	**β = -.50 (p = .008)**	9.6%
Shopping	**F(2,72) = 3.5 (p = .036)**	6.3%	**β = .62 (p = .028)**	6.4%	**β = .69 (p = .016)**	7.7%
Communication	**F(2,71) = 5.9 (p = .004)**	11.9%	**β = .47 (p = .022)**	6.6%	β = .12 (p = .554)	0.4%
Quality of Life						
Global Life Satisfaction	F(2,72) = 1.2 (p = .307)	.5%	β = -.09 (p = .259)	1.7%	β = -.01 (p = .878)	0.03%
Daily Activities	F(2,72) = .47 (p = .627)	-1.5%	β = -.04 (p = .476)	0.7%	β = .05 (p = .344)	1.3%
Social Relations	F(2,72) = .92 (p = .405)	-.2%	β = -.03 (p = .575)	0.4%	β = .07 (p = .191)	2.4%

Post-hoc examinations of relationships between the executive functioning constructs and independent living tasks were conducted for the mildly impaired group only, and the results were similar to those found among the entire schizophrenia sample.

7. Discussion

The main purpose of the current study was to comprehensively characterize the nature of executive functioning deficits in schizophrenia. The specific aims were 1) to compare the various executive functioning abilities in patients with schizophrenia relative to neuropsychiatrically healthy individuals; 2) to determine whether executive functions comprised a unitary construct, or represented multiple constructs in schizophrenia; and 3) to examine the relationships of executive functions to everyday living and level of psychopathology in schizophrenia. Results for each aim have been discussed separately.

Nature of executive functions in schizophrenia versus healthy comparison subjects:

Consistent with our first hypothesis, relative to healthy subjects, people with schizophrenia had significantly lower levels executive functioning, which included verbal abstraction, conceptualization and sorting, cognitive flexibility, planning, and response inhibition. More importantly, these differences were noted in samples that were matched on age, education, ethnicity and gender, and also had similar levels of verbal functioning (current for the comparison subjects and premorbid estimates for the patients).

Earlier studies have demonstrated that people with schizophrenia have impairments in executive functions, albeit measured with different tests, such as the widely used Wisconsin Card Sorting Test. For example, in their classic meta-analysis of studies of neuropsychological functioning in schizophrenia, Heinrichs and Zakzanis reported a moderately large effect size for the WCST, i.e., $Mean_d = 0.95$ ($SD_d = 0.44$). However, they also reported that the effect size of the WCST was significantly related to IQ score (measured with the WAIS-R). Other studies have reported that executive functions in schizophrenia are impaired regardless of estimated premorbid IQ or current IQ (e.g., Kremen et al., 2001). Our findings supported those reported in the meta-analysis: Although our schizophrenia sample, whose mean estimated premorbid VIQ was within the average range, performed more poorly than the healthy comparison subjects, they did not on average, have impaired performances on any of the executive functioning tasks.

In order to parse out difficulties in multi-level executive tasks, i.e., tasks demanding more than one cognitive skill, from those demanding more basic level cognitive components, we also examined whether the magnitude of these differences was greater in schizophrenia than among the healthy comparison sample. There were greater differences between basic skills and multi-level skills among schizophrenia patients on visuomotor number-letter switching and its basic components, such as visual scanning and attention, number sequencing, letter sequencing and motor speed. In contrast, there were no such basic-versus-multilevel differences when examined in terms of category fluency switching, design fluency switching, or color-word switching and their respective component skills.

The component skills of the visuomotor number-letter task may be considered to be more fundamental cognitive skills, required for all neurocognitive functions, e.g., the motor speed task requires the subject to trace a dotted line as fast as possible, or the visual scanning task requires subjects to cross out any "3s" on a page. None of these functions was impaired among patients with schizophrenia.

