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Detecting Executive Function Subtypes in Individuals with Schizophrenia and Healthy Controls

Jessica Pommy

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**DETECTING EXECUTIVE FUNCTION SUBTYPES IN
INDIVIDUALS WITH SCHIZOPHRENIA AND
HEALTHY CONTROLS**

by

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ABSTRACT

Executive functioning (EF) impairments observed in schizophrenia (SZ) occur prior to onset of psychosis and are predictive of functional outcomes. There is significant variability in the nature and severity of EF deficits, however, and a better understanding of this heterogeneity could provide insight into the neurodevelopmental processes underlying both SZ and EFs. Using an approach similar to Fair et al., 2012, the present analysis examined heterogeneity in EFs and attempted to identify EF subtypes within healthy controls (HC) and individuals with SZ. EFs were assessed using the Trail Making Test, Verbal Fluency test, Tower of London, and Continuous Performance Test. A 4-factor model of EF (fluency, planning, shifting, attention) was tested in the sample using a Confirmatory Factor Analysis (CFA). The presence of EF subtypes was

assessed separately in both groups using community detection (CD), an analytic technique based in graph theory that enables an unbiased analysis of community structure within complex networks. Results from the CFA supported a 4-factor model of EF. The CD analyses indicated greater modularity in SZ, and upon initial inspection, identified 7 EF subtypes in the SZ group that nested within 5 EF subtypes in the HC group. The impact of EF profiles on diagnostic accuracy was assessed using a machine learning approach. Results revealed improved diagnostic accuracy for a majority of the EF subtypes when EF profile was considered. Consistent with findings reported by Fair and colleagues, results support the existence of similar cognitive subtypes in the context of both normal and aberrant neurodevelopment.

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Introduction

Executive functioning (EF) is a multidimensional construct that encompasses a variety of complex, higher-level cognitive functions. In broad terms, EF is conceptualized as a set of interrelated cognitive processes that enables one to carry out goal-directed behavior and navigate through novel or unstructured situations (Banich, 2009; Elliott, 2003; Lezak, Howieson, & Loring, 2004). As might be expected, deficits in EF can severely impact one's ability to successfully engage with and adapt to the environment (Lezak et al., 2004). In light of the functional consequences associated with EF impairments, it is not surprising that low EF is one of the most frequently observed neuropsychological deficits associated with psychiatric illness (Testa & Pantelis, 2009) and it has been linked to a variety of psychopathological disorders: schizophrenia (Kerns, Nuechterlein, Braver, & Barch, 2008), Tourette syndrome (Eddy, Rickards, & Cavanna, 2012), posttraumatic stress disorder (Aupperle, Melrose, Stein, & Paulus, 2012), attention deficit hyperactivity disorder (Ozonoff & Jensen, 1999), autism (Ozonoff & Jensen, 1999), and epilepsy (MacAllister & Schaffer, 2007). In particular, it appears that psychiatric disorders with late childhood or adolescent onset, such as schizophrenia, are associated with more severe EF impairments (Testa & Pantelis, 2009). This suggests that the neurodevelopmental processes underlying EF may provide insight into the etiology of neuropsychiatric conditions like schizophrenia (De Luca & Leventer, 2010; Testa & Pantelis, 2009).

A closer examination of the nature of EF, both within the context of a psychiatric neurodevelopmental disorder and within the context of typical

development, would inform our understanding of the construct of EF more broadly, as well as provide further insight into the role of EF as it occurs within the context of aberrant neurodevelopment. Schizophrenia may be the optimal neurodevelopmental psychiatric disorder to pursue for several reasons, including the severity and variability of EF deficits observed in this population, as well as the development and course of the disorder. Although a variety of methodologies have been employed to study EFs, a cognitive subtyping approach was selected as it was thought to be a more appropriate way to capture the variability frequently observed across EFs.

We will begin with a brief overview of the construct of EF and a discussion of several prominent EF models each from a different theoretical framework, concluding with the developmental model selected for the present analyses. Next, a discussion of schizophrenia will be provided, which will include a summary of the psychiatric and cognitive symptoms associated with the disorder and its development and course. We will then focus on EF within the context of schizophrenia, including the associated EF deficits and neurobiological correlates. Given the significant heterogeneity associated with EF and with schizophrenia (Raffard & Bayard, 2012), a brief discussion of the issue of heterogeneity is warranted to highlight our methodological rationale. Finally, an overview of cognitive subtypes will be provided, including an overview of methods used to detect cognitive subtypes and support for the method selected, Community Detection.

The Construct of Executive Function

EF encompasses a range of cognitive processes including planning, shifting, sustained attention, impulse control, flexibility, and selective attention. A bewildering array of tests have been developed that purport to assess EF including neuropsychological assessments and behavior rating measures. While neuropsychological measures attempt to capture the specific cognitive process underlying EF, behavior-rating measures attempt to capture EF difficulties as they manifest in everyday activities. Given the majority of EF models are based upon neuropsychological measures, a comprehensive discussion of EF behavior ratings is beyond the scope of this paper. For an in-depth discussion of behavior ratings of EF as they compare to the neuropsychological assessments of EF, interested readers are referred to Toplak and colleagues (2013).

Neuropsychological assessments used to measure EF range from individual measures like the Stroop Test and the Wisconsin Card Sorting Task to EF batteries such as A Developmental NEuroPSYchological Assessment (NEPSY) (Korkman, Kirk, & Kemp, 1998) and the Delis-Kaplan Executive Function System (D-KEFS) battery (Delis, Kaplan, & Kramer, 2001). There are commonalities across the multitude of EF tests, as well as differences between tests. EF tests in general attempt to measure goal-directed behaviors that require a self-regulation component. However, there is significant variation in the specific sub-processes of EF that individual tests attempt to measure, in part, a reflection of variations within specific models of EF. Despite this great diversity of tests and EF models, individual measures are typically correlated, and a

relatively strong and reliable first principal component emerges. Ettenhofer and colleagues, for example demonstrated that although individual measures of EF have modest reliability, the latent EF construct has very high reliability over time (Ettenhofer, Hambrick, & Abeles, 2006). As mentioned above, differences in the theoretical frameworks employed have resulted in different EF models. The models reviewed below, generally agree on the construct validity of EF, however, they differ in the methodological approach used to define it.

Models of Executive Function

Clinical model of executive function. Executive functions were first characterized in clinical populations following damage to the frontal lobes. Consequently, the presence of EF deficits has been used to develop EF models. Lezak and colleagues (2004), for example, conceptualized EF within a clinical neuropsychological framework of behavior. According to this perspective, behavior is characterized by three separating, yet interacting systems: 1) cognition, 2) emotionality, and 3) executive functions (Lezak et al., 2004). According to this model, each dimension of behavior is an integral component that can be considered independently. Briefly, the cognitive dimension addresses specific cognitive abilities underlying a given behavior, the emotionality dimension addresses emotions and feelings associated with a given behavior, and the EF dimension addresses if and how the behavior is 'expressed' from start to finish (Lezak et al., 2004). The EF dimension is further divided into four individual components including: volition, planning, purposive action, and effective performance. Within the proposed model, EF is differentiated from the

cognitive dimension, however, EF is still thought to impact one's ability to *plan*, *execute*, and *monitor one's own performance* during cognitive tasks (Lezak et al., 2004). While this view of EF is clinically meaningful, it has been suggested that neuropsychological assessments used in clinical settings may not adequately represent the construct of EF as it appears in a real world context (Burgess et al., 2006).

Lezak and colleagues have acknowledged some of the challenges in establishing ecological validity in the assessment of EF. Often the "real world" difficulties associated with executive dysfunction are best captured by novel tasks, however, practical limitations often make this difficult to achieve within a clinical setting (Lezak et al., 2004). Alternatively, while naturalistic observation would provide additional, meaningful information that may help the clinician more accurately assess the subdivisions of EF, this method is also difficult to implement (Lezak et al., 2004). Fortunately, the clinical methods available, Lezak and colleagues suggest, may be a helpful substitute for assessing EF deficits as they appear in a patient's daily life.

Clinical models of EF, such as Lezak's model, use assessments to approximate the difficulties experienced by patients in real-world situations. An alternative approach based in psychometrics, however, uses the assessments believed to tap EF as the foundation to create additional models of EF.

Psychometric approach to executive function. While the clinical approach focuses primarily on manifestations of EF deficits in patient populations, the psychometric approach concentrates on the assessments

believed to measure EF. Two different approaches to EF are seen throughout the literature, in earlier models EF was conceptualized as a single, unitary construct, however this has largely been replaced by an alternative view that considers EF to be better understood as a collection of related but distinct components (Best & Miller, 2010). One approach used by unitary models of EF is the latent-variable approach. A single higher-order EF factor is identified from multiple tests of EF. For example, Ettenhofer et al. (2006) described a single latent EF factor identified from five commonly used tests of EF (i.e., Stroop test, WCST, Trail Making Test, Letter Fluency, and Category Fluency). This approach was used to demonstrate EF is both a stable and reliable trait (Ettenhofer et al., 2006).

Alternatively, several unitary models of EF have been proposed that conceptualize EF in relation to other cognitive domains (Purdy, 2011). For example, some models emphasize the attentional aspect of EF (W. Norman & Shallice, 1986) or conceptualize EF within a working memory framework (Baddeley & Logie, 1999). Further, efforts have been made to consider EF relative to intelligence. While measures of EF correlate with Spearman's "g" or general ability, there are important distinctions between these constructs (Blair, 2006). For example, research has demonstrated that the updating factor of EF was highly correlated with measures of intelligence even after covarying other EF measures, while inhibiting and shifting EF factors were not correlated with intelligence (Friedman et al., 2006). Thus executive functioning is related to general intelligence, but it can also be differentiated from it (Friedman et al., 2006; Friedman et al., 2008; Jester et al., 2009; T. Lee et al., 2012).

