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Patients with schizophrenia often exhibit structural brain abnormalities, as well as neurological soft signs, consistent with its conceptualization as a neurodevelopmental disorder. Neurological soft signs are mild, presumably nonlocalizing, neurological impairments that are inferred from performance deficits in domains such as sensory integration, motor coordination, and motor sequencing. The vulnerability for schizophrenia is presumed to be expressed across a broad continuum of impairment referred to as schizotypy. It is hypothesized that nondisordered people along the schizotypy continuum should exhibit elevated rates of neurological soft signs. The present study examined the relation of psychometrically identified positive and negative schizotypy with neurological soft signs using the Neurological Evaluation Scale (NES) in a nonclinically ascertained sample of young adults (n = 177). As hypothesized, negative, but not positive, schizotypy was related to increased neurological soft signs in tasks that assessed fine and gross motor coordination, motor sequencing, eye movement abnormalities, and memory recall. However, positive schizotypy was associated with increased neurological soft signs in tasks related to sensory integration dysfunction. In general, the positive x negative schizotypy interaction term was unrelated to individual neurological soft sign tasks. The findings support: a) the theory that the vulnerability for schizophrenia is expressed across a broad continuum of subclinical and clinical impairment referred to as schizotypy; b) the multidimensional structure of schizotypy;

and c) the notion that schizotypy is an appropriate construct for understanding the etiology and development of schizophrenia-spectrum disorders.

NEUROLOGICAL SOFT SIGNS IN PSYCHOMETRICALLY IDENTIFIED SCHIZOTYPY

by

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CHAPTER I

INTRODUCTION

Patients with schizophrenia exhibit structural brain abnormalities, as well as neurological soft signs, consistent with the conceptualization of schizophrenia as a neurodevelopmental disorder. Current neurodevelopmental models posit that the vulnerability for schizophrenia is expressed across a dynamic continuum of clinical and subclinical impairment referred to as schizotypy. The present study examined the expression of neurological soft signs in psychometrically identified positive and negative schizotypy.

Schizophrenia

Schizophrenia involves a family of severe mental disorders that, in their extreme, are characterized by the presence of psychotic and residual symptoms, as well as a marked decline in functioning (American Psychiatric Association, 2000). These symptoms are often classified as positive, negative, and disorganized. Positive (or florid) symptoms reflect an excess or distortion of normal functions such as delusions and hallucinations. Negative (or deficit) symptoms reflect a diminution or loss of normal functions such as social anhedonia, affective flattening, alogia, and avolition. Cognitive and behavioral disorganization includes formal thought disorder, inappropriate affect, and gross disruptions in behavior. Attenuated and transient forms of positive and negative symptoms are often exhibited by nondisordered people who are presumed to be

vulnerable for schizophrenia, whereas disorganized symptoms appear to be more of a disease marker for full-blown schizophrenia (i.e., disorganized symptoms predominately occur in prodromal and spectrum disorder patients, not in nondisordered schizotypes).

Current etiological models conceptualize schizophrenia as a neurodevelopmental, rather than a neurodegenerative, disorder[1] (e.g., Weinberger, 1987; Meehl, 1990; Andreasen, 1999; Keshavan, Kennedy, & Murray, 2004). The neurodevelopmental hypothesis posits that the liability for schizophrenia arises from neural dysmaturation – a subtle disruption in brain development that begins in the prenatal period and culminates in late adolescence or early adulthood (Andreasen, 1999). Neural dysmaturation does not necessarily lead to schizophrenia, but rather is expressed across a continuum of impairment referred to as schizotypy (Meehl, 1990). This formulation suggests that schizophrenia and schizophrenia-spectrum disorders can be best conceptualized as the most severe manifestations of schizotypy. Thus, neural dysmaturation appears to be necessary, but not sufficient for the development of full-blown schizophrenia, and is expressed across the schizotypy continuum.

The process of neural dysmaturation is presumed to result from the interaction of multiple risk factors including genetic inheritance, gene expression, pre- and perinatal insults, and other biopsychosocial stressors. Although neural dysmaturation occurs across development, there are several critical periods in which disruptions in neural development markedly heighten the risk for schizotypy, and thus schizophrenia (e.g.,

[1] The etiology of schizotypy and spectrum disorders involves a process of disrupted neural development. However, it has been suggested that negative symptom schizophrenia, as well as the consequences of the disorder, may result in neurodegeneration in patients with an unremitting course of illness (Jarskog, Gilmore, & Lieberman, 2004).

Cannon et al., 2003). These include disruptions in crest cell migration during the second trimester in utero, perinatal complications (often involving periods of hypoxia), and disruptions in the timing and nature of synaptic pruning (apoptosis). Synaptic pruning is a normal molecular process that typically occurs in adolescence and results in massive planned cell death and neural reorganization (Andersen, 2003). It ideally results in increased synaptic (and by extension, cognitive) efficiency. Disruptions in the timing and nature of synaptic pruning can result in brain organization that leaves an individual vulnerable for schizophrenia (Keshavan, Anderson, & Pettegrew, 1994).

The neurodevelopmental hypothesis has been supported by the presence of neurological abnormalities in patients with schizophrenia. For example, first-episode patients often have increased ventricular and decreased hippocampal, cerebellar, and whole brain volume (e.g., Steen, Mull, McClure, Hamer, & Lieberman, 2006; Bottmer et al., 2005). These findings are consistent with functional deficits reported both in fMRI (e.g., Keedy, Ebens, Keshavan, & Sweeney, 2006) and neuropsychological studies (e.g., Antonova, Sharma, Morris, & Kumari, 2004). In addition, patients with schizophrenia have elevated rates of atypical handedness including left-, mixed-, and ambiguous-handedness (Satz & Green, 1999). Green, Satz, Smith, & Nelson (1989) suggest that disruptions in neural development could partially erode the substrate for manual dominance, resulting in less complete dominance and mixed-handedness. Crow (e.g., Crow et al., 1989) maintains that schizophrenia results, in large part, from disruptions in cerebral lateralization, not only in motor functioning, but in cognitive and affective processing as well. Taken together, the presence of a wide array of neurological

abnormalities in the premorbid, acute, and residual phases of schizophrenia supports a neurodevelopmental process that predates the clinical manifestation of schizophrenia and remains relatively stable over time.

Schizotypy

Schizotypy represents the personality expression of the neurodevelopmental vulnerability for schizophrenia (Meehl, 1990). Although the majority of people with this vulnerability will never decompensate into clinical schizophrenia[2], they often exhibit mild or transient features of the disorder including cognitive, emotional, and biobehavioral symptoms. This suggests that schizotypy is expressed along a dynamic continuum ranging from relative psychological health to subclinical deviance to schizophrenia-spectrum personality disorders to full-blown schizophrenia. In other words, schizophrenia and schizophrenia-spectrum personality disorders represent the most deviant clinical expressions along this continuum. In addition, schizotypy is multidimensional in nature, with positive and negative schizotypy being the most consistently replicated factors (e.g., Claridge et al., 1996; Kwapil, Barrantes-Vidal, & Silvia, 2008; Vollema & van den Bosch, 1995). Taken together, schizotypy appears to be expressed along a dynamic continuum with features paralleling those associated with full-blown schizophrenia.

There is considerable evidence that supports the schizotypy continuum as an expression of neurodevelopmental vulnerability for schizophrenia. First of all, patients

[2] Meehl (1990) suggested that about 10% of the population is schizotypic and that about 10% of schizotypes will decompensate into schizophrenia (neatly arriving at the 1% lifetime prevalence rate for schizophrenia). Meehl's conjectures were not empirically derived or tested; however, subsequent taxometric analyses have supported his estimates (e.g., Lenzenweger & Korfine, 1992; Horan, Blanchard, Gangestad, & Kwapil, 2004).

with schizophrenia are known to exhibit mild and transient signs of the disorder long before they decompensate (e.g., Walker, Savoie, & Davis, 1994; Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994). Second, compensated relatives of patients with schizophrenia (who are presumed to share genetic liability) often exhibit signs of schizotypy, including cognitive, affective, and biobehavioral symptoms (e.g., Erlenmeyer-Kimling et al., 1993; Cannon et al., 1994). Third, putative schizotypes identified by clinical status or psychometric inventories exhibit similar patterns of cognitive and biobehavioral deficits (e.g., impairment in sustained attention, dermatoglyphic anomalies, and some evidence of atypical handedness) as patients with schizophrenia (e.g., Bergida & Lenzenweger, 2006; Chok, Kwapil, & Scheuermann, 2005; Chapman & Chapman, 1987), albeit to a lesser degree.