While more complex measures of perceptual-motor speed, such as the Tactual Performance Test or the Block Design subtest of the WAIS batteries have presented particular difficulties for schizophrenia patients (e.g., Heaton, Paulsen, McAdams, Kuck, Zisook, et al., 1994), they also require skills besides pure motor speed, e.g., spatial ability. The, D-KEFS Trails Motor Speed task, on the other hand, may be considered a more "pure" task of motor speed. Similarly, attention, especially sustained attention as measured by the Digit Vigilance Test is consistently impaired in schizophrenia (Chan, Yip, & Lee, 2004); the D-KEFS Trails Visual Scanning task mainly measures scanning, can be used to detect any visual fields defects, and requires a much shorter duration of sustained attention than does the Digit Vigilance Test.

Contradictory to our *a priori* hypothesis, the non-switching components of the verbal and design fluency require basic fluency ability, which in itself may be impaired in schizophrenia (Moore et al., 2006). Similarly, there were no basic-versus-multilevel differences in the color-word interference task; schizophrenia patients did considerably worse than healthy subjects on both its

multi-level components, i.e., inhibition (on which they had the lowest performance across all tasks) and inhibition/switching, but they also did worse on the basic components of this task, i.e., color naming and word reading. Given the level of sustained attention required even for these more basic tasks, it may be argued that they present some difficulty for patients with schizophrenia, who are known to have attention deficits (Heaton et al., 1994; Heinrichs & Zakzanis, 1998). However, it had been previously suggested that people with schizophrenia tend to show greater-than-normal speed when naming the ink color in the Color Naming task (reviewed by Perlstein et al., 1998). As already mentioned, this was not found to be the case with our current sample, whose performance on color naming was, on average, about two scaled scores below that of the healthy comparison sample.

In our exploratory latent profile analysis, we found three distinct profiles of executive functioning skills among the schizophrenia patients; roughly half the sample could be classified as "average" performers, i.e., comprising of individuals with average executive functioning abilities. Approximately 38% of the sample fell within the "mildly impaired" class, while about 10% performed within the high average/superior range on the executive functioning tasks. We expected to find normal performances among at least a third of our sample, given previously reported findings that between 25-30% of schizophrenia patients are neuropsychologically normal (e.g., Palmer et al., 1997). That more than half our sample had average or high average executive functioning skills, could be attributed to the fact that this particular sample consisted of a subset of people who expressed interested in cognitive or work rehabilitation, and on average, had at least one year of college education. Furthermore, they also tended to levels of estimated premorbid VIQ comparable to the general (non-ill) population, and minimal psychopathology, and most (about 76%) lived independently in the community. Individuals in the high average/ superior group tended to have the highest level of education (i.e., mean = 14.9 years, SD = 1.6), which was significantly greater than people in both the average and mildly impaired classes. People in the high average and average groups had significantly less severe symptoms of thought disorder, and higher levels of estimated premorbid VIQ than did people in the mildly impaired group.

Of note, significantly higher proportions of non-Caucasian patients with schizophrenia were classified as mildly impaired on the executive functioning tasks. Examination of performances between the Caucasian and non-Caucasian subjects within healthy comparison sample indicated that non-Caucasians performed significantly worse on roughly half the tasks, some of which may be cultural biased (e.g., abstracting proverbs). That non-Caucasians have lower scores on neuropsychological tests is not a novel finding, and is well-documented in previous published reports (reviewed by Manly, 2005; Taylor & Heaton, 2001). The current D-KEFS norms are not corrected for education or ethnicity (Delis et al., 2000c), and our results suggest that education and ethnicity-corrected norms will be useful in order to make a more accurate decisions regarding whether an individual of non-Caucasian ethnicity is clinically impaired versus intact (Heaton, Nayak, & Taylor, 2004).