Unitary models of EF have largely been replaced by models that conceptualize EF as multidimensional. Although these models differ regarding the specific number of components identified and the specific assessments used to create EF factors, these models typically rely on factor analysis methods and agree that EF can be differentiated into independent processes. For example, Busch presented a model of EF using a sample of TBI patients (Busch, McBride, Curtiss, & Vanderploeg, 2005). A principal components analysis (PCA) was performed on multiple measures of EF. The authors identified three components. The first component, a higher-order EF component was thought to reflect two different processes: cognitive flexibility and self-generative behaviors. The second component identified was a mental control factor and the third component was comprised of memory error measures. Another study that utilized a factor analysis technique for characterizing EF identified six different independent EF components based on an exploratory factor analysis of 19 different EF tests (Testa, Bennett, & Ponsford, 2012). The first factor was interpreted to represent prospective working memory, the second factor was characterized to represent shifting ability, the third factor was thought to represent problem solving and task management, the fourth factor represented inhibitory control, the fifth factor represented selection and use of strategies, and the sixth factor represented self-monitoring and utilization of feedback. Another study used confirmatory factor analysis and structural equation modeling to identify EF factors across 10 tests in a sample of older adults (Hull, Martin, Beier, Lane, & Hamilton, 2008). In this case, two of the three predicted factors were

estimated: a working memory factor and a shifting factor. The third factor predicted, inhibitory control, was not supported by the model.

An influential, alternative model proposed by Miyake and Friedman, the “unity/diversity framework” for EF, attempted to integrate unitary and multidimensional frameworks of EF (Miyake & Friedman, 2012). This model accounts for both the correlation observed between different measures EFs, by suggesting there is a common underlying EF factor, and it accounts for the observation that different measures of EF do not correlate perfectly and likely require subtle but distinctly different abilities. Using a latent variable approach, the authors described three different EFs: updating, shifting, and inhibition, as well as a common factor tapped by each of the three EFs. The authors demonstrated the stability of these EF factors using longitudinal analyses. According to preliminary analyses discussed by the authors, the common EF factor was stable over a six-year time span ($r = 0.82$), as were two of the distinct EF factors ($r = 1.0$ for updating factor and $r = 0.93$ for shifting factor (Miyake & Friedman, 2012). Although the models discussed above often differ regarding the specific tests used to assess EF and in the way they “breakdown” the EF construct, there is nonetheless significant overlap between models.

Anatomical approach to executive function. While some researchers approach the study of EF from a functional or psychometric approach others rely more heavily on an anatomical approach. There is a general consensus that the prefrontal cortex and their connections play an important role in EF. The construct of EF may be broken down into subcomponents localized to subregions

of the prefrontal cortex. For example, Stuss and Alexander (2007) identified three primary executive functions associated with specific parts of the prefrontal cortex. “Initiating and sustaining a response” was associated with activation of medial frontal regions, “task setting” was associated with activation in left lateral regions, and “self-monitoring of task performance” was associated with right lateral activation. A recent meta-analytic review, however, did not find a consistent direct relationship between EF measures and the frontal cortex as previously hypothesized (Alvarez & Emory, 2006). Three commonly used measures of EF, the Wisconsin Card Sorting Test, Phonemic Verbal Fluency, and Stroop Color Word, were reviewed in relation to frontal lobe lesion studies and neuroimaging studies. Although frontal lobe regions were associated with these three tests of EF, many other regions were involved as well. The authors concluded these measures are sensitive to frontal lobe damage; however, they are not specific to frontal lobe damage. This limitation of the anatomical approach has consequently led to the development of more complex models attempting to localize aspects of EF within the brain using a cognitive neuroscience framework.

Cognitive neuroscience approach to executive function. Advances in neuroimaging analysis techniques have enabled researchers to develop more detailed models of EF. It is now possible to assess changes in neural activity during performance on a variety of EF tasks. Research in this area has provided support for the involvement of more complex neural networks during EF tasks. For example, Sharp and colleagues assessed frontal systems associated with attention, error processing, and response inhibition (Sharp et al., 2010).

Successful stopping on a response inhibition task was associated with activation in the pre-sensory motor area (pre-SMA) and right inferior frontal gyrus.

Interestingly, pre-SMA activation, more specifically differentiated attentional capture from successful stopping. This suggested pre-SMA activation is associated with successful inhibition of a motor response. Further, unsuccessful attempts at stopping, i.e., error processing, was associated with activation of the anterior cingulate cortex. This model serves as an example of how newer methodologies have enabled more precise models of EF.

In an attempt to integrate neurobiological, psychological, and computational levels of analysis, Banich proposed an integrated model of EF: the Cascade-of-Control model (Banich, 2009). The model identifies four regions of the prefrontal cortex that each contribute to EF: the posterior and mid dorsolateral prefrontal cortex, and the posterior and anterior dorsal anterior cingulate cortex. This model was based on temporal activation of these brain regions during EF tasks. Each brain region was considered a necessary component in a sequence of activations in the brain during EF. Advances in neuroimaging technologies enabled the creation of a more detailed, temporal model of EF. The need for integration across levels of analysis, as suggested by Banich, remains an important endeavor for the field. For example, longitudinal research suggests EF is not a unitary construct across the lifespan and different developmental trajectories have been proposed for different types of EF (De Luca & Leventer, 2010). Consequently, models of EF that integrate EFs across developmental periods have been proposed, as well.

Developmental perspective on executive function. Developmental trajectories of EFs have been observed across the human lifespan. This has led to models of EF founded in a developmental framework. Best and Miller (2010), for example, reviewed developmental trajectories for 3 EFs: working memory, updating, and shifting. In this model the authors highlighted EF changes observed after five years of age using the “unity/diversity” model discussed earlier. Likewise Anderson proposed a four-factor executive control system that involved attentional control, goal setting, information processing, and cognitive flexibility (Anderson, Jacobs, & Anderson, 2008). Similarly, in a succinct review, Jurado and Rosselli (2007) presented a four-factor model of executive functioning using a developmental framework to conceptualize each factor. Based on evidence from biological and developmental literature, four separate factors were proposed: attentional control, planning, set shifting, and verbal fluency. The first factor to develop is attentional control, which includes inhibitory control and selective and divided attention. Set shifting and planning abilities develop next, followed by verbal fluency. The authors discussed the role of executive function in developmental disorders and aging populations, as well.

Although a variety of EF models exist, there is substantial overlap between models. Models vary in how EF subprocesses are conceptualized relative to one another; however, there is general agreement as to the real-world behaviors associated with this construct. Given that the individual assessment measures selected and the populations investigated vary significantly across the literature it is not surprising that there are slight differences between EF models.

The model proposed by Jurado and Rosselli was selected for this proposal as a framework to assess executive functioning profiles because it utilized a developmental approach that was relevant for schizophrenia.

Schizophrenia

There is significant evidence in the literature to support the characterization of schizophrenia as a neurodevelopmental disorder (Murray & Lewis, 1987; Weinberger, 1987). Although EF deficits are observed across a range of neurodevelopmental disorders, schizophrenia provides a unique opportunity to investigate the heterogeneity of EF in the context of a complex psychiatric condition. A brief discussion of schizophrenia will be provided below including: a review of the psychiatric symptoms; a summary of the associated cognitive deficits; and a description of the development and course of the disorder. We will then focus specifically on EF within schizophrenia, including the associated EF deficits and neurobiological correlates. This will be followed by a brief discussion on the issues of heterogeneity in EF and schizophrenia and the rationale for the methods used.

Presentation, Development, and Course. Schizophrenia is a severe and debilitating disorder. Individuals diagnosed with schizophrenia represent a heterogeneous group in severity and presentation of symptoms, age of onset, and functional outcomes. The Diagnostic Statistical Manual for Mental Disorders, Version 5 (DSM 5), characterizes schizophrenia as a psychotic disorder, indicated by the presence of delusions, hallucinations, disorganized thinking, grossly disorganized or abnormal motor behaviors, and/or negative symptoms

(American Psychiatric Association, 2013). The cognitive impairments identified in schizophrenia are considered a core component of the disorder and a significant predictor of functional outcomes (Green, Kern, & Heaton, 2004; Minzenberg & Carter, 2012; Nuechterlein et al., 2011). Schizophrenia has been associated with a wide range of neurocognitive deficits across most cognitive domains including: attention, language, memory, and executive function (Palmer, Dawes, & Heaton, 2009). The largest effect sizes are observed on tests measuring episodic memory and processing speed, followed by tests of crystallized verbal knowledge and visual-spatial abilities (Palmer et al., 2009). Impairments in working memory and executive function have also been reported and will be emphasized in the following section (Kerns et al., 2008; J. Lee & Park, 2005; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009).

Although there is some variability in the development and course of schizophrenia, it is a chronic disorder characterized by three phases: prodromal, active, and residual. While the psychotic symptoms of schizophrenia often appear between late teens and middle thirties and frequently decrease in severity over the lifespan, the cognitive impairments associated with schizophrenia appear to be a relatively stable component of the disorder. Early motor, social, and cognitive developmental delays are frequently observed during childhood and prior to the first psychotic episode. A one-third to one-half standard deviation decline in cognitive functioning may occur from premorbid to schizophrenia onset (Palmer et al., 2009). However, following onset, neuropsychological symptoms appear to be stable or remit slightly. Further

despite the range of symptoms mentioned above, neuropsychological deficits associated with schizophrenia are one of the best predictors of outcome, better than the psychological symptoms (Palmer et al., 2009), and EF deficits, specifically, have been linked to functional impairments in schizophrenia (Semkovska, Bedard, Godbout, Limoge, & Stip, 2004). Consequently, an understanding of nature and origin of EF deficits in schizophrenia may have important real-world implications.

EF: Deficits and Neurobiological Underpinnings. As mentioned earlier, individuals with schizophrenia demonstrate impaired performance on a range of EFs including fluency, planning, impulse control, and cognitive flexibility. These deficits have been linked to alterations in neurobiological functioning, appear prior to the onset of psychosis, and are observed among relatives of individuals with schizophrenia. Taken together, this suggests EF deficits in schizophrenia represent meaningful differences in neurodevelopment, and a better characterization of EF deficits among individuals with schizophrenia may explain the significant heterogeneity observed in this population as a whole.

Different patterns of cortical activation during EF tasks have been observed in schizophrenia. For instance, individuals with schizophrenia show reduced planning ability on the TOL relative to healthy controls; and these deficits are associated with reduced activity in the prefrontal cortex (Zhu et al., 2010). Similarly, reduced activation in the right ventrolateral prefrontal cortex was observed in individuals with schizophrenia relative to healthy controls during a task of motor response inhibition (Kaladjian et al., 2007). Further, differences

in brain activity during EF tasks have been shown to have diagnostic implications for identifying individuals with schizophrenia. For example, neural activation during tasks of verbal fluency have been used to identify individuals with schizophrenia relative to individuals with bipolar disorder and healthy controls (92% accuracy) suggesting that the neurobiological underpinnings of EF have important implications for both understanding and identifying schizophrenia (Costafreda et al., 2011).