Taken together, this evidence suggests that the schizotypy continuum is a promising construct from which to study the neurodevelopment of schizophrenia. In addition, the identification and study of nondisordered schizotypes: 1) avoids confounds associated with the catastrophic sequelae of schizophrenia itself (such as hospitalization, medication, and social stigma); 2) should enhance our understanding of the etiology and development of schizophrenia spectrum disorders, including the identification of risk and protective factors; and 3) is essential for the development and implementation of prophylactic treatment interventions.

Lenzenweger (1998) reviewed the relative strengths and weaknesses of three broad (and by no means mutually exclusive) methods for identifying schizotypy: familial, clinical, and psychometric-laboratory index approaches. The familial method is the best-

known, due in large part to landmark studies of the offspring of schizophrenic patients including the work by Fish (e.g., 1987), the Copenhagen High-Risk Project (e.g., Cannon & Mednick, 1993), and the New York High-Risk Project (e.g., Erlenmeyer-Kimling et al., 1998). The clinical method identifies high-risk individuals based upon schizophrenia-spectrum diagnoses, such as schizotypal personality disorder, or prodromal status. This method has been employed by Cornblatt and colleagues' Research and Prevention Clinic at Hillside Hospital (e.g., Cornblatt, 2001). The final method involves the use of psychometrically sound research instruments designed to identify symptom, trait, neurocognitive, and biobehavioral markers of vulnerability. Although all three methods have their strengths and limitations, the psychometric high-risk method provides several notable advantages. First, these measures can be used to screen a large number of individuals from the general population, rather than selecting participants based upon clinical status or consanguinity. Given that only about 15% of patients with schizophrenia have a known 1st degree relative with the disorder, family studies provide a stratified group of at-risk participants that is not wholly representative of future sufferers. Psychometric screening inventories also tend to be relatively noninvasive and inexpensive to administer and score. Finally, they can be used in conjunction with other measures of risk including family studies – as has been demonstrated by research such as the New York High Risk Project (e.g., Erlenmeyer-Kimling et al., 1993).

Importantly, identifying people along the schizotypy continuum with psychometric risk inventories has reliably predicted schizophrenia symptoms or spectrum disorders at follow-up assessments. For example, Chapman et al. (1994) re-interviewed

95% of 534 putatively schizotypic and control participants at a ten-year follow-up assessment. They found that participants initially identified by the Magical Ideation (Eckblad & Chapman, 1983) and Perceptual Aberration (Chapman, Chapman, & Raulin, 1978) Scales had higher rates of psychosis compared to control participants at the follow-up assessment. Moreover, participants who were identified by the scales at the initial assessment, but did not develop psychosis, still displayed more schizotypal, paranoid, and psychotic-like symptoms compared to the control group at the follow-up assessment. Finally, Chapman et al. found that 40% of participants who initially scored high on the Magical Ideation scale and above the mean on the Revised Social Anhedonia Scale (Eckblad, Chapman, Chapman, & Mishlove, 1982) exhibited psychosis at the follow-up assessment. In addition, Kwapil (1998) found that 24% of participants identified by the Revised Social Anhedonia Scale compared to 1% of the controls exhibited schizophrenia-spectrum illnesses at the ten-year follow up assessment.

In summary, the neurodevelopmental vulnerability for schizophrenia is expressed across a dynamic continuum referred to as schizotypy. Although the majority of schizotypes will never decompensate into full-blown schizophrenia, it is hypothesized that they will exhibit subtle signs of the disorder that are suggestive of neurological abnormalities or neural dysmaturation.

Neurological Soft Signs

Neurological abnormalities are traditionally divided into “hard” and “soft” signs. Hard signs are clear neurological insults that are localizable to specific brain pathology resulting from illness, injury, or toxins. In contrast, soft signs are presently considered

mild, nonlocalizable, neurological abnormalities that are inferred from performance deficits in domains such as sensory integration, motor coordination, and motor sequencing (Buchanan & Heinrichs, 1989). Rather than diagnosing specific brain pathology, the current view holds that elevated levels of neurological soft signs indicate a generalized disruption in neural circuitry between cortical and subcortical areas (e.g., Heinrichs & Buchanan, 1988). In this way, neurological soft signs may reflect a phenotypic expression of neural dysmaturation. In fact, Chan and Gottesman (2008) recently suggested that neurological soft signs may represent an endophenotype for schizophrenia (i.e., a phenotypic expression that is more proximal than the disorder to the genetic diathesis). However, the distinction between hard and soft signs tends to be artificial, as neurological soft signs are often grouped to reflect their likely neuroanatomical and neurofunctional involvement (Bombin, Arango, & Buchanan, 2005). In fact, the advent of sophisticated structural and functional imaging capabilities has increasingly linked neurological soft signs to identifiable, albeit subtle, neurological abnormalities. Some researchers suggest discarding the term “neurological soft signs” for a more general term such as “neurological exam abnormalities” (Sanders & Keshavan, 1998). However, the term “neurological soft signs” will be used throughout this paper to be consistent with the schizophrenia literature.

A paucity of studies have examined the neuroanatomical correlates of neurological soft signs. However, these studies support the notion that neurological soft signs tap an underlying deficit in neural circuitry. For example, Dazzan et al. (2004) found both motor and sensory neurological soft signs were related to a decrease in gray

matter volume in subcortical structures for patients with first-episode psychosis. Sensory integration deficits were also related to a reduction in cerebral cortex volume. Furthermore, Dazzan et al. (2006) reported that healthy individuals with increased rates of neurological soft signs displayed an associated reduction of cortical areas similar to those seen in the above study with patients with psychosis. In addition, Keshavan et al. (2003) found that in first-episode patients with psychosis, greater impairment on a cognitive/perceptual neurological soft sign factor was associated with smaller volumes in the left heteromodal association cortex and the cerebellum; however, motor abnormalities were related to reduced right and left caudate and cerebellar volumes, but not the heteromodal cortex. These findings support the current view that neurological soft signs suggest a general impairment in subcortical and cortical regions and functional systems. Future research employing more precise technology may help link neurological soft signs to specific brain pathology.

Assessment of neurological soft signs in schizophrenia. The reliable assessment of neurological soft signs provides a useful index of neurodevelopmental disruption. A number of batteries are used to assess neurological impairment in schizophrenia including the Neurological Evaluation Scale (NES; Buchanan & Heinrichs, 1989), the Cambridge Neurological Inventory (Chen et al., 1995), the Woods Scale (Woods, Kinney, & Yurgelun-Todd, 1986), the Heidelberger Scale (Schroder et al., 1991), the Condensed Neurological Examination (Rossi et al., 1990), and the Modified Quantified Neurological Scale (Convit, Jaegar, Lin, Meisner, & Volvaka, 1988). The NES is the most widely used structured examination to assess neurological impairment in

schizophrenia. Therefore, the proposed study and literature review will focus on this measure. However, this is not meant to imply that the other measures are not useful tools to assess neurological impairment in schizophrenia.