We also wanted to examine whether there were any potential differences between the specific executive functioning abilities (the specific constructs were determined by an exploratory factor analysis conducted separately), executive functioning abilities within each of the classes, compared with overall executive functioning ability. We found that patients in the mildly impaired group had relative strengths on cognitive flexibility/switching and relative weaknesses in abstraction/conceptualization, while the high average group showed the opposite pattern. The average group varied across the tasks, but in general, their pattern on the abstraction and switching constructs was similar to that of the mildly impaired group, but to a much lesser extent, i.e., their performances lay much closer to the mean. Of note, the switching tasks of the D-KEFS are considered to be among the most difficult neurocognitive tasks given the complexity of the instructions, the tasks themselves, and because multiple cognitive skills must be simultaneously utilized in order to successfully complete them.

These finding are particularly interesting for several reasons; a) They indicate that executive functioning impairments in schizophrenia may be primarily characterized by abstraction deficits; b) Patients with schizophrenia with mild cognitive impairments may have a differential deficit between different types of executive functioning tasks; and c) People will not necessarily

perform worse on neuropsychological tests of greater difficulty than those that are relatively easy (cf., Chapman & Chapman, 1973).

To summarize the findings in this section, in general, patients with schizophrenia had lower executive functioning skills than in the general, neuropsychiatrically healthy population with comparable verbal intelligence. However, consistent with previous reports of multiple neurocognitive abilities among individuals with schizophrenia (e.g., Nayak Savla, Moore, Roesch, Heaton, Jeste, et al., 2006), there was heterogeneity in executive functions in schizophrenia. Higher functioning, community living patients with schizophrenia may have mildly impaired, average or high average on different executive functioning skills, and predictors of the level of executive functioning abilities tended to be education, ethnic-group membership, level of psychopathology, and level of premorbid cognitive functioning. Impairments in executive functions in schizophrenia may be greater in abstraction than in switching abilities.

Shared versus Independent Variance of various executive functioning skills:

We hypothesized that rather than a unitary construct, executive functions are comprised of distinct ability areas, including cognitive flexibility, abstraction/conceptualization, planning and response inhibition. Our hypothesis was partly supported by the data, in that cognitive flexibility and abstraction emerged as independent constructs in an exploratory factor analysis; all the switching components of the tasks loaded on cognitive flexibility, while tasks demanding novel concept formation, abstraction, deductive reasoning, and planning loaded on abstraction. The sorting task loaded on both factors (although more on abstraction), which is appropriate, since it requires abstraction and conceptualization skills as well as flexible thinking.

There continues to be debate about whether people with schizophrenia have a generalized cognitive deficit, or differential deficits in multiple neurocognitive domains (cf. Dickinson et al., 2004); the emergence of two meaningful constructs, as well as the relative strengths on cognitive flexibility and relative weaknesses on abstraction in schizophrenia patients with mildly

impaired overall executive functions support the presence of differential impairments among executive functions, if not other neurocognitive functions, in schizophrenia.

While patients with schizophrenia have been clinically noted as having "concrete thinking," there are surprisingly few studies that have formally assessed abstract thinking (such as simple abstraction and deductive reasoning). The Wisconsin Card Sorting Test and the Category Test have been used fairly extensively to measure executive functions in general among people with schizophrenia, and may be conceptualized as measures of both novel concept formation and cognitive flexibility, and performance on both tests is typically impaired in schizophrenia (Laws, 1999; Heinrichs & Zakzanis, 1998). Previous studies of cognitive flexibility alone (e.g., measured via the Trails Making Test, Part B) demonstrated that schizophrenia patients took significantly longer to complete the task than did healthy comparison subjects. To our knowledge, this is the first study that has compared abstraction and cognitive flexibility separately among people with schizophrenia.

An exploratory factor analysis conducted in the healthy comparison sample also yielded a 2-factor solution, but its member components differed from those in the factors in the schizophrenia sample. Furthermore, not only did most of the tasks load on the first factor, but it was also particularly difficult to characterize the factors. It is a common practice to use factor analysis as a means to establish construct validity, but Delis and colleagues have persuasively argued that it might not be an appropriate method because even loosely related variables can appear to represent a single construct when mediated by intact neurocognitive processes (Delis, Jacobson, Bondi, Hamilton, & Salmon, 2003). We believe that the murky nature of the factor components among the healthy subjects was at least partly due to this problem.