EF deficits have been observed during the early prodromal phase and likely represent neurodevelopmental impairments present prior to development of psychosis (Frommann et al., 2011; Koutsouleris et al., 2012). Individuals that are at high-risk for developing schizophrenia have been shown to exhibit EF deficits as well. Moreover, EF deficits among high-risk individuals have been associated with alterations in activation of specific cortical-subcortical neural networks (Koutsouleris et al., 2010). Further, alterations in the normal development of EF during adolescence have been observed in individuals at risk for schizophrenia (Bhojraj et al., 2010). More specifically, high-risk adolescents did not demonstrate the same improvements on specific EF tasks (WCST: perseverative errors) relative to healthy controls over a 2-year time frame (Bhojraj et al., 2010). Overall, research suggests EF impairments are observed early in life and may reflect different neurodevelopmental trajectories. Efforts to examine EF in relatives of individuals with schizophrenia have been informative as well. First-degree relatives of individuals with schizophrenia exhibit significant impairments in EF relative to other tests of cognitive functioning (Snitz, Macdonald, & Carter,

2006). Across 43 cognitive test scores, the largest effect sizes predicting relative-status were on Trails B, a measure of shifting, and on measures of impulsivity and reaction time. Further, higher order executive functions represented 4 of the 6 largest effect sizes identified in the study.

EF in schizophrenia has been associated with specific alterations in neurobiological function, likely represent changes in neurodevelopment that occur prior to the development of psychosis, and are observed in individuals at-risk for developing schizophrenia and among relatives of individuals with schizophrenia. In sum, EF deficits in schizophrenia appear to represent neurodevelopmental changes that may be linked to etiological processes and potentially can explain the significant heterogeneity observed in this population.

Schizophrenia and EF: Significant Heterogeneity. As was highlighted previously, schizophrenia is heterogeneous disorder associated with a range of psychiatric and cognitive symptoms. While neuropsychological deficits in schizophrenia are relatively stable within individuals they vary widely across individuals (Palmer et al., 2009). EFs in particular, are associated with significant heterogeneity in both the general population (Braver, Cole, & Yarkoni, 2010) and among individuals with schizophrenia (Raffard & Bayard, 2012). The significant variability in executive functions across individuals likely reflects both genetic and environmental influences (Braver et al., 2010), however, specific determinants of EF strengths and weaknesses have yet to be elucidated. When assessing variables characterized by increased heterogeneity, alternative methodological approaches are often warranted to better capture the nature of these variables

(Gates, Molenaar, Iyer, Nigg, & Fair, 2014). A brief discussion of cognitive subtypes in schizophrenia will be provided below, including efforts to use EF measures to classify individuals with schizophrenia. Methods to identify subtypes will then be discussed, including, the Community Detection approach utilized in this study.

The variability in cognitive performance across individuals with schizophrenia has led to increased efforts to identify neurocognitive patterns of strengths and weaknesses to better differentiate schizophrenia subtypes, and also to predict long term functioning (Levin, Yurgelun-Todd, & Craft, 1989; Palmer et al., 2009). A variety of different cognitive subtypes of schizophrenia have been proposed. Turetsky and colleagues (2002) proposed the existence of three subtypes of schizophrenia using memory assessments. Other work has found support for cognitive subtypes based on verbal memory (Bruder, Wexler, Sage, Gil, & Gorman, 2004). According to the review by Palmer et al., (2009), studies that utilized cluster analyses typically identified four subtypes. One subtype is “cognitively intact”, one shows profound impairments across domains, and two intermediate types show more impairment in a specific domain. The cognitive subtypes have been linked to demographic variables, such as years of education, but not with specific psychological symptoms.

A similar pattern of cognitive subtypes specific to EFs was observed in individuals with schizophrenia compared to healthy controls (Raffard & Bayard, 2012). As a whole, individuals with schizophrenia performed worse than controls on measures of EF. However, there was greater variability in performance on EF

tests among individuals with schizophrenia. Four subtypes were observed at approximately equal proportions in the schizophrenia sample: impaired performance on all four EF measures (24 percent of the sample), impaired performance on two EF measures (23 percent), impaired performance on three EF measures (23 percent), and impaired performance on only one measure of EF (27 percent). Although most of the schizophrenia sample displayed impairments on one or more measures of EF, a small percentage (6 percent) displayed no impairments. In general, cognitive subtyping approaches in schizophrenia have typically focused on *degree* of impairment rather than *pattern* of impairment. An understanding of the specific patterns of strengths and weaknesses, particularly within EF maybe an informative approach to explain heterogeneity in schizophrenia beyond a level of severity approach. There are a variety of more formal methods in existence for identifying cognitive subtypes; several will be briefly reviewed below.

Addressing Heterogeneity: Cognitive Subtyping Approaches

Cluster analyses are frequently used to identify cognitive subtypes. Hierarchical cluster analysis methods have been used to identify cognitive subtypes in a variety of samples, including delinquent adolescents (Teichner et al., 2000), individuals with schizophrenia (Hill, Ragland, Gur, & Gur, 2002), individuals infected with HIV (Dawes et al., 2008), and normal aging individuals (Foss, Formigheri, & Speciali, 2009). One of the primary challenges with cluster analyses is determining the most appropriate number of clusters (Burns & Burns, 2008). The number of clusters selected for the final model and the interpretation

of the meaning of the selected clusters is determined by the researcher (Ahlquist & Breunig, 2011). In two-step cluster analyses, however the number of clusters can be automatically determined. This method has been used to identify subtypes of dyslexia (Heim et al., 2008). Regardless of the type of clustering technique used, however, it is difficult to establish whether the clusters identified are representative of the true underlying structure or if they represent an artifact of the statistical analysis (Hand, Mannila, & Smyth, 2001). Palmer commented however, that there are “interpretative limitations” with cluster analyses and in some instances “cluster determination may be arbitrary” (Palmer et al., 2009, p. 371).

Latent class analyses can also be applied to detect cognitive subtypes. For example, Todd and colleagues used latent class analysis to detect subtypes of ADHD (Todd et al., 2002). Difficulties associated with identifying the number of classes in the data that correspond to the underlying structure of the data remains a challenge in this method as well as within cluster analyses (Jung & Wickrama, 2007).

Fair and colleagues presented an alternative method to analyze the underlying structure of complex neuropsychological constructs such as EF (Fair, Bathula, Nikolas, & Nigg, 2012). The authors demonstrated a novel application of graph analytic techniques traditionally applied to neural networks. More specifically, using community detection, a statistical analysis technique founded in graph theory, the authors identified distinct neuropsychological subgroups, i.e. “specific data-driven phenotypic subtypes” (p. 6770) in normal healthy controls

that inform the heterogeneity of symptoms found in individuals with ADHD. Interestingly, the authors demonstrated that heterogeneity in ADHD profiles were “nested” within normal variation (i.e. the healthy control profiles). Furthermore, the authors demonstrated that when profiles were considered, diagnostic accuracy improved considerably. In sum, the authors identified a novel way for detecting subtypes within groups of people and furthermore, the authors were able to successfully demonstrate the clinical utility of this approach.

The work by Fair and colleagues demonstrated the value of assessing traits in both impaired populations and typically developing populations and presented a novel way to identify subtypes. Recent work has applied graph theory techniques to the complex structural and functional networks within the brain (Bullmore & Sporns, 2009). Networks can be characterized based on a variety of different properties, including connectedness and small worldness (Newman, 2006). Community Detection is an approach to determine the presence of modularity within a given network. More specifically, modularity is observed in networks that are comprised of modules, or clusters of densely connected nodes. Modularity occurs when the number of connections between nodes within a module is greater relative to the number of connections to nodes outside of the module. Community detection methods are preferable to more traditional methods to detect subtypes because community detection determines the number of clusters to be detected and allows for the possibility of detecting no clusters (Newman, 2006). Additionally, Fair and colleagues were able to assess the value of the model for individual classification and found higher

accuracy of diagnostic classification when neurocognitive subtypes were considered (Fair, Bathula, et al., 2012). This approach was selected to assess the potential presence of neuropsychological subgroups in sample of individuals with schizophrenia and a sample of normal, healthy controls based on measures of EF. It was hypothesized that distinct EF subtypes would be detected and would enhance diagnostic classification.

Methods

Participants

Data was collected from four different sites: the Mind Research Network/University of New Mexico in Albuquerque, New Mexico, the University of Minnesota, Massachusetts General Hospital, and the University of Iowa. Patients were recruited from hospitals and outpatient clinics associated with the sites. Patients with a history of neurologic or psychiatric diseases other than schizophrenia were excluded. Additionally, patients who experienced head injuries, a history of substance dependence or abuse, or an IQ less than or equal to 70 were excluded. All study participants underwent an extensive clinical diagnostic assessment that included either the SCID-I/P or NP (First, Spitzer, Gibbon, & Williams, 2002) or the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen, Flaum, & Arndt, 1992). Control participants were recruited using flyers, newspaper ads, and word-of-mouth. Finally, for the present analyses, individuals for whom complete EF data was not available were also excluded. Participants included 128 individuals diagnosed with schizophrenia (32 females, 96 males) and 157 typically developing individuals (60 females, 97 males). Demographic characteristics of the sample, including ethnicity, age, and SES are provided in Table 1.

Measures

The Tower of London is a test of planning, problem solving, and inhibition. It requires individuals to build towers that match a model using the fewest number of moves possible. Individuals must look ahead to determine the order of moves needed to rearrange three color rings (Lezak et al., 2004). The TOL requires sustained

attention, planning ability, and goal management (Packwood, Hodgetts, & Tremblay, 2011). Frontal and parietal lobe activation has been observed during TOL performance (Newman, 2011).