Neurological Evaluation Scale. The NES was developed based on a literature review of neurological status of patients with schizophrenia (Heinrichs & Buchanan, 1988). Three broad categories of neurological soft signs emerged. These categories, based on conceptual considerations of neuroanatomy and function, comprise the NES subscales of sensory integration, motor coordination, and motor sequencing (Buchanan & Heinrichs, 1989). Sensory integration dysfunction indicates a deficit in combining information from different sensory inputs, such as failing to match a pattern of auditory stimuli with a corresponding pattern of visual stimuli. Motor coordination dysfunction suggests a deficit in general motor coordination, such as having difficulty walking in a straight line, heel to toe. Motor sequencing dysfunction indicates a deficit in coordinating and sequencing repetitive motor actions, such as failing or hesitating to change hand positions between a fist and a ring. In addition, the NES includes an "other" composite which includes tasks that assess fine motor movement, memory recall, and eye movement abnormalities. Finally, the battery assesses cerebral dominance in terms of hand, foot, and eye use.

The NES consists of 26 tasks, with 14 of these assessed and scored bilaterally. Most subtests are scored ordinally; however, recent studies suggest that a continuous scoring method that includes error count and latency may be superior to the original

system (Sanders et al., 1998; Sanders et al., 2006). See Table 1 for a summary of the subtests that comprise each subscale.

The NES literature is inconsistent regarding the scoring of the 14 bilateral tasks with studies using summed scores (e.g., Bollini et al., 2007), mean scores (e.g. Malla et al., 1997), the higher of the two scores (e.g. Scheffer, 2004; Keshavan et al., 2003), or failing to report the analytic strategy at all. Note that psychometric limitations of these approaches are discussed later. The lack of discussion surrounding this issue is surprising given the potential utility of understanding the relation between neurological soft signs and cerebral lateralization in the neurodevelopment of schizophrenia.

Neurological Soft Signs and Schizophrenia

Numerous studies indicated that neurological impairment is greater in patients with schizophrenia than among nonpsychiatric controls (e.g., Heinrichs & Buchanan, 1988; Bombin et al., 2005). Approximately 50-65% of patients relative to 5% of nondisordered comparison participants exhibit neurological soft signs. Furthermore, multiple studies have reported increased neurological soft signs in first-episode patients with schizophrenia compared to control groups (Bombin et al., 2005), suggesting that neurological soft signs do not simply reflect consequences of chronic illness. Sanders, Keshavan, and Schooler (1994) and Scheffer (2004) found that neuroleptic naïve patients with first-episode schizophrenia were more impaired on the NES total and subscale scores than healthy comparison participants. Venkatasubramanian et al. (2003) found similar results, as never treated, drug naïve patients with schizophrenia scored significantly worse than healthy control participants on the NES subscales. Keshavan et

al. (2003) reported that patients with first-episode schizophrenia were especially impaired on sensory and cognitively related NES tasks compared to patients with nonschizophrenic psychosis and healthy comparison participants. On motor tasks, however, both the schizophrenia and nonschizophrenia psychosis groups had higher ratings than the control group.

Gross neurological impairment is more prevalent in males compared to females with schizophrenia. However, a majority of studies suggest that the presence and severity of neurological soft signs does not differ by sex (Bombin et al., 2005). In addition, although some researchers found that medication use influences performance on neurological examinations (e.g., Merriam, Kay, Opler, Kushner, & van Praag, 1990; Goldstein et al., 2005), Bombin et al. reported that most studies did not find a relation between neurological soft signs and antipsychotic medication use.

Neurological soft signs and course of schizophrenia. Neurological soft signs appear to be present prior to the onset of schizophrenia. For example, increased motor abnormalities have been found in preschizophrenic children (e.g., Walker & Lewine, 1990; Walker, Savoie, & Davis, 1994; Rosso et al., 2000) and may reflect neural dysmaturation that begins in prenatal development (Walker et al., 1994). Moreover, neurological soft signs appear to remain relatively stable over time. A number of cross-sectional studies did not find an association between neurological soft signs and illness length (e.g., Gupta et al., 1995; Ismail, Cantor-Graae, Cardenal, & McKeil, 1998; Venkatasubramanian et al., 2003; Chen, Lam, Chen, & Nguyen, 1996). However, Yazici, Demir, Yazici, and Gogus (2002) found schizophrenia illness duration positively

correlated with the NES motor sequencing subscale score and suggested that this neurological soft sign domain may progressively deteriorate with age. Several longitudinal studies examined the progression of neurological impairment over the course of the schizophrenia. Neither Smith, Hussain, Chowdhury, and Sterns (1999), nor Emsley, Turner, Oosthuizen, and Carr (2005) found significant changes in overall neurological soft sign impairment over five-year and one-year periods, respectively. However, Emsley et al. reported performance on motor sequencing tasks in patients with first-episode schizophrenia significantly improved at three months, but did not change at six or twelve months. Conversely, Madsen, Vorstrup, Rubin, and Larsen (1999) found a higher incidence of neurological abnormalities over a five-year period. Given that patients with unremitting symptoms also received higher or more continuous doses of medication, it is difficult to disentangle the effects of symptom course and severity from the consequences of medication (Bombin et al., 2005). Chen, Kwok, Au, Chen, and Lau (2000) reported higher rates of neurological soft signs in chronic patients over a three-year period, but suggested that the findings may be due to the potential deterioration process that occurs late in illness. Taken together, neurological soft signs seem to predate the appearance of schizophrenia, be present at illness onset, and remain relatively stable over time.

Neurological soft signs and symptom dimension. Multiple studies have assessed the relation between the positive and negative (deficit) symptom dimensions of schizophrenia and neurological soft signs. Evidence suggests an association between negative symptoms and neurological soft signs (e.g., Merriam et al., 1990; Smith,

Kadewari, & Rosenberger, 1999; Scheffer, 2004). Specifically, negative symptoms are consistently associated with neurological impairment related to sensory integration and motor sequencing (Bombin et al., 2005). Buchanan, Kirkpatrick, Heinrichs, and Carpenter (1990) found that deficit patients exhibited significantly more neurological soft signs than nondeficit patients, and this difference was even larger on the NES sensory integration subscale. Moreover, several studies found that overall neurological impairment was related to severity of negative symptoms (e.g., Yazici et al., 2002; Scheffer, 2004). However, a few studies (e.g., Bartko, Zador, Horvath, & Herezeg, 1988; Rubin et al., 1994; Chen, Lam, Chen, & Nguyen, 1996) failed to find a significant relation between negative symptoms and neurological impairment. Bombin et al. suggested that these studies did not include tasks that assessed neurological soft signs in the domains of motor sequencing and sensory integration.

In contrast to the negative symptom dimension of schizophrenia, there is little evidence to suggest a relation between neurological soft signs and positive symptoms (Bombin et al., 2005). Multiple studies failed to find an association between neurological soft signs and the positive dimension (e.g., Braun et al., 1995; Buchanan, Koeppl, & Breier, 1994; Yazici et al., 2002). Although some studies (e.g., Compton et al., 2007; King, Wilson, Cooper, & Waddington, 1991; Mohr et al., 1996; Scheffer, 2004) did find a significant relation between neurological soft signs and positive symptoms, these studies also reported a relation between neurological soft signs and negative symptoms. This may reflect the co-occurrence of positive and negative symptoms in these groups (Bombin et al, 2005). Moreover, Scheffer reported an association between positive and

negative symptoms and neurological soft signs at baseline, but only negative symptoms remained related to neurological soft signs at a 6-week follow-up. In addition, Schroder et al. (1991) and Whitty et al. (2003) found a reduction in neurological soft signs upon acute psychotic state remission. This suggests the prevalence of neurological soft signs oscillates with positive symptoms and remains constant with negative symptoms, consistent with the episodic nature of positive symptoms as opposed to the trait-like expression of negative symptoms. Moreover, acute positive symptoms may interfere with accurate neurological assessment because hallucinations and delusions may interfere with patients' ability to understand and comply with task directions (Bombin et al., 2005). Thus, there is considerable evidence suggesting an association between neurological soft signs and the negative symptom dimension of schizophrenia, but the relationship with the positive symptom dimension appears weak at best.