We also demonstrated the existence of multiple executive functioning constructs by specifying path models between working memory (the supervisory attentional system of which is closely related to executive functioning) and cognitive flexibility, as well as between abstraction and sorting, and abstraction and logical reasoning. Our hypotheses that intact cognitive flexibility will be contingent upon intact working memory, and intact sorting ability and verbal reasoning will

be contingent upon simple abstraction were supported by the data. Working memory and cognitive flexibility is consistently found to be impaired in the general schizophrenia population (e.g., Keefe, 2000; Goldstein, 1990), and our findings imply that they are closely related to each other.

Relationships of executive functioning tasks with levels of psychopathology and independent living:

In order to examine the relationships between psychopathology and executive functions, we hypothesized that negative symptoms and symptoms of thought disorder, but not positive symptoms, would affect abstraction and cognitive flexibility abilities among people with schizophrenia. While thought disorder had a direct effect on both executive functioning constructs, neither positive nor negative symptoms did. There is at least one previous report that supports the finding that thought disorder is associated with executive functioning impairments (Stirling, Hellewell, Blakely, & Deakin, 2006). Thought disorder was measured by four from the PANSS, i.e., conceptual disorganization, difficulty in abstract thinking disorientation, and poor attention (based on a factor analysis by Higashima et al., 1998). The presence and level of the thought disorder symptoms for each study participant with schizophrenia was clinically determined by trained raters as part of a larger scale of clinical symptom evaluation (i.e., the PANSS), and our finding that they were significant predictors of performance on neuropsychological measures of executive functioning supports concurrent validity of these items. More relevant to our study goals, is the implication of this finding that executive function deficits may be particularly associated with patients with schizophrenia who also have a thought disorder; this implication is further supported by our finding that significantly higher levels of thought disorder were present among the group of patients with mildly impaired performances on all the D-KEFS tasks, compared with the average and high average groups. That we did not find negative symptoms to have any effect on performance on the executive function tasks may be attributed to the fact that our schizophrenia sample consisted of higher functioning individuals

living in the community, who on average, only had minimal negative symptoms with little variance among individual patients. Our hypothesis that executive functioning constructs will have moderate to strong relationships with functional capacity was only partly supported by our data; overall functional capacity, and specific functions such as financial skills and skills needed to use public transportation were moderately associated with both abstraction and cognitive flexibility. Similar patterns of association were noted in the subset of patients with mild impairments in overall executive functioning. In contrast to these findings, other studies have reported moderate to strong relationships between the functional capacity and abstraction/cognitive flexibility (albeit measured with the WCST perseverative responses, Category Test total errors, and Trail Making Part B), including one from our research group at UCSD (Twamley, Doshi, Nayak, Palmer, Golshan, et al., 2002).

We did not find any significant relationships between the executive functioning constructs and subjective and objective quality of life, which was consistent with other recently reported findings (Narvaez, Twamley, McKibbin, Heaton, & Patterson, 2008). There was also no significant relationship between the executive functions and the level of independence in living among people with schizophrenia; part of the explanation for this finding may be the lack of variability in living situation in the current sample (nearly 76% were living independently in the community).

Strengths and Limitations of the Study:

To our knowledge, this is the first study to comprehensively characterize executive functioning abilities in schizophrenia using a large battery of co-normed measures including the standard multi-level tasks, and measures of the basic/component abilities underlying each task. Executive functions have never been previously examined in this manner among people with schizophrenia, despite suggestions in the literature that they may be particularly important predictors of everyday functioning (Green et al., 2000). One of the greatest strengths of this study is that we were able to individually match the schizophrenia and healthy comparison samples to age, education, ethnicity and gender. Our samples were also matched on general verbal ability

(although an estimate of verbal ability in the case of the schizophrenia patients), therefore our inferences about the samples' executive functioning skills were not confounded by verbal skills.