The California Computerized Assessment Package (CalCAP) is a computerized continuous performance test that assesses sustained attention and reaction time. It is scored based on a normative sample of 656 men, age 21-72 with a mean education level of 16 years. Performance is based on reaction time measures, the number of “hits” and “false positives”, and the participant’s ability to detect the signal from distractor items. The CalCap has high internal consistency on reaction time measures ($r = 0.77$ to $r = 0.95$) and low test-retest reliability on reaction time measures at a six month follow-up visit ($r = 0.43$ to $r = 0.68$) (Miller, 2002). Reaction time measures were reported to correlate with Trails B time ($r = 0.17$ to $r = 0.32$), verbal fluency ($r = 0.13$ to $r = 0.25$). Serial Pattern Matching 1 (Sequential Reaction Time 1): press key if they see two of the same numbers in sequence. Serial Pattern Matching 2 (Sequential Reaction Time 2): press key if they see two numbers in sequence.

The Trail Making Test (TMT) is two part timed test of attention, processing speed, and cognitive flexibility (Strauss, Sherman, & Spreen, 2006). Trails A is a simple test of visual attention, motor speed, sequencing ability, and visual tracking. Trails B requires additional cognitive flexibility and set shifting. Performance on TMT is scored based upon the number of seconds taken to complete the task, though number of errors is also recorded. Reliability coefficients reported vary significantly and differ based upon population and age (Lezak et al., 2004; Strauss et al., 2006). However, most reliability coefficients reported are above 0.6, a majority are in 0.80’s, and several are in

0.90's range (Lezak et al., 2004). Lower reliability coefficients however were reported in a sample of individuals with schizophrenia (Trails A $r = 0.36$; Trails B $r = 0.63$) (Strauss et al., 2006). Effects for age, education, and linguistic ability have been reported. Lower performance on TMT has been observed in individuals with depression, schizophrenia, dementia, and traumatic brain injury. Trails B was reported to be associated with percent of perseverative errors, measure of cognitive flexibility from the Wisconsin Card Sorting Test. Trails A was reported to correlate with Digit Symbol, Digit Backward, and Stroop Color-Word scores. Trails B was found to correlate with Digit Symbol, Digit Backward, Switch-cost, and Stroop Color-Word scores (Sanchez-Cubillo et al., 2009). Research has supported the use of a Trails B minus Trails A (B-A) difference score to quantify the additional burden of shifting. Trails B minus Trails A difference score has been shown to minimize the visuospatial and working memory demands to better capture the demands of shifting set (Sanchez-Cubillo et al., 2009).

Verbal fluency measures assess spontaneous generation of words within a restricted "search category" (Strauss et al., 2006). Two different types of verbal fluency are measured by the Controlled Oral Word Association test, Semantic Fluency and Phonemic Fluency. In both tasks individuals are given one minute to generate as many words as they can within specific parameters. Both versions measure "the speed and ease of verbal production" (Lezak et al., 2004). These tasks require both an "intact semantic store" and an effective search strategy (Strauss et al., 2006). Two different store and search processes are required: clustering and switching (Troyer, Moscovitch, & Winocur, 1997). Internal consistency was reported for individual letters of the COWA. Coefficient alphas generated for the total number of words generated across trials (F, A,

and S) were reported to be high ($r = 0.83$) (Strauss et al., 2006). Test-retest reliability was found to be high in normal adults on both short-term and long-term follow-ups (r 's >0.70) (Strauss et al., 2006). Small but reliable practice effects have been observed (Strauss et al., 2006). The correlation among semantic fluency tasks was found to be moderately large ($r = 0.66-0.71$). The correlation among phonemic fluency tests has been observed to be large ($r = 0.85$ to $r = 0.94$) (Strauss et al., 2006). Education, age, reading level, and IQ effects have been observed (Strauss et al., 2006). Two similar tests of verbal fluency are included in the Delis-Kaplan Executive Function System (DKEFS) (Delis et al., 2001). The internal consistency and test-retest reliability for Verbal Fluency Condition 1: Letter Fluency Total Correct is high ($r = 0.80$ to $r = 0.89$), the internal consistency is marginal for Condition 2: Category Fluency ($r = 0.60$ to $r = 0.69$) and the test-retest reliability is adequate ($r = 0.70$ to $r = 0.79$) (Strauss et al., 2006).

Procedures

Data previously collected as part of a larger investigation of schizophrenia that also incorporated neuroimaging and genetics was analyzed. A comprehensive neuropsychological battery was administered to participants, tapping multiple cognitive domains. Specific tests from the battery hypothesized to assess different components of EF were selected for the present analysis. Tests were individually administered according to standardized procedures in quiet testing rooms.

Confirmatory Factor Analysis

A confirmatory factor analysis was conducted using the statistical analysis package for latent variables, Mplus, to identify specific neuropsychological components

(Muthén & Muthén, 1998-2010). The four-factor developmental model of EF was assessed (See Figure 1). Measures from the verbal and category fluency tests of the Delis–Kaplan Executive Function System (D-KEFS) including: Category fluency total words animals, total words fruit, and total number of words for FAS will be included on the verbal fluency factor (Delis et al., 2001). Two measures from the California Computerized Assessment Package (CalCap) computerized reaction time test that require divided attention will be included on the attention factor (Serial Pattern Matching 1: False Positive Errors and Serial Pattern Match 2: False Positive Errors) (Miller, 1990). Excess moves on the three, four, and five ring problems from the computerized version of the Tower of London test (TOL) were included on the Planning Factor (Shallice, 1982). Trails B errors and the Trails B minus Trails A difference score (B-A) from the Trail Making Test were included on the Set Shifting Factor. Multiple EF models were assessed in addition to the primary model of interest described above, including a single factor model, three-factor model, and the four-factor model with an additional single, higher-order factor. Factors within each model were allowed to correlate. Measurement invariance was assessed to examine the fit of the model in the two samples separately using the procedures outlined by Vandenberg and Lance (2000).

Community Detection

All CD analyses were conducted within the schizophrenia sample and the healthy control sample separately. Thus, correlation matrices were generated separately for the two groups using factor scores generated from the CFA. More specifically, the correlation of each individual with every other individual across the four factor scores was generated within the SZ and TD samples. This resulted in one 128-by-128 matrix

for the SZ sample and one 156-by-156 matrix for the TD sample. A threshold was applied to each correlation matrix that functioned as a cut-off for determining connected and unconnected nodes within the network. There are a variety of different methods available for determining the most appropriate threshold. Similar to the approach reported by Fair et al., a threshold was applied that ensured “reachability” was equal to one, meaning that every individual was connected to every other individual within the network by a least one path. This prevented the creation of a network where some individuals remained unconnected to any other individuals.

All community detection analyses were conducted in MATLAB (MathWorks) using the Brain Connectivity Toolbox (BCT). Modularity (Q) was calculated using the Leading Eigenvector method for Optimization of modularity as described in Newman (2006) and utilized in Fair et al., (2012).

Machine-Learning: Support Vector Machine-based approach

Machine Learning techniques have provided the field a variety of different approaches for classifying and making predictions about data. At the most basic level, machine learning involves the use of an algorithm or “machine” selected to “learn” specific parameters needed to correctly categorize data. The machine is then used to predict group membership of new, unclassified data. The support vector approach is a relatively newer machine learning technique that has been employed successfully in a variety of different contexts, including pattern recognition and classification (Hearst, Scholkopf, Dumais, Osuna, & Platt, 1998). A SVM was used in the present analyses to assess whether individuals could be classified more accurately when community profiles were considered. SVM-based pattern analysis techniques have frequently been applied to

neuroimaging analyses (Dosenbach et al., 2010; K. A. Norman, Polyn, Detre, & Haxby, 2006; Wang, Childress, Wang, & Detre, 2007; Yang, Fang, & Weng, 2012). For example, Dosenbach and colleagues (2010) demonstrated SVM-based MVPA could be used to predict an individual's brain maturity based on functional connectivity patterns (Dosenbach et al., 2010). Similarly, Fair and colleagues (2012) demonstrated individuals with ADHD could be classified into one of two distinct ADHD subtypes based on patterns of functional connectivity (Fair, Nigg, et al., 2012). The current analyses utilized a Leave-One-Out SVM, as was employed for portions of the analyses described by Fair and colleagues (2012). A Leave-One-Out SVM, or LOOM (Leave-One-Out Machine), is beneficial when examining smaller datasets, as it uses a Leave-One-Out Cross-Validation technique, where each individual is "held out" once as the test set, while the remaining dataset is used as the training set (Weston, 1999).

In order to assess the impact of community membership on classification accuracy, the SVM LOOM was applied first to the entire dataset to assess the classification accuracy based solely on the neuropsychological test scores. Next, a separate SVM LOOM was trained and evaluated within each community. The classification accuracy rate of the LOOM was then averaged across all trials.

All analyses were conducted in MATLAB (MathWorks) using the machine learning toolbox SPIDER. The LOOM algorithm within SPIDER was created by Jason Weston.

Results

Data Reduction

All neuropsychological test scores were standardized and three of the ten scores (Fluency: FAS total words, Fluency: Animals total words, Fluency: Fruits total words) were reverse-scored, such that higher scores represented poorer performance across all measures of EF. Multivariate normality of test score distributions was assessed to ensure test score distributions met the homogeneity of variance assumption required for the CFA. Square root transformations were applied to seven of the ten EF measures (Trails B: time, Trails B: errors, CalCap SEQ1: False positive errors, CalCap SEQ2: False positive errors, Three-Ring Tower of London: Excess moves, Four-Ring Tower of London: Excess moves, Five-Ring Tower of London: Excess moves) with significantly elevated levels of kurtosis (observed kurtosis greater than 10) and/or skewness (observed skewness greater than 2).

Participant Characteristics

Groups did not differ significantly on age ($p=0.450$). The SZ sample consisted of significantly more males and individuals of ethnic minority. SES and FSIQ were significantly lower in the SZ group relative to the control group (SES: $p<0.001$, $F=54.391$; FSIQ $p<0.001$, $F=16.167$). Across all EF measures the control group performed better than the SZ group. All group differences on measures of EF were statistically significant. Cognitive performance of the sample is provided in Table 2.