Neurological soft signs and other forms of psychopathology. Neurological soft signs have been observed in patients with disorders other than schizophrenia (Bombin et al., 2005). However, individuals with schizophrenia exhibit more neurological soft signs than patients with substance abuse (Kinney, Yurgelun-Todd, & Woods, 1999; Mohr et al., 1996), bipolar disorder (Kinney et al., 1999), obsessive compulsive disorder (Bolton et al., 1998), nonschizophrenic psychosis (Keshavan et al., 2003), and mood disorders (Krebs, Gut-Fayand, Bourdel, & Olie, 2000; Boks, Liddle, Burgerhof, Knegtering, & van den Bosch 2004). Although neurological soft signs are not unique to schizophrenia, examining these characteristics across the schizotypy continuum may further enhance our ability to identify individuals at risk for schizophrenia and related disorders.

Neurological Soft Signs and Schizotypy

The continuum model of schizotypy posits that nondisordered individuals along the schizotypy continuum should experience mild and transient forms of the symptoms and impairment experienced by patients with schizophrenia, including the expression of neurological soft signs. A few studies suggest that the rates and severity of neurological soft signs in putative schizotypes is between that of patients with schizophrenia and healthy controls (e.g., Cantor-Graae et al., 1994; Chen et al, 2000; Lawrie et al., 2001). Yazici et al. (2002) reported that nonpsychotic siblings of patients with schizophrenia scored between patients and healthy controls on all NES subscales. Ismail, Cantor-Graae, and McNeil (1998) found both patients with schizophrenia and their nonpsychotic siblings scored significantly higher than normal comparisons on neurological abnormalities, including hard signs, soft signs, and primitive reflexes. Moreover, levels of neurological soft signs were positively correlated within patient-sibling pairs. Hans et al. (1999) reported that adolescent offspring of patients with schizophrenia showed poorer neurobehavioral functioning relative to offspring of healthy controls. In contrast, other studies (e.g., Appels et al., 2002; Egan et al., 2001) failed to find significant differences in neurological impairment between normal controls and nonpsychotic relatives of patients with schizophrenia. Taken together, the dose-wise relation of neurological soft signs with schizophrenia and schizotypy suggests that soft signs are a promising marker of schizotypy and vulnerability for developing spectrum disorders.

At the time of this review, four published studies examined the relation between neurological soft signs and psychometrically identified schizotypy in nonclinically

ascertained samples. Barrantes-Vidal et al. (2002) found that negative and combined positive-negative schizotypy clusters reported more neurological soft signs than the control or positive schizotypy clusters. In contrast, Obiols, Serrano, Caparros, Subira, and Barrantes-Vidal (1999) failed to find a relationship between neurological soft signs and positive or negative schizotypy. Barkus, Stirling, Hopkins, and Lewis (2006) reported that high scorers on the Unusual Experiences subscale from the Oxford Liverpool Inventory of Feelings and Experiences (Mason, Claridge, & Jackson, 1995) and the Launay-Slade Hallucination Scale (Launay & Slade, 1981) (two scales that tap positive schizotypy) scored significantly higher than control participants on the NES "total" and "others" subscales. However, they did not examine the presence of negative schizotypy in their sample. Bollini et al. (2007) found that interviewer-assessed, but not self-reported, schizotypy was related to increased neurological soft signs. In general, however, a paucity of studies have examined neurological soft signs in psychometrically identified schizotypy.

Limitations of Previous Research

Although the presence and relation between neurological soft signs and schizophrenia is well-documented, limitations in the manner in which the NES is used and the results are reported weaken conclusions that can be drawn from the literature. For example, the internal consistency of each NES subdomain is rarely reported. Although a few studies have reported adequate internal consistency values, the heterogeneity of schizophrenia, raters, and research questions prevents the assumption of adequate internal consistency across studies. In addition, information about the distributions of scores on

individual NES tasks and subdomains is rarely described in the literature. This is problematic for a number of reasons: 1) it is difficult to evaluate whether the analytic strategy was appropriate to use with the nature of data (e.g., parametric analyses are unfit for highly skewed data); and 2) it prevents researchers from determining whether NES tasks are useful to detect less severe manifestations of neurological impairment. In addition, a large proportion of studies do not report interrater reliability values from the actual study, but rather agreement values from rater training (i.e., subjects who were not included in the study, but used to familiarize the raters with the NES battery). Given the complexity of the NES battery and the attention to detail needed to accurately measure each task, interrater reliability is needed to ensure measurement reliability. Moreover, bilateral task scores are often collapsed by taking the average or the higher of the two ratings, without considering whether this is conceptually or empirically justified. For example, studies typically do not report whether performance on the two hands are correlated before combining them. Studies that do not collapse bilateral task scores typically only differentiate between right and left hand performance across subjects, rather than dominant and nondominant hand performance. Finally, the majority of studies either do not examine the effects of symptom dimensions or use zero-order correlations to assess the relation between neurological soft signs and positive and negative symptoms. This analytic strategy does not remove the variance associated with one symptom dimension from the other and fails to provide information about the unique contribution of each dimension to the prediction of neurological soft signs.

Goals and Hypotheses of the Present Study

The present study examined the relations of psychometrically identified positive and negative schizotypy, and their interaction, with neurological soft signs in a nonclinically ascertained sample of young adults. Unlike many psychometric schizotypy studies that arbitrarily select high and low scorers, this study examined the relationship of positive and negative schizotypy with neurological soft signs across a broad range of the continua. Consistent with the schizophrenia literature, it was hypothesized that negative, but not positive, schizotypy would be associated with elevated NES scores. Furthermore, it was predicted that the interaction of positive-negative schizotypy would account for significant increments in variance over and above the schizotypy main effects, given the findings of Barrantes-Vidal et al. (2002) and Barkus et al. (2006).

The extent to which neurological soft signs were reported in a nonclinically ascertained sample was examined. One goal was to determine whether measures like the NES, which were developed for use with schizophrenia patients, would be useful for detecting mild neurological soft signs across the schizotypy continuum. This was of particular interest given the lack of information in the literature regarding the distribution of neurological soft signs. In addition, the traditional ordinal scoring system (Buchanan & Heinrichs, 1989) was compared to a continuous scoring method that included error count and latency (Sanders et al., 1998; Sanders et al., 2006) to determine whether measuring neurological soft signs continuously would capture more variance in a nonclinically ascertained sample.

The study also addressed a number of the methodological limitations of previous studies employing the NES. First of all, the internal consistency of each NES subdomain was examined to assess the extent to which each composite tapped meaningful variance pertaining to that neurological soft sign domain. Secondly, a detailed manual was developed and interrater reliability was computed to maximize the reliable and valid assessment of neurological soft signs. Third, the relation between neurological soft sign performance on bilateral tasks (across hands) was inspected to determine the most appropriate analytic strategy for the data. Finally, regression, rather than zero-order correlation, was employed to assess the unique relation of neurological soft signs with positive and negative schizotypy, and their interaction term.

CHAPTER II

METHOD

Participants

The initial sample included 201 college undergraduates enrolled in introductory psychology courses at the University of North Carolina at Greensboro. Participants were excluded from the study if they: 1) had a self-reported head injury that resulted in loss of consciousness or medical history with clear evidence of neurological illness or injury; 2) ever used medications with neurological side effects including anti-convulsants or anti-psychotics; or 3) had a history of substance abuse that suggested marked functional impairment. Based on these criteria, 3 participants were dropped due to head injury, medical illness, and/or medication use indicative of neurological insult, and 2 subjects were dropped due to a history of substance abuse. In addition, 18 subjects were dropped due to unusable schizotypy questionnaire data and one subject was dropped due to noncompliance with the procedures. This resulted in a final sample of 177 participants. The sample size provided adequate power (>.80) to obtain a medium effect size based upon Cohen's (1992) recommendations (n = 76, α = .05). A medium effect size was hypothesized based on the results from Barkus et al. (2006). The mean age of the sample was 19.6 (age range = 15.1 - 32.8). The sample was 74.6% female and 25.4% male, and 62.1% Caucasian, 24.9% African-American, 4.5% Asian, 2.3% Hispanic, .6% Native-

American, and 4.0% “other,” with 1.7% of the sample not reporting their ethnicity. The demographic characteristics were consistent with the university demographics.