There were some limitations in the present study, which must be considered in drawing conclusions from the findings. Foremost, this study was largely based on secondary analyses of existing data (although we did prospectively collect data from 17 additional schizophrenia patients). This resulted in several constraints on the data: (a) the SC and HC data were not collected in parallel, so the possibility of examiner or cohort effects cannot be completely ruled out. However, the former limitation is balanced by the fact that the D-KEFS was administered via conscientious attention to the standardized administration method; also, use of data from the D-KEFS standardization sample permitted one-to-one matching of patients to controls on key demographic variables, resulting in a level of comparability not typically achieved in prospectively collected patient control samples. Another potential limitation is that the data from schizophrenia patients were largely drawn from a sample of participants volunteering for cognitive/vocational rehabilitation studies; the effects of this sampling source on potential sampling bias are uncertain. Nonetheless, the demographic and clinical characteristics of the patient sample, as listed in Table 6.1., appear grossly comparable with those generally seen in outpatient samples of persons with schizophrenia (e.g., Kremen et al., 2001). Our schizophrenia sample also consisted of a large proportion of patients with schizoaffective disorder, which could be considered by some to be a separate comparison group with schizophrenia, given its mood component. We decided to consider the two categories of patients under the broad classification of schizophrenia for several reasons; a) our sample only had mild psychopathology, and were indistinguishable from one another on any demographic or clinical characteristics and b) previous research has suggested that there are minimal (if any) neurocognitive differences, including those on executive functions (e.g., Reichenberg, Harvey, Bowie, Mojtabai, Rabinowitz, et al., 2008). In our post-hoc examinations of the two subgroups of patients, we found the patients with schizophrenia and those with schizoaffective disorder to be indistinguishable on any of the executive functioning tasks.

Implications of the Study

The current study has theoretical and pragmatic implications. Executive functions are universally acknowledged as vital to optimal daily functioning, yet have so far remained a nebulous and poorly defined construct. On a theoretical level, the clarification of the independence in specific types of executive functions contribute to the overall efforts to identify meaningful neurocognitive subtypes, and to link neurocognitive deficits to the underlying pathology in neurological systems or processes. On a clinical level, this study sheds light on the importance of including measures of abstraction along with those of cognitive flexibility in a comprehensive neuropsychological assessment in schizophrenia, and considering the relative strengths and weaknesses within the executive functioning domain to identify targets for rehabilitation/vocational planning for patients with schizophrenia. Also, patients with even mild severity of thought disorder may have impaired executive functioning, and treatment recommendations may need to be tailored accordingly.

Future Directions:

Despite more than a century of research, little is known about schizophrenia's effect on the brain, partly because of the heterogeneity among individuals with illness, and partly because of lack of adequate methodology to study its complex presentation. In this study, we attempted to deconstruct neuropsychological tasks and examine individual, rather than group profiles in schizophrenia, which we believe is an important step toward a better understanding of the individual differences among people with the illness.

From a clinical research perspective, the next step would be to examine the relationships between abstraction and cognitive flexibility and real life functioning among patients with schizophrenia, in areas such as medication adherence, decision making capacity, driving ability, academic/vocational functioning, and other instrumental activities of daily living, in order to better determine the types of strategies needed to rehabilitate patients with the illness. Our study also demonstrated the need for developing education and ethnicity corrected norms, in order to

determine the neurocognitive status of examinees in a more accurate manner, as well as reiterated the need for deconstructing ethnic group membership, which may be proxy for socioeconomic and acculturation variables underlying differences in neuropsychological test performances.

From a basic sciences perspective, it would be interesting to examine the relationships between executive functioning, as well as other neurocognitive functions and potential mediating neural pathways, particularly frontal-subcortical circuits among individuals in schizophrenia on a profile, rather than group basis.

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