Confirmatory Factor Analyses

Several EF models were compared in addition to the primary model of interest described. The four-factor model exhibited the best [$\chi^2(29)=27.895$, RMSEA=0.000,

CFI=1.0, TLI=1.003]. In addition to the four-factor model, a single factor model, two-factor model, and three-factor model were assessed [1 Factor Model: $\chi^2(44)=222.779$, RMSEA = 0.119, CFI = 0.72, TLI = 0.650, SRMR = 0.077; 2 Factor Model: $\chi^2(42)=142.282$, RMSEA = 0.092, CFI = 0.843, TLI = 0.794, SRMR = 0.068; 3 Factor Model: $\chi^2(39)=109.074$, RMSEA = 0.079, CFI = 0.89, TLI = 0.845, SRMR = 0.056]. Additionally, the four-factor model of EF with an additional fifth, higher order factor was assessed [$\chi^2(37)=41.477$, RMSEA = 0.021, CFI = 0.993, TLI = 0.99, SRMR = 0.032]. Additional measures, including processing speed and fine motor skills were examined as well, however, the four-factor model remained the best characterization of EF in the sample [4 Factor Model with processing speed factor: $\chi^2(90)=635.752$, RMSEA = 0.146, CFI = 0.697, TLI = 0.596, SRMR = 0.083; 4 Factor Model with Fine Motor skills covariate: $\chi^2(41)=46.722$, RMSEA = 0.022, CFI = 0.992, TLI = 0.987, SRMR = 0.3]. The four-factor EF model was then assessed with all factors regressed age [$\chi^2(35)=39.771$, RMSEA = 0.022, CFI = 0.993, TLI = 0.988, SRMR = 0.3] and regressed on estimated FSIQ and age [$\chi^2(41)=44.99$, RMSEA = 0.018, CFI = 0.995, TLI = 0.993, SRMR = 0.028]. Factor loadings for the final model regressed on age are provided in Figure 1. Measurement invariance was assessed to examine the fit of the model in the two samples separately. Configural measurement invariance were assessed in MPLUS using the 4 factor model of EF. Results revealed configural invariance was not supported and measurements were invariant across groups. Upon closer examination of the factor structure within each group it was noted that factor loadings of several test scores did not sufficiently load onto the EF factor predicted within the control sample. More specifically, it appeared there may have been a ceiling effect for several of the test

scores within the control group. Overall, the EF model exhibited a better fit in the schizophrenia sample relative to the typically developing sample.

Community Detection Results

Modularity was detected in both the schizophrenia (SZ) group and the typically developing (TD) group. Modularity within the SZ group was greater relative to the TD group (SZ: $Q = 0.7011$; TD: $Q = 0.5409$). Five modules (i.e. communities) were identified within the TD group and seven modules were identified within the SZ group. The modules identified within each group were conceptualized as potential EF profiles and were examined to identify any strengths and/or weaknesses.

In order to capture within-group strengths and weaknesses, a total EF score was calculated separately for the SZ and TD groups to represent each group's mean level of performance across all four EF factors. Similar to the approach described by Fair and colleagues (2012), a "primary" factor(s) approach was taken, meaning each profile was characterized by the "stand out" factor(s). Unlike the approach by Fair and colleagues, the current approach utilized both strengths and weaknesses. Mean factor scores within each profile were compared to the corresponding group's total EF score. A weakness was defined as a factor score greater than $\frac{1}{2}$ standard deviation below the group EF mean, while a strength was defined as a factor score greater than 1 standard deviation above the group EF mean. To more accurately capture the pattern of scores within each profile, the presence of "relative strengths" was defined as a strength that was greater than $\frac{1}{2}$ a standard deviation above the mean. EF profiles for both groups are provided in Figure 2 and Figure 3.

Results revealed similarities in EF profiles in the SZ group and TD group. More specifically, the 7 SZ profiles appeared to be nested within the 5 TD profiles, resulting in 5 EF profiles, with 2 additional subtypes within the SZ group. Within the TD sample, EF profile 1 was characterized by a **strength in verbal fluency**, with intact performance on additional EF measures. EF profile 2 was characterized by a **weakness in shifting**, and relative strengths in fluency and planning. EF profile 3 was characterized by **weaknesses in attention and planning**, with relative strengths in shifting and fluency. EF profile 4 was characterized by a **strength in shifting, a weakness in planning**, and a relative strength in fluency. Finally, EF profile 5 was characterized by a **weakness in attention**.

EF profiles were then compared based on age, sex, SES, ethnicity, FSIQ, and psychiatric symptoms using a Multivariate Analysis of Variance. The five profiles identified in the control group did not differ on age, SES, sex or site. Differences in FSIQ were significant ($F = 3.242, p = 0.014$). More specifically, post hoc tests revealed EF profile 1 exhibited greater intelligence relative to EF profiles 2 and 5 ($p < 0.05$). Demographic characteristics of the 5 communities, including ethnicity, age, and SES are provided in Table 3.

Within the SZ sample, EF profile 1 was characterized by a relative **strength in verbal fluency**. EF profile 2A was similar to the second profile identified in the TD group as it was characterized by a **weakness in shifting**, with a modified pattern of scores on additional measures. EF Profile 2B was characterized by a **strength in planning**. Notably this community was the smallest identified module and it may not represent a reliable EF profile within the SZ population. It was matched with the second

TD profile, the only TD profile that exhibited a strength in planning. EF profile 3A was characterized by a **weakness in planning** and exhibited a similar pattern of scores as the third profile identified in the TD group. EF profile 3B was characterized by a **weakness in attention**, however, exhibited a similar pattern of scores as the third profile identified in the TD group. EF profile 4 was characterized by a **strength in shifting** similar to the fourth profile TD group. Finally, EF profile 5 was characterized by a **weakness in attention** similar to the fifth profile identified in the TD group.

EF profiles were then compared based on age, sex, SES, ethnicity, FSIQ, and psychiatric symptoms using a Multivariate Analysis of Variance. The seven profiles identified in the SZ group did not differ on age, SES, or site. While the typically developing profiles differed on FSIQ across profiles, FSIQ was not significant within the SZ group. Profiles differed significantly on sex. Specifically, women were predominantly represented within profile 1, profile 3A, and profile 3b. Profiles were also compared based on several symptom measures. With the exception of total akathisia, a measure of restlessness, profiles did not differ in terms of positive symptoms, negative symptoms, or disorganized symptoms. Demographic characteristics of the 7 communities, including ethnicity, age, and SES are provided in Table 4.

Support-Vector Machine-Based Learning Results

Entire Sample. Based solely on the four executive function factors identified in the CFA, the LOOM SVM exhibited better than chance diagnostic classification. The accuracy of the LOOM SVM classifier was 69.19%.

Within EF Profiles. When the LOOM SVM was employed within EF profiles, the accuracy of diagnostic classification improved. More specifically, within Profile 1, the accuracy of the classifier was 86.84%; within Profile 2A the accuracy of the classifier was 84.62%, within Profile 2B the accuracy of the classifier was 91.18%, within Profile 3A was 93.94%, within Profile 3B was 94.87%, within Profile 4 the accuracy of the classifier was 96.55%, and within Profile 5 the accuracy of the classifier was 66.1%. Overall, this suggests if the EF profile is considered, the rate of accuracy is improved in 6 of the 7 profiles. When diagnostic accuracy was averaged across all 7 profiles (mean accuracy: 87.72%), accuracy remained significantly greater ($\chi^2 = 29.12$, $p < 0.01$). Diagnostic accuracy rates for the entire sample and for individual profiles are provided in Figure 4.

Discussion

The primary aim of this study was to better characterize the heterogeneity of EFs within the context of normal and aberrant development. Fair and colleagues (2010) presented a novel methodological approach for characterizing significant neurocognitive heterogeneity within normal and aberrant development. The authors utilized methods traditionally used to study networks to assess whether individuals within the sample clustered together based upon neuropsychological performance. A similar approach was used in the current analyses to examine heterogeneity in EFs within individuals with schizophrenia and typically developing individuals. The factor scores from a confirmatory factor analysis of EF were used to generate correlation matrices within the typically developing sample and the schizophrenia sample, separately. Each correlation matrix then served as a connectivity matrix of individuals within each diagnostic group. Community detection analyses were then applied to both connectivity matrices to assess the degree of modularity (i.e. clustering) within each group separately. These analyses revealed the presence of clusters or subgroups within the sample, meaning individuals were more closely connected (via the connectivity matrix) to individuals within their cluster compared to individuals outside of their cluster. The profiles identified within the typically developing sample and the schizophrenia sample were then characterized and matched based upon defining strengths and weaknesses. Finally, a machine learning algorithm was used to assess whether EF profile membership could enhance diagnostic accuracy. The algorithm was first trained to classify individuals on diagnosis within the entire sample based on the neuropsychological test scores alone. Next, the accuracy of diagnostic classification

was examined within each of the EF profiles separately. The percentage of individuals accurately classified by diagnosis was then compared across the two methods.

A Four-Factor Model of EF

In the present study, the four-factor model of EF proposed by Jurado and Rosselli (2007) was supported in the combined sample. This suggests that verbal fluency, attention, planning, and shifting ability are each distinct factors of EF that can be examined separately. Notably, the model proposed by Jurado and Rosselli (2007), though based within neurodevelopmental literature is, nonetheless, theoretical. Consequently, there are a number of potential neuropsychological measures in existence with the potential to tap the EF constructs outlined by the model. While the neuropsychological measures selected for the current analyses have demonstrated excellent construct validity and reliability, it is nonetheless possible that alternative measures of EF could be considered when assessing the model. Consequently, a brief examination of the nature of each of the four factors as defined within the context of this study was thought to be beneficial. We will then discuss the major limitations of the current model and how these were addressed.

Upon further examination of the model used in the current analyses, it was concluded that the Attention Factor represented in these analyses was more accurately characterized as a measure of Impulse Control. Notably, Jurado and Rosselli (2007) incorporated a variety of attention measures within the proposed Attention Factor, including sustained attention, divided attention, and selective attention. Additional measures of attention were considered in the present analyses (e.g. processing speed), however, the final model selected, using impulse control measures, was the best fitting

model. Second, while the Fluency factor captured both categorical and semantic verbal fluency skills, it did not encompass nonverbal fluency skills. Consequently, this factor is more aptly characterized as Verbal Fluency. Third, while the Shifting Factor does represent one's ability to quickly and accurately shift between two different sets of information based on Trails B performance, additional measures of shifting exist (e.g. WCST) that might reveal shifting abilities in other contexts. Fourth, the Planning Factor is based upon errors in planning ability. In future studies, it would be beneficial to examine specific aspects of planning to tease apart components of planning (e.g. formation versus execution of a plan).