Materials

Schizotypy Questionnaires. The schizotypy questionnaires included the Perceptual Aberration, Magical Ideation, Physical Anhedonia (Chapman, Chapman, & Raulin, 1976) and Revised Social Anhedonia Scales, and a 13-item infrequency scale (Chapman & Chapman, 1983). The Perceptual Aberration Scale contains 35 items that tap psychotic-like perceptual experiences and bodily distortions. The Magical Ideation Scale consists of 30 items that assess belief in improbable or invalid causality. The Revised Social Anhedonia Scale includes 40 items that tap asociality and indifference towards interpersonal relationships. The Physical Anhedonia Scale is comprised of 61 items that assess deficits in sensory and aesthetic pleasure. The Perceptual Aberration and Magical Ideation Scales assess positive schizotypy, and the Physical Anhedonia Scale taps negative schizotypy. The Revised Social Anhedonia Scale appears to assess both positive and negative schizotypy. Exploratory and confirmatory factor analyses of the four scales reliably produce two factors, positive and negative schizotypy, that account for 80% of the variance (Brown, Silvia, Myin-Germeys, Lewandowski, & Kwapil, 2008; Kwapil et al., 2008; Lewandowski, Barrantes-Vidal, Nelson-Gray, Clancy, & Kwapil, 2006). Participants were assigned positive and negative schizotypy dimensional scores, based upon factor loadings derived from a sample of 6,137 college students (Kwapil et al., 2008). The schizotypy questionnaires are widely used and have good internal consistency (.82-.92). The 13-item infrequency scale was designed to screen out participants who

respond in a random or “fake-bad” manner. Following the recommendations of Chapman & Chapman (1983), participants who endorsed more than two of these items were omitted from further study.

Neurological evaluation. The neurological evaluation was conducted using the NES. The NES is a structured instrument used to assess the presence of neurological soft signs in schizophrenia. The original NES consists of 26 tasks, with 14 measures assessed and scored separately for the right and left side of the body. The battery includes tasks that test sensory integration, motor coordination, and motor sequencing. The NES also assesses fine motor movement, short-term memory, and eye movement abnormalities, and uses a performance-based version of the Annett Questionnaire (Annett, 1967) to assess cerebral dominance. The NES tasks are scored ordinally on a 3-point scale: 0=no abnormality; 1=mild, but definite impairment; and 2=marked impairment. The snout and suck reflexes are scored as either 0 or 2. Continuous data including error count and completion time were also recorded when possible, consistent with revised scoring recommendations by Sanders et al. (1998; 2006). In addition, the original NES battery was supplemented with the go-no-go task (Merriam et al., 1990; Sanders et al., 2006) and the palmomental reflex (Sanders et al., 1994; Keshavan et al., 2003).

The original administration and scoring instructions for the NES were rather limited. Therefore, a detailed administration and scoring manual was developed to maximize the reliability and validity of the study. One of the authors of the NES was consulted to clarify several of the procedures (R.W. Buchanan, personal communication, March 15, 2007).

All neurological evaluations were performed by a trained graduate student or undergraduate research assistant. A total of 50% (89/177) of the participants were scored independently by the administrator and a separate rater who also attended the session in order to assess interrater reliability.

Screening Questionnaire. The screening questionnaire consisted of questions regarding corrected vision and hearing, medical history, current medication use, drug and alcohol use, and history of head injury.

Procedures

Most participants attended a two-hour departmental mass screening session at which they completed a brief demographic questionnaire and the schizotypy questionnaires ranging from two to twelve weeks prior to the neurological assessment. The schizotypy scales measure trait-like characteristics and have good stability across this time frame (Chapman, Chapman, & Kwapil, 1995). Note that participants who did not complete the schizotypy questionnaires at the departmental mass screening or had invalid questionnaires from mass screening (due to incomplete forms or elevated infrequency score) completed the schizotypy questionnaires at the time of neurological assessment. Participants then volunteered or were invited to take part in the study. In order to ensure adequate inclusion of participants reporting high levels of schizotypy, participants who received standard scores $\geq$ 1.5 on either the positive or negative schizotypy dimensions from the mass screening assessments were recruited

(oversampled). A total of 24% of the final sample was recruited in this manner, and a total of 40% of the recruitment list agreed to take part in the study[3].

The NES and screening questionnaire were individually administered to each participant during a one-hour testing session. Participants who had corrected vision or hearing needed to have their correction with them to take part in the study. Consent was obtained from each participant prior to study enrollment. Participants younger than 18 years old provided consent from their parents/guardians to participate in the study, as well as personally providing assent.

[3] The recruited group included participants who received standard scores $\geq$ 1.5 on either schizotypy dimension and participants with scores below the cut-offs. Note that in general, the assessors were not aware of whether the participants volunteered or were recruited. Furthermore, none of the recruiters, assessors, or raters were aware of any of the participants' scores on the schizotypy measures.

CHAPTER III

RESULTS

Statistical analyses were conducted using MPlus version 5.1 (MPlus 5.1, 2008) and SPSS version 15 (SPSS, 2006). A series of preliminary analyses were conducted to examine the nature of the schizotypy and NES data.

Schizotypy Data

Participants were assigned positive and negative schizotypy dimensional scores based on a sample of 6,147 college students (Kwapil et al., 2008). The mean, range, and distribution of scores were examined for the positive and negative schizotypy dimensions (positive schizotypy: mean = -.01, standard deviation = 1.23, minimum = -1.54, and maximum = 4.85; negative schizotypy: mean = .29, standard deviation = 1.20, minimum = -1.79, and maximum = 3.30). Both positive and negative schizotypy had unimodal distributions. The schizotypy dimensions correlated, $r = .25$, $p < .001$.

Relation between Positive and Negative Schizotypy and Handedness

Following the recommendations made by Annett (1967), a total of 89% (n=158) of participants were classified as right-handed, 7% (n=12) of participants were classified as left-handed, and 4% (n=7) of participants were classified as mixed-handed. Given the small number of mixed-handed participants, handedness was reclassified as right and nonright, in order to examine the relation of handedness and schizotypy. Binary logistic regression was used to examine the relation between positive and negative schizotypy

and handedness. Positive and negative schizotypy were entered at the first step, so the effect of each dimension could be assessed with the other partialed out. The positive x negative schizotypy interaction was entered at the second step to examine its effect over and above the main effects. There was no relation between positive schizotypy (odds ratio = 0.85, 95% confidence interval = 0.54 -1.33), negative schizotypy (odds ratio = 1.11, 95% confidence interval = 0.75 - 1.65) or the positive x negative schizotypy interaction (odds ratio = 1.27, 95% confidence interval = 0.96 - 1.68) and handedness.

Relation between Dominant and Nondominant Hand Performance

Polychoric correlations (Drasgow, 1988) were used to examine the relation between dominant and nondominant hand performance[4] for bilateral tasks for ordinal and error count data. A polychoric correlation is appropriate with ordered or categorical data to measure agreement, in this case dominant and nondominant hand performance agreement, and is interpreted in the same manner as a Pearson correlation coefficient. Examining the relation between dominant and nondominant hand performance allowed us to determine whether it would be appropriate to combine scores from bilateral tasks into a single score (e.g., the higher or average score across dominant and nondominant hands). However, as seen in Table 2, there was little support for combining ordinal or error count data for bilateral tasks. Therefore, ordinal and error count data were analyzed separately for dominant and nondominant hands for all subsequent analyses.

Pearson correlations were used to assess the relation between dominant and nondominant hand performance for latency data, given that the latency distributions were

[4]Since there was a subset of mixed-handed participants in the sample, dominant handedness was assigned to each participant's writing hand (and nondominant handedness was assigned to the opposite hand).

continuous and normally distributed. Latency data for dominant and nondominant hands were highly correlated (see Table 2). Therefore, latency tasks with $r > .80$ were combined into a single variable by taking the average of the dominant and nondominant hands. This included the latency data for Rapid Alternating Movements, Finger-Thumb Opposition, Fist-Ring, and Fist-Edge-Palm, but not Gaze Impersistence.