An additional consideration alluded to in earlier sections, is the fact that "pure" measures of executive function are very difficult to achieve. The very nature of neuropsychological tests inherently requires the utilization of multiple skills, making it challenging to disentangle more specific skills. For instance, all measures of EF used in the current analyses were administered under timed conditions, adding an additional processing speed confound. Further, several of the neuropsychological measures used in the current study require some degree of fine motor manipulation and thus add an additional confound of fine motor skills. While processing speed and motor skills remain an issue across neuropsychological studies, attempts were made to specifically address this in the current analyses. Specifically, measures considered to be more "pure" measures of processing speed and motor function were included in additional models of EF but were deemed a poor fit, suggesting the final model selected remained the best fitting model.

Finally, measurement invariance was not supported in the current analyses. This is a notable limitation of the current study. In part, this likely reflects differences in heterogeneity between the two groups across measures. However, this also suggests the possibility that EF measures may “tap” different constructs in the two groups. Alternatively, it is possible that there is an unidentified factor selectively influencing EF skills within the schizophrenia sample. Additionally, it is worth noting that CFAs are sensitive to sample size and when the model was examined within each group separately, it is possible there was not sufficient power to assess the model. Further, it was believed that the Community Detection analyses might be an alternative way to address this issue.

To the best of our knowledge, the present analysis is the first published attempt to empirically establish Jurado and Rosselli’s model of EF. Despite the limitations discussed above, the results from this study suggest the neurodevelopmental model of EF can be demonstrated within the context of normal and abnormal development.

EF Profiles

In the present analyses EF profiles were identified within a sample of typically developing controls and a sample of individuals with schizophrenia using community detection procedures. Within the typically developing control group, 5 different EF profiles were observed. Each profile reflected a different pattern of EF strengths and/or weaknesses. Within the schizophrenia sample, 7 different EF profiles were observed. Interestingly, each of the 7 profiles appeared nested within the 5 EF profiles observed in the typically developing sample. A discussion of the nature of each of the 5 EF profiles

will be provided, followed by a discussion of the major limitations and how these were addressed.

The first profile was characterized by a relative strength in verbal fluency that is likely driven by intelligence. The second profile represented a weakness in shifting with intact impulse control. The third profile demonstrated an impairment in inhibitory control with intact shifting ability. The fourth profile exhibits a distinct impairment in planning relative to other EF tasks. The fifth profile, exhibited less variability overall, with a relative strength in planning and relative weakness in attention.

Overall, our approach aimed to consider potential “trade offs” between different EFs. While Fair and colleagues characterized neuropsychological profiles based on the primary impairment(s), we attempted to consider both strengths and weaknesses. Arguably, an approach aimed at characterizing not only relative impairments, but also relative strengths, is more congruent with the characterization of neuropsychological scores in clinical practice. Further, this approach has the potential to generate a more holistic picture of the individual’s functioning in the world. Nonetheless, there are alternative ways one might define a “weakness” or “strength”. For instance, one could define a weakness based on standardized scores in the entire sample, standardized scores based only on the typically developing sample, or based on normative data. Additionally, one could also characterize profiles based on additional factors such as slopes within each profile or degree of variability within each profile. Notably, when examining matched profiles some profiles exhibited greater similarity than others (i.e. some profiles “matched” better than others). Profile 2B, for instance, exhibited a planning strength, however, the pattern of scores differed on other factors. Given the

very small sample size of profile 2B ($n = 9$) this profile likely reflects an idiosyncratic cluster specific to the current sample. Finally, when considering profile matching, it is also possible that certain EF profiles may exist within schizophrenia that are not represented within the normal population.

The EF subtypes identified in the present analyses are based upon the four EF factors from the CFA. Consequently, different models of EF could potentially lead to the identification of different EF profiles. This is a limitation of the current study. Future studies would benefit from incorporating additional models of EF. Further, the current analyses are limited by a small sample size. It would be beneficial to attempt additional subtyping approaches to further validate the ones identified in the current study.

Diagnostic Accuracy

In the present study considering an individual's EF profile improved diagnostic accuracy for a majority of the EF profiles identified. As described above, efforts were made to match profiles based upon *both* EF strengths and weaknesses. While there are alternative ways one could match EF profiles, the current approach does appear to be a clinically meaningful method. Presumably, if profiles were matched arbitrarily one would not expect to observe improvements in diagnostic accuracy. When examining the method for matching profiles presented in Fair et al., (2012), similar challenges were observed. Fair and colleagues acknowledged profiles did not match perfectly on all cognitive factors. Rather, they focused on the defining factor(s) that characterized a given profile. Future studies with the benefit of larger samples can explore further various approaches to matching cognitive profiles.

Overall, the increased accuracy in diagnostic prediction was quite profound for a majority of the EF profiles. When accuracy rates were averaged across all 7 profiles, the overall accuracy was increased by 18.5%. While Fair and colleagues, reported diagnostic accuracy rates between 61.9% and 84.1% when cognitive profiles were considered, the current results suggest even greater improvements in diagnostic accuracy (66.1% to 96.55%). Across the 7 profiles, diagnostic accuracy was lowest for EF profile 5. In part this may reflect greater variability in scores within the schizophrenia sample relative to the typically developing sample. Alternatively, perhaps this profile could be characterized differently resulting in a better fit. Future studies with larger sample sizes may be able to further examine this particular subtype.

Overall, the increased diagnostic accuracy observed when EF profiles were considered has significant implications for clinical and etiological research approaches. First, at a clinical level, these findings suggest EF profiles have the potential to aid in earlier detection of schizophrenia. Further, theoretically, these profiles could be associated with clinical correlates, such as response to intervention. At an etiological level, these findings support the notion of examining EF profiles in the context of other research areas. If consideration of EF profiles improves detection of diagnosis potentially, consideration of EF profiles could improve the detection of specific neural and genetic factors associated with the disorder. For instance, consideration of EF profiles might improve detection of different frontal lobe abnormalities in schizophrenia.

Conclusions

EF profiles can explain normal variation in EFs. Using a strengths and weaknesses approach, this study has characterized normal variation in EFs into 5 EF profiles. The

EF factors examined were based upon a developmental conceptualization of EFs suggesting that the EF profiles may represent different developmental trajectories within the normal population. One could speculate that these profiles may represent individual differences in the types of strategies one employs when navigating through novel environments and solving problems. Presumably, these profiles could also represent trade offs in skill sets. There is some evidence in the literature to support trade-offs between different EF factors. For instance, Miyake et al. presented evidence for a trade off between staying on task and shifting ability. Future research examining potential trade-offs during the development of cognitive skills would be of interest and could potentially explain the given profiles observed in the typically developing sample. For instance, Life History Theory, an evolutionary framework for characterizing the timing of major life events, may provide a meaningful way for characterizing trade-offs in EFs.

Variation in EF in schizophrenia is nested within normal variation. EF

heterogeneity in schizophrenia appears to be nested within normal EF variation. The literature typically has emphasized a deficit-approach to examining EFs in schizophrenia. While there is ample support to suggest individuals with schizophrenia exhibit impairments in EFs, this is the first study to demonstrate these impairments occur within the context of normal EF variation. Notably, there are also slight variations in the EF profiles observed within the schizophrenia group compared to the typically developed sample. Potentially, these differences may provide insight into how neurodevelopmental processes go awry in schizophrenia. For example, a longitudinal study of adolescents at risk for schizophrenia found that individuals at risk for developing schizophrenia did not demonstrate the same age-related improvements in

shifting ability exhibited in the typically developing control group (Bhojraj et al., 2010). Future studies that examine these profiles in individuals at risk for schizophrenia compared to healthy controls would be useful. Additionally, analyses to further elucidate possible neurobiological correlations associated with specific profiles would be of interest. For example, EF profiles may represent different etiological pathways characterized by different genetic variables. Further, these differences may represent differences in brain structure and function. An examination of gray matter variations, for instance, may reveal differential patterns of gray matter volumes across the different profiles.

Clinical applications of EF profiles for schizophrenia. Results from this study have the potential to improve patient care in several ways. Evidence from the literature and evidence from the current analyses provides further support for considering schizophrenia as a neurodevelopmental disorder, much like autism is conceptualized. Although onset of psychosis and a diagnosis of schizophrenia typically occur during young adulthood, there is a significant body of literature that supports neurodevelopmental aberrations much earlier in life. Utilizing neuropsychological markers, such as EF profiles, in the diagnostic process has the potential to increase early detection of schizophrenia. Early detection is of particular importance, given evidence from the literature that suggest earlier interventions can reduce the severity of symptoms and potentially even prevent onset of psychosis. Further, understanding the heterogeneity among schizophrenia populations has the potential to improve treatment recommendations. Potentially EF profiles could explain other aspects of heterogeneity including differences in long-term outcome and response to specific interventions. For

instance, within this sample, a comparison of EF profiles within the schizophrenia sample revealed significant differences between profiles on the Barnes Akathisia Scale, a measure of neurological symptoms associated with use of antipsychotic medications. Although it is impossible to know retrospectively if these individuals were more vulnerable to the side effects of antipsychotic medications, future studies could prospectively examine clinical issues such as vulnerability to medication side effects.

The findings presented here suggest EF has the potential to inform diagnostic issues and should be considered as part of the diagnostic process. Currently, schizophrenia is conceptualized with the Diagnostic Statistical Manual (DSM) as a psychotic disorder. However, with increasing interest in understanding the neurocognitive deficits associated with schizophrenia, it has been suggested that schizophrenia is better conceptualized as a disorder of cognition (Kahn & Keefe, 2013). Results presented here provide further support for future versions of the Diagnostic Statistical Manual (DSM) conceptualizing schizophrenia as a cognitive disorder.

Table 1

Sample Demographics

	SZ	TD	Significance
Sample Size	128	157	---
Age, years Mean (S.D.)	33.14 (10.908)	31.59 (11.349)	0.332
Sex (M, F)	96, 32	97, 60	0.022
Ethnicity (% Hispanic)	14%	18%	0.340
(% non-Caucasian)	17%	10%	0.055
SES Mean (S.D.)	3.46 (0.98)	2.70 (0.56)	<0.001
Parent SES Mean (S.D.)	2.82 (0.988)	2.73 (0.746)	0.470

Note: SES, Socio-economic status; M, male; F, female; S.D., standard deviation; N.S., not significant. Significance levels were determined by independent samples t-test and χ^2 analysis.

Table 2

Cognitive Performance

	SZ	TD	Significance
Trails B Time – Trails A Time	-0.396 (1.176)	0.323 (0.678)	<0.001
Trails B: Errors	-0.159 (1.087)	0.130 (0.906)	0.017
CalCap SEQ1: False positive errors	-0.293 (1.082)	0.239 (0.860)	<0.001
CalCap SEQ2: False positive errors	-0.307 (1.175)	0.250 (0.746)	<0.001
Three-Ring Tower of London: Excess moves	-0.335 (1.067)	0.273 (0.852)	<0.001
Four-Ring Tower of London: Excess moves	-0.295 (1.048)	0.240 (0.893)	<0.001
Five-Ring Tower of London: Excess moves	-0.346 (1.134)	0.2826 (0.772)	<0.001
Fluency: FAS (number of words)	-0.301 (1.030)	0.246 (0.906)	<0.001
Fluency: Animals (number of words)	-0.475 (0.958)	0.387 (0.859)	<0.001
Fluency: Fruits (number of words)	-0.471 (0.846)	0.384 (0.953)	<0.001
Fluency Factor	-0.784 (0.821)	0.131 (0.726)	<0.001
Planning Factor	-1.056 (0.936)	-0.289 (0.585)	<0.001
Shifting Factor	-0.952 (1.183)	-0.218 (0.680)	<0.001
Attention Factor	-1.161 (0.913)	-0.398 (0.584)	<0.001
EF Mean	-0.988 (0.803)	-0.194 (0.477)	<0.001

Note: CalCap, California Computerized Assessment Package; S.D., standard deviation. Significance levels were determined by independent samples t tests.

Table 3

Healthy Control Communities Demographics

	Profile 1	Profile 2	Profile 3	Profile 4	Profile 5	Significance
N	47	26	18	18	48	----
Age, years						
Mean (S.D.)	31.91 (10.886)	31.50 (10.428)	34.56 (11.330)	29.61 (11.247)	30.96 (12.493)	0.755
Sex (M, F)	27, 20	19, 7	8, 10	12, 6	31, 17	0.321
Ethnicity						
(% Hispanic)	21%	31%	17%	11%	13%	0.314
(% non-Caucasian)	9%	8%	13%	17%	10%	0.761
SES						
Mean (S.D.)	2.53 (0.546)	2.73 (0.533)	2.72 (0.575)	2.67 (0.485)	2.85 (0.583)	0.223
Parent SES						
Mean (S.D.)	2.55 (0.775)	2.88 (0.711)	2.83 (0.514)	2.61 (0.502)	2.83 (0.859)	0.262
FSIQ						
Mean (S.D.)	122.17 (17.99)	114.34 (17.38)	116 (12.95)	115.94 (11.25)	111.4 (11.52)	0.019

Note: SES, Socio-economic status; M, male; F, female; S.D., standard deviation; N.S., not significant; FSIQ, Full Scale Intelligence Quotient; Significance levels were determined by a Multivariate Analysis of Variance test.

Table 4

Schizophrenia Communities Demographics

	Profile 1	Profile 2A	Profile 2B	Profile 3A	Profile 3B	Profile 4	Profile 5	Significance
N	30	27	9	22	16	12	12	---
Sex (M, F)	17, 13	23, 4	9, 0	16, 6	9, 7	11, 1	11, 1	0.027
Age, years Mean (S.D.)	34.17 (11.733)	33.07 (11.259)	28.33 (9.394)	33.68 (10.714)	36.19 (12.106)	36.42 (9.385)	26 (6.060)	0.140
Ethnicity (% minority)	3%	30%	11%	41%	13%	8%	0%	0.240
(% non Caucasian)	6.7%	33.3%	22.2%	40.9%	25%	16.7%	0%	0.012
SES Mean (S.D.)	3.38 (1.049)	3.44 (1.083)	3.33 (0.707)	3.18 (0.958)	3.94 (0.929)	3.67 (0.778)	3.42 (0.996)	0.021
Parent SES Mean (S.D.)	2.75 (1.175)	3.00 (1.118)	2.44 (0.882)	2.45 (0.596)	2.88 (0.957)	3.50 (0.674)	2.83 (0.937)	0.046
FSIQ	102.1 (20.366)	95.037 (17.7145)	108.33 (17.468)	96.6818 (17.2029)	96.56 (14.6877)	100 (11.7859)	103.33 (16.88)	0.202
Positive Symptoms	5.03 (2.371)	4.85 (3.009)	5.67 (1.50)	4.5 (2.721)	4.5 (3.286)	5.42 (2.778)	4.33 (3.651)	0.884
Negative Symptoms	8.17 (3.949)	7.7 (4.664)	8.22 (3.632)	7.86 (4.178)	8.25 (4.041)	8.58 (2.429)	8.25 (4.595)	0.997
Disorganized Symptoms	1.90 (2.074)	1.44 (1.695)	2.67 (2.693)	1.68 (1.729)	2.44 (2.22)	1.75 (2.34)	1.5 (1.567)	0.600
BA Total	1.17 (2.036)	0.81 (0.921)	0.89 (1.965)	1.41 (2.261)	1.38 (1.455)	2.00 (2.629)	1.0 (1.651)	0.010

Note: SES, Socio-economic status; M, male; F, female; S.D., standard deviation; N.S., not significant; FSIQ, Full Scale Intelligence Quotient; BA, Barnes Akathisia Scale; Significance levels were determined by multivariate analysis of variance test.

Factor loadings for final EF model

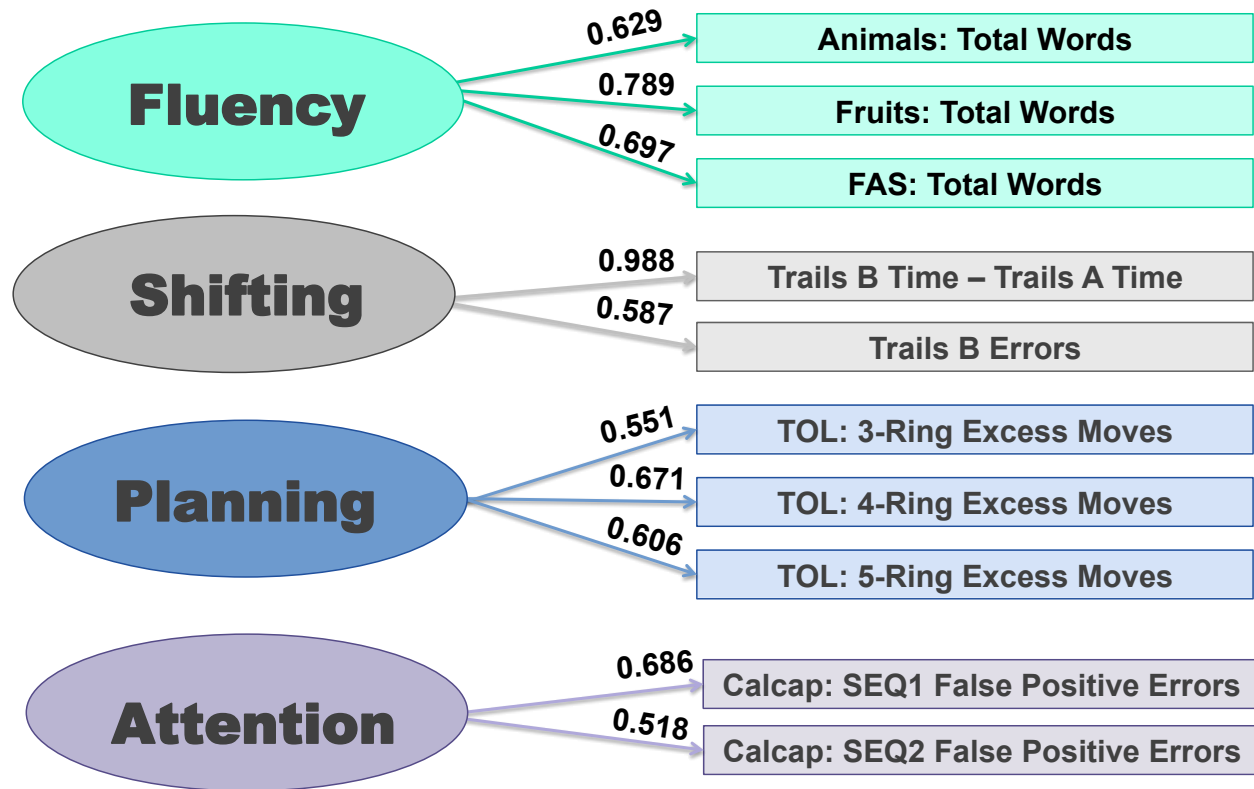


Figure 1

Note: Calcap, California Computerized Assessment Package; TOL, Tower of London.