Descriptive Statistics and Interrater Reliability of Neurological Soft Signs

Table 3 presents the mean, standard deviation, minimum, maximum, skew, interrater reliability, and analysis plan for each NES subtest. Traditionally, interrater reliability is estimated by Cohen's kappa coefficient (Cohen, 1960). This statistic is appropriate when the same 2 judges rate a variable of interest. Since pairs of raters (selected from 6 total judges) rated 50% of the NES sessions (89 out of the 177 sessions), Cohen's kappa statistic was deemed inappropriate. Therefore, a one-way random effects model was used to analyze interrater reliability, based on the recommendations of Shrout and Fleiss (1979). A one-way random effects model[5] is used when each participant is rated by a pair of raters from a larger population of judges. In addition, this model assumes that it is not possible to separate the effects due to judges, to the interaction between judge and target, and to random error. Interrater reliability was excellent with mean = .90 and standard deviation = .11 for ordinal data, mean = .93 and standard deviation = .08 for error count data, and mean = .99 and standard deviation = .01 for

[5] A one-way random effects model assumes the following linear model: $x_{ij} = u + b_j + w_{ij}$, where x_{ij} denotes the *i*th rating for the *j*th target; "u is the overall population mean of the ratings; b_j is the difference from u of the *j*th target's so-called true score (i.e., the mean across many repeated ratings on the *j*th target); and wij is a residual component equal to the sum of the inseparable effects of the judge, the judge x target interaction, and the error term" (Shrout & Fleiss, 1979, p.421).

latency data (see Table 4 for the interrater reliability values for each subtest). Overall, 87% of the tasks had interrater reliability above .80.

Given the concerns noted previously regarding the applicability of the NES for use with a nonclinical sample, subtests were dropped that exhibited poor interrater reliability (< .70) or minimal response variance ($\sigma \leq .32$). The following tasks were dropped from the subsequent analyses: Romberg, Stereognosis (ordinal and error count data for dominant hand only), Rapid Alternating Movements (ordinal and error count data for dominant hand only), Finger-Thumb Opposition (ordinal data only), Glabellar reflex (ordinal data only), Face-Hand Test, Snout Reflex, Suck Reflex, and Palmomental Reflex.

Note that there were no differences in neurological soft sign rates across sex or ethnicity. In addition, neurological soft signs were unrelated to age (although the age range was rather restricted in the present study).

NES Subtest Analyses

In order to examine the relations of positive and negative schizotypy with individual NES tasks, a series of regression analyses were conducted with the ordinal, error count, and latency NES subtest scores as the dependent variables. In every analysis, positive and negative schizotypy were entered at the first step, so the effects of each could be assessed with the other partialed out. The positive x negative schizotypy interaction was entered at the second step to examine its effect over and above the main effects.

Note that the skew statistic and qualitative inspection of each distribution for ordinal and error count data revealed that the distributions for every NES variable were highly skewed in the positive direction, which was expected given the nonclinical sample and the low base-rate of neurological soft signs. Therefore, traditional ordinary least squares linear regression was deemed inappropriate due to the severe violation of normality. Categorical regressions were used to analyze ordinal data, negative binomial regressions were used to analyze error count data, and linear regressions were used to analyze latency data. Categorical regression is a nonlinear function that does not assume an interval scale across categories, but retains the rank order of the variables (Cohen, Cohen, West &, Aiken, 2003). Negative binomial regression is a generalized linear model that accounts for a highly positively skewed distribution and is used with count data (Agresti, 2007). The negative binomial distribution is unimodal, positively skewed over nonnegative integer values, and unlike a Poisson distribution, does not assume equivalence of the mean and variance. Negative binomial regression is similar to Poisson regression; however, it includes the *D* parameter in the model which allows the variance to be greater than the mean.[6] Analysis of the *D* parameter indicated that the error count data had negative binomial, rather than Poisson, distributions.

Table 4 presents the regression analyses for each NES subtest. In general, negative, but not positive, schizotypy was related to neurological soft signs. In particular, negative schizotypy was associated with increased neurological soft signs in tasks that

[6] Note that a Poisson distribution assumes that the mean and variance are equivalent. However, subject heterogeneity often results in a variance that is larger than the mean, which is called overdispersion. Overdispersion is measured by the dispersion parameter (*D*), which summarizes the extent of overdispersion relative to a Poisson distribution (Agresti, 2007).

assessed fine[7] and gross motor coordination, motor sequencing, eye movement abnormalities, and memory recall. Positive schizotypy was associated with elevated neurological soft sign for tasks related to sensory integration dysfunction. The positive x negative schizotypy interaction term was generally unrelated to neurological soft signs tasks.[8] Note that there was no evidence of a speed-accuracy tradeoff on any of the timed tasks given that the correlation between latency and performance ranged from r = -.02 to .52 for ordinal scores and r = -.03 to .48 for error count scores (negative correlations indicate a speed accuracy trade-off).

NES Composite Analyses

Prior to examining the relation of schizotypy with the NES composite scores, the internal consistency of the composites was examined. Coefficient alpha is problematic with highly skewed count and ordinal data and as a result it is difficult to disentangle whether a low alpha value is due to the nature of the distribution or the extent to which the items hang together. As an alternative procedure, a series of exploratory factor analyses (EFA; P. J. Silvia, personal communication, August 1, 2008) were conducted to examine the internal consistency of both the original, ordinal NES composites and the ordinal NES composites excluding dropped tasks (see Table 5). In the present case, EFA is comparable to confirmatory factory analysis for each composite, as each task loads

[7]The schizophrenia literature is inconsistent regarding its classification of involuntary motor abnormalities. Therefore, tasks that were in the "others" domain that seemed to tap subtle, diminished coordination or control of movement were described as deficits in fine motor coordination.

[8]Familywise alpha adjustment was not applied to the results in the present study as it has been criticized to the extent that it is overly conservative and reduces statistical power (e.g., O'Keefe, 2003). However, when either the original Bonferroni correction or a modified Bonferroni procedure (e.g., Simes, 1986) was applied to the data, the majority of the tasks for positive schizotypy lost significance whereas the results for negative schizotypy were substantively unchanged.

onto only one composite measure. Consistent with the NES subtest analyses, ordinal composites were specified as categorical distributions. EFA results for original NES composites revealed acceptable internal consistency for motor sequencing and poor internal consistency for motor coordination and sensory integration. Note that it was not possible to compute EFA for the original "other" or NES total composites as one task (Snout Reflex) had no variance. EFA results for the NES composites excluding the dropped tasks revealed acceptable internal consistency for motor sequencing (this subdomain remained unchanged), improved but still relatively low internal consistency for sensory integration, and poor internal consistency for motor coordination, "other", and NES total. Note that it was not possible to run EFA for error count composites.

Table 6 presents the results for the negative binomial regression analyses for the NES composites excluding dropped tasks. As hypothesized, negative, but not positive, schizotypy was related to motor coordination, motor sequencing, "other," and "total" NES domains. In addition, the positive x negative schizotypy interaction was significantly related to motor coordination and NES "total", suggesting that participants with high scores on negative schizotypy but low scores on positive schizotypy performed worse in these domains, over and above the schizotypy main effects (see Figures 1 and 2). Contrary to our hypothesis, positive, but not negative, schizotypy was related to the sensory integration dysfunction NES domain. The pattern of results was the same with the ordinal data for the original NES composites (including all tasks), as well as the error count data for the sensory integration and motor sequencing NES composites (with and without dropped tasks). Note that it was not possible to compute error count composites

for motor coordination, “others”, or NES “total” as there were some tasks that were not rated continuously within each domain.

CHAPTER IV

DISCUSSION

The Schizotypy Framework

Current neurodevelopmental models posit that the vulnerability for schizophrenia is expressed across a dynamic continuum of clinical and subclinical impairment referred to as schizotypy. This formulation suggests that schizophrenia-spectrum disorders represent the most deviant expressions of illness along the schizotypy continuum. In addition, schizotypy is conceptualized as multidimensional in nature, with positive and negative schizotypy being the most consistently replicated factors. There are many benefits to studying the multidimensional construct of schizotypy. First of all, it will allow us to investigate relevant etiological factors relatively untainted by the consequences of the illness itself. Second, the identification of nondisordered schizotypes will allow us to examine factors that either increase the likelihood of or protect against the transition into schizophrenia-spectrum disorders. Finally, considerable effort has been made towards the identification of prophylactic treatment interventions – given that the leading treatments for schizophrenia are not curative, but rather provide some degree of symptomatic relief and relapse prevention for patients. However, the development and implementation of preventative treatments is predicated on the reliable identification of people at risk for developing schizophrenia and related disorders. The schizotypy framework provides a promising structure for developing such interventions.

Numerous lines of evidence support the use of psychometric screening inventories as promising points of entry for identifying schizotypic individuals. As noted, scores on psychometric scales predict clinical symptoms and neurocognitive impairment in both disordered and nondisordered schizotypes. Furthermore, psychometric inventories are found to predict the development of schizophrenia-spectrum disorders in longitudinal studies (with effect sizes that rival or exceed those of family studies). The use of psychometric instruments has been criticized for the extent to which it identifies false positives. Obviously, this issue depends in large part on the construct being measured. If the target is the development of schizophrenia, the method does result in many false positives. However, if the target is identifying schizotypy *a la* Meehl or Claridge, this remains an open question – open in large part because we lack a gold standard and must rely on construct validation of an open construct. In fact, this criticism seems to confuse construct validity (appropriate in the case of schizotypy), with a diagnostic-based criterion validity (seemly more suitable in the case of prodromal cases who are teetering on the brink of schizophrenia). Construct validity demands more patience to formulate and test hypotheses than does criterion validity. For example, in the Chapman et al. (1994) follow-up study, between 5% and 50% of the at-risk samples were psychotic at age 30. What does this mean about the remaining 50-95% of the sample? Lacking further longitudinal assessments, we do not know if they are false positives, if they are schizotypes who will decompensate in the future, or if they are schizotypes who are and will remain compensated (likely due to protective factors that we fail to recognize at this point).

Construct validation of multidimensional schizotypy requires developing methods for identifying schizotypy and then testing predictions about the nature, etiology, and expression of schizotypy (across the entire range of the construct). Often this involves predictions about mild and transient manifestations of full-blown schizophrenic pathology in nondisordered schizotypes. For example, the finding that psychometrically assessed positive schizotypy in nondisordered participants is associated with interview reports of psychotic-like symptoms both cross-sectionally and longitudinally (e.g., Kwapil et al., 2008; Kwapil, Chapman, & Chapman, 1999) supports the multidimensional framework of schizotypy. Furthermore, the combination of schizotypic signs from multiple domains (e.g., psychometric screening, subclinical symptoms, neurocognitive impairment, and family history) should enhance our identification of individuals at markedly high risk for transitioning into spectrum disorders.

Neurological Soft Signs and Schizotypy

This study aimed to further the validation of the multidimensional construct of schizotypy by investigating the relation between neurological soft signs and psychometrically identified positive and negative schizotypy. It appears to be the most comprehensive assessment of neurological soft signs in a nonclinically ascertained sample to date. Specifically, previous studies suffered from limitations such as: 1) failing to examine dimensions of schizotypy; 2) employing measurement of neurological soft signs that was limited in terms of domains assessed or the measures employed; and/or 3) failing to consider psychometric properties of the data and using inappropriate statistical analyses.

As hypothesized, negative, but not positive, schizotypy was related to increased neurological soft signs in tasks that assessed fine and gross motor coordination, motor sequencing, eye movement abnormalities, and memory recall. However, positive schizotypy was associated with elevated neurological soft signs in tasks related to sensory integration dysfunction. In general, the positive x negative schizotypy interaction term was unrelated to neurological soft signs tasks. These results are generally consistent with the schizophrenia literature and support the multidimensional framework of schizotypy. Note that the psychometric screening inventories did not inquire about neurological, neurocognitive, or neuromotor deficits – so the results are not simply due to overlapping content in the predictors and criteria. Furthermore, the schizotypy dimensional scores identified elevated rates of neurological soft signs in participants who were drawn from a nonclinically ascertained sample and who were functioning well enough to enroll in a major university (making for an especially conservative test of the hypotheses).

The present findings are consistent with the notion that negative schizotypy serves as a trait-like expression of subtle neurological impairment, whereas positive schizotypy reflects an oscillating neurochemical imbalance. Although the above statement is undoubtedly an oversimplification of the complex processes underlying the development of positive and negative schizotypy (e.g., it is well known that hypodopaminergic functioning is related to negative schizotypy), it does suggest that the etiology underlying the dimensions may be separate, but related disease processes. Conceptualizing and measuring positive and negative schizotypy (and by extension schizophrenia) in this

manner may help to clarify mixed findings in literature – which often treats schizophrenia spectrum disorders as discrete and homogenous entities.

The finding that elevated neurological soft sign tasks assessing fine and gross motor coordination and motor sequencing were related to negative schizotypy support current neurodevelopmental models of schizophrenia. Specifically, Andreasen's (1999) theory of 'cognitive dysmetria' suggests that disruptions in the cortico-cerebellar-thalamic-cortical circuit (CCTCC), which is normally used to coordinate and sequence motor and cognitive activity, leads to abnormal output that characterizes the expression of schizotypy (and thus, schizophrenia). Moreover, Andreasen suggested that three "nodes" in the CCTCC may be particularly important in schizophrenia – the cerebellum, the prefrontal cortex, and the thalamus. It is well known that the cerebellum is involved in motor movement and increasing evidence corroborates its role in the etiology of schizophrenia (in contrast to previous views that the cerebellum played little role in the expression of higher human functions). In fact, brain imaging studies have shown that volumetric decreases in the cerebellum are related to deficits in tasks associated with motor coordination (e.g., Bottmer et al., 2005) and motor sequencing (e.g., Keshavan et al., 2003) in patients with first-episode schizophrenia. Moreover, in her seminal studies employing archival videotapes, Walker et al. (1990) showed that abnormal motor movements in early childhood discriminated siblings who developed schizophrenia from siblings who did not and later predicted enlarged ventricles in adult patients (Walker, Lewine, & Neumann, 1996). The finding that motor deficits appear prior to the onset of cognitive and affective symptoms of schizotypy and schizophrenia is consistent with the

"back to the front" theory of synaptic pruning in adolescence (Rappaport, Addington, & Frangou, 2005). Taken together, the findings from the present study and previous literature suggest that neural dysmaturation may disturb the CCTCC and result in abnormal motor movement that can be observed along the negative schizotypy continuum dating back to early childhood. Thus, motor dysfunction may serve as an early risk marker for schizophrenia.

Deficits in memory recall were also associated with negative schizotypy. This is consistent with an extant literature suggesting that memory dysfunction is a hallmark feature of schizophrenia. Imaging studies (e.g., Crespo, Paradiso, Andreasen, O'Leary, 1999) have linked memory recall deficits to decreases in cerebral blood flow across the CCTCC in patients with schizophrenia, supporting a generalized neurological deficit across interconnected "nodes". In addition, the finding that verbal memory dysfunction has been observed at illness onset and in putative schizotypes (e.g., Eastvold, Heaton, & Cadenhead, 2007) supports its use as a risk marker for schizophrenia. Speaking more broadly, one question is whether biobehavioral markers such as neurological soft signs and cognitive deficits such as memory recall tap the same underlying neural substrate. Although this relation needs to be investigated more thoroughly, memory recall was either unrelated or modestly correlated with neurological soft signs tasks in the present study, suggesting that they may be related but distinct phenomena. Therefore, assessing these risk measures in conjunction with one another may increase our ability to reliably identify people along the negative schizotypy continuum.

The present study also found that negative schizotypy identified elevated levels of eye movement abnormalities. This is consistent with a considerable literature documenting the presence of smooth pursuit eye and saccadic movement abnormalities in patients with schizophrenia (e.g., Levy & Holzman, 1997) and putative schizotypes identified by consanguinity (e.g., Holzman, Soloman, Levin, & Waternaux, 1984) or psychometric inventories (e.g., Gooding, Miller, & Kwapil, 2000). Eye movement abnormalities are thought to reflect an impaired motion processing system in the middle temporal lobe, rather than a deficit in vision, *per se* (Holzman, 2000). This suggests that neural dysmaturation may affect the motion processing circuit and result in abnormal eye movements across the negative schizotypy continuum. Admittedly, the tasks embedded within the NES are rather crude estimates of eye movement abnormalities. However, consistent with our hypotheses, these deficits were still seen along the negative schizotypy continuum which suggests that they may be particularly useful biobehavioral risk markers for schizophrenia.

Contrary to the predictions, positive schizotypy was associated with deficits in a few tasks related to sensory integration dysfunction. The literature generally supports an association between this domain and negative symptoms; therefore it is unclear why the opposite results were found in the present study. One hypothesis is that the sensory integration tasks are too easy for use with a high functioning sample and thus the results represent a Type I error rather than an underlying relation between positive schizotypy and sensory integration. An alternative explanation may relate to sensory gating – the central nervous system's ability to regulate sensitivity to sensory input from the

environment (Braff & Geyer, 1990). One study recently showed that deficits in sensory gating were associated with elevated positive symptoms in patients with schizophrenia (Johannesen, Bodkins, O'Donnell, Shekhar, & Hetrick, 2008). It may be that in order to integrate information from different sensory domains, one must first regulate or "block out" irrelevant sensory stimuli. Therefore, sensory integration and sensory gating may be overlapping constructs that influence one another and affect the expression of positive symptoms. Ultimately, however, this needs to be examined empirically.

Finally, the positive x negative schizotypy interaction term was generally unrelated to neurological soft signs tasks after partialing out variance associated with the main effect. The general lack of findings between the positive schizotypy main effect and the schizotypy interaction term further supports negative schizotypy as an expression of neural dysmaturation. A relation between neurological soft signs and the main and interaction effects may be seen at clinical levels of positive symptom schizophrenia (e.g., experiencing hallucinations and delusions). However, this may be due to the disruption of positive symptoms on a participant's ability to understand instructions and perform tasks accurately – rather than neurological impairment, *per se*.

Taken together, the results from the present study suggest that neurological soft signs may serve as an index of neural dysmaturation and thus may be a useful marker of risk for schizophrenia. In fact, neurological soft signs, particularly those related to motor coordination, recently have been proposed as an endophenotype for schizophrenia (Chan & Gottesman, 2008). Specifically, Chen and Gottesman suggested that neurological soft signs meet the criteria for qualifying as an endophenotype as they: 1) are associated with

schizophrenia in the population; 2) are heritable; 3) are primarily state-independent; 4) are found in unaffected family members at higher rates than the general population; 5) co-segregate within families; and 6) can be measured reliably. However, given that neural dysmaturation is not unique to schizotypy or schizophrenia, it is necessary to measure neurological soft signs in conjunction with other biobehavioral markers. We plan to assess the relation between neurological soft signs and other markers such as obstetric complication, dermatoglyphic and minor physical anomalies, neurocognitive functioning, as well as interview measures, in order to increase the reliable identification of people along the schizotypy continuum.

The Utility of the Neurological Evaluation Scale

Another goal of this study was to address the methodological limitations of previous research and to determine whether the NES is a useful measure for nonclinically ascertained samples. Specifically, this study extended the NES literature by: 1) examining the distribution and interrater reliability of individual tasks and using appropriate statistical analyses; 2) assessing the internal consistency of the composites; 3) comparing an ordinal and continuous scoring modality; and 4) measuring the agreement between dominant and nondominant hand performance on bilateral tasks. Recommendations are offered for future research employing the NES.

NES tasks. Individual NES tasks were highly positively skewed, with a few tasks displaying little response variance and/or unacceptable interrater reliability. The tasks that were excluded from the present study are relatively consistent with the recommendations made by Sanders et al. (1998), who proposed an abbreviated version of

the NES. Therefore, it is recommended that these tasks should either be dropped from future studies with nonclinical samples or modified to increase the difficulty level or measurement sensitivity. For example, one task that was dropped from this study was the Romberg – a task on which patients with schizophrenia typically perform deviantly. Rather than visually examining the degree of "sway" (as is done with the NES), a modified version of the Romberg task could use force platforms that measure shifts in mass while participants stand upright (e.g., Marvel, Schwartz, & Rosse, 2004). This measurement technique may help to reliably detect milder expressions of this neurological soft sign in nondisordered schizotypes.

One concern prior to the start of the study was whether participants drawn from a nonclinical sample would exhibit variability on the tasks or whether the tasks would be so simple that most or all participants would perform without errors. Overall, the results indicate that the latter was not the case and that the variability in task performance was systematically related to schizotypy. However, as noted, several tasks were dropped because of little or no variance in participants' performance. The question remains whether this indicates that: 1) the neurological processes tapped by these tasks really are not exhibited by nondisordered schizotypes (i.e., that they represent episode markers rather than broad indicators of schizotypy), or 2) the tasks were too simple to capture subtle deviancy presumed to characterize schizotypy. Ultimately, this needs to be examined empirically.

In addition to modifying or dropping certain subtests, it is suggested that future studies report specific distribution values (e.g., skew and kurtosis statistics) for each NES

task. Given the dearth of information about this issue in the literature, the present study measured neurological soft signs across the schizotypy continuum to examine the underlying nature of each task. Nearly all subtests were highly positively skewed; therefore, parametric analyses, which are ordinarily used in the NES literature, were deemed inappropriate for the nature of the data. Following this, it is recommended that future researchers consider whether parametric or nonparametric statistical techniques should be used before beginning their analyses, particularly for nonclinical samples. Not only will reporting distributions help researchers develop a statistical plan, but it will aid in research design. Since neurological soft signs were highly positively skewed in the present study, a more powerful approach may have been to sample participants from the high and low end of positive and negative schizotypy, rather than across the entire continuum. However, this solution may be unsatisfactory because it relies on setting arbitrary cut-points and assumes that there is not meaningful variance related to schizotypy below a certain level. Alternatively, nonlinear regressions could examine whether there is a curvilinear relation that suggests a point of inflection. Taken together, researchers should explicitly examine and report distribution and interrater reliability values to strengthen their own study and inform future research projects.

NES composites. Given that internal consistency values of NES composites are rarely reported in the literature, the present study examined the internal consistency of all NES subdomains. Only the motor sequencing composite (both original and excluding dropped tasks) had acceptable internal consistency. In order to strengthen the reliability of this domain even further, it is recommended that tap reproduction should be dropped

from the composite given its low correlation with the other measures. Sensory integration, motor coordination, “others” and NES “total” had relatively poor internal consistency. Thus, the present status of these composites does not appear to be useful for nonclinical samples. This suggests that the composites need to be recreated or modified to increase the reliability of these neurological soft sign domain. In addition, future research should consider developing a “motor sequencing latency” composite, since the measures within this domain correlated highly with one another. Note that composite regression analyses were not run with latency data given that not all tasks within the composite could be scored in this manner. Regardless of the option that is chosen, internal consistency values need to be reported for composite indices. Given the relatively poor internal consistency of the NES subdomains (with the exception of motor sequencing), composite results (Table 6) should be interpreted cautiously. However, since the consensus in the schizophrenia literature strongly holds that negative, but not positive symptoms are related to neurological soft signs, it may be that the effect of negative schizotypy on