EF Profiles: Strengths and Weaknesses

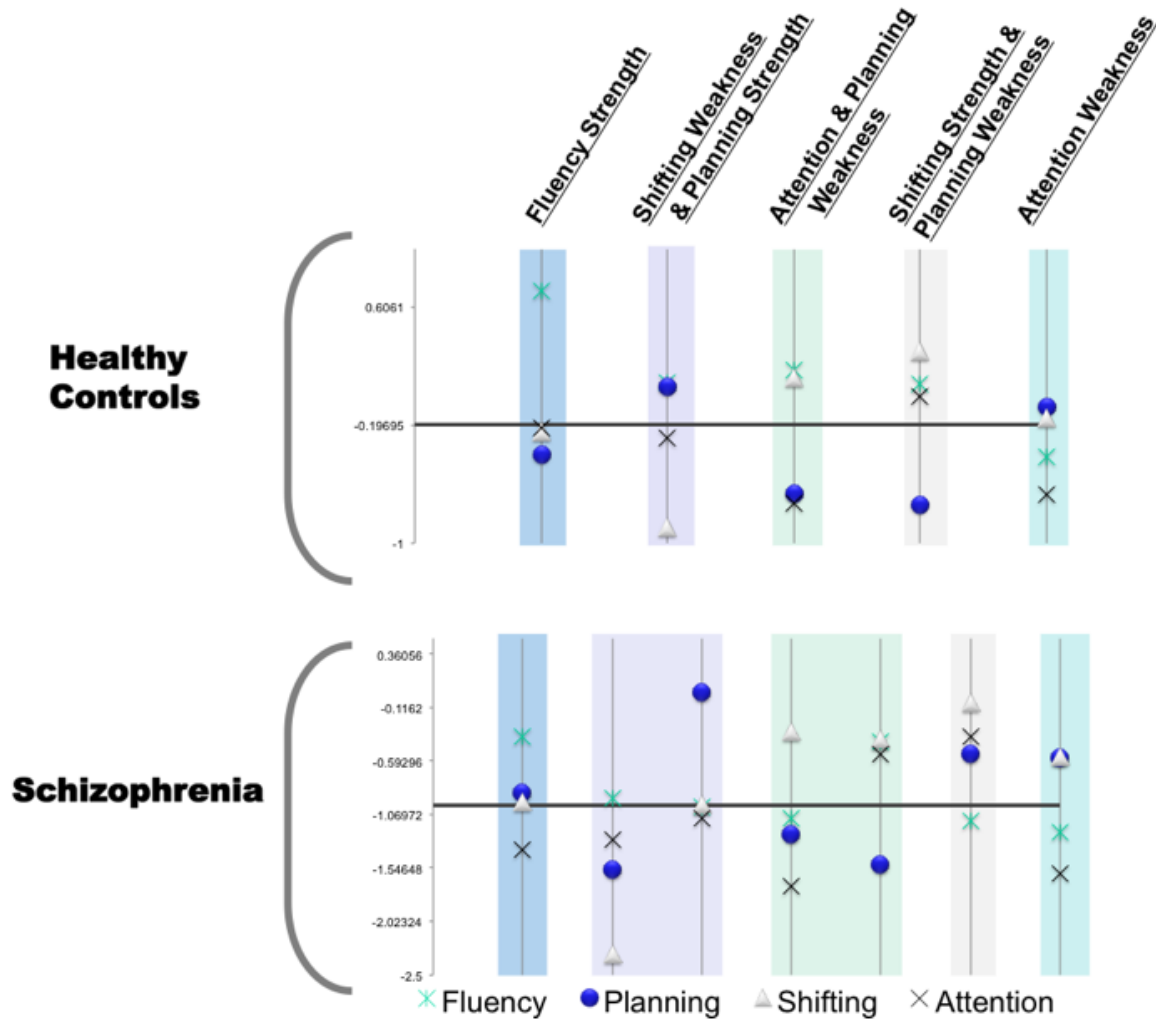


Figure 2

Note: EF profiles are labeled based on the defining EF strengths and/or weaknesses. Matching profiles are highlighted with the same color (EF 1: blue, EF 2: purple, EF 3: green, EF 4: gray, EF 5: aqua). Mean factor scores for each of the EF profiles are shown with a corresponding symbol (Fluency Factor Mean: turquoise asterisk; Planning Fluency Factor Mean: blue circle; Shifting Factor Mean: silver triangle; Attention Factor Mean: black “X”). The horizontal axis represents the within group EF total score. The vertical axis represents the mean factor score. Higher scores indicate better performance.

EF Profile Patterns

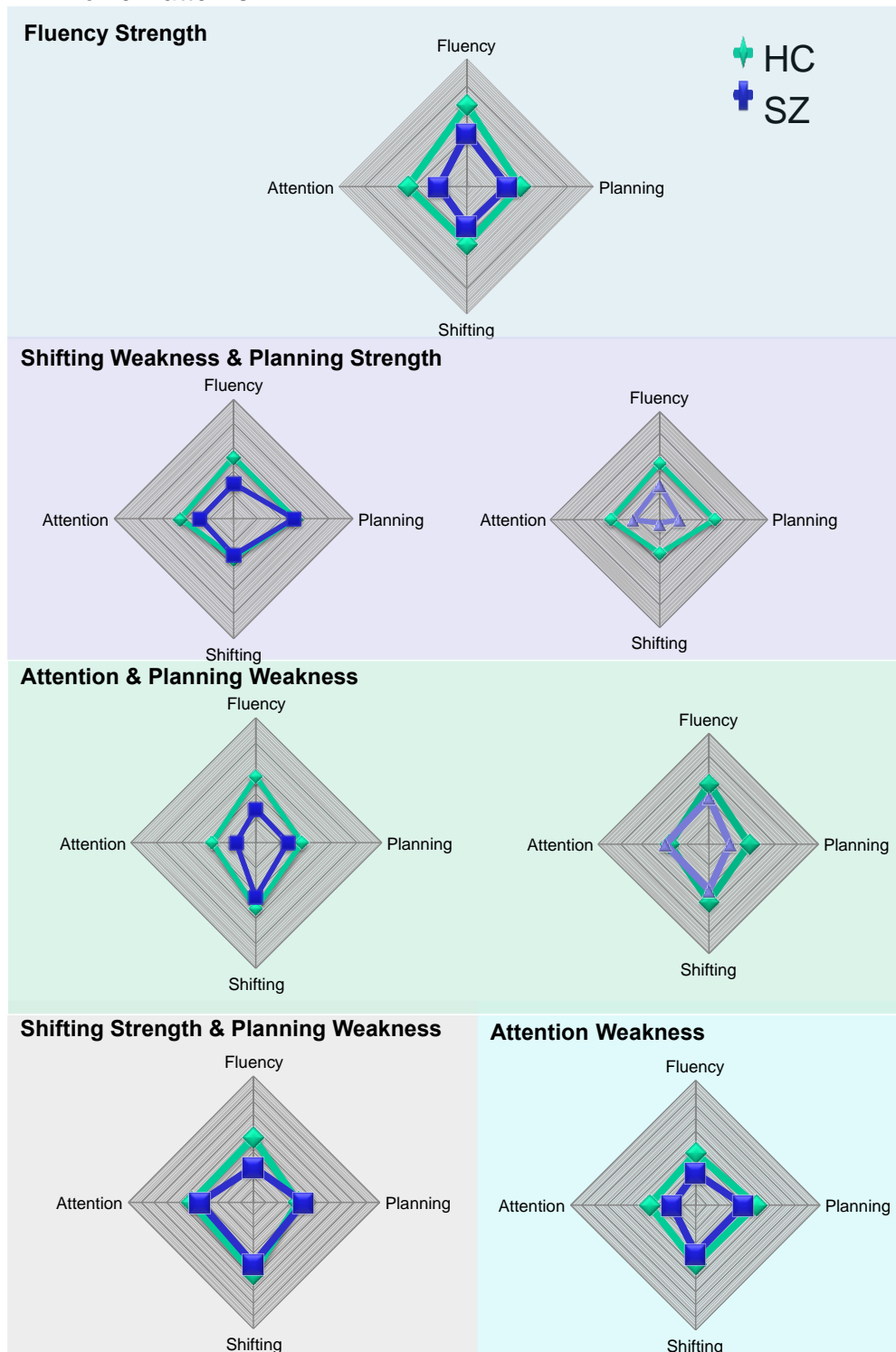


Figure 3

Note: The pattern of EF scores for each profile is visually represented. Each node represents the within profile mean factor score. Factor scores further away from the center represent better performance. The TD EF profiles are depicted in green while the SZ EF profiles are shown in blue and purple.

Diagnostic Accuracy Rates

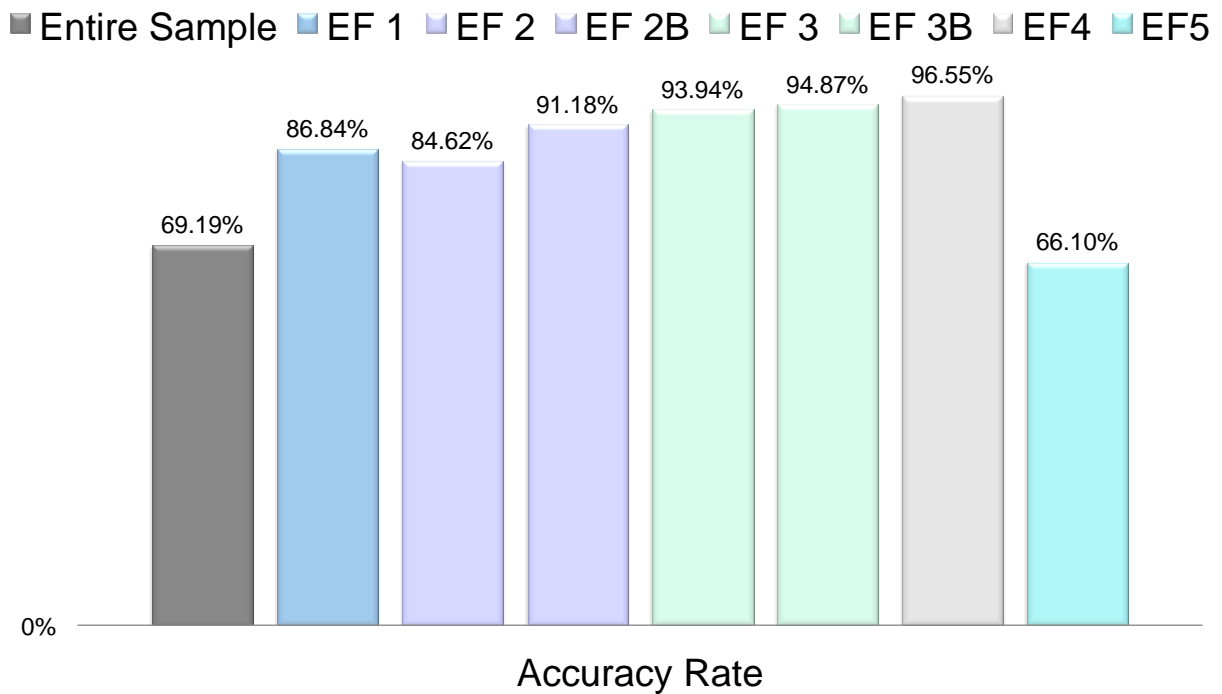


Figure 4

Note: The percentage of individuals accurately classified by diagnosis via the LOOM SVM is shown for each EF profile. The vertical axis represents percentage of individuals accurately classified. Each EF profile is depicted in a different color (EF profile 1: blue; EF profile 2A and EF profile 2B: lavender; EF profile 3a and EF profile 3B: light green; EF profile 4: light gray; EF profile 5: aquamarine). The charcoal bar on the far right represents diagnostic accuracy when EF profiles membership is not considered.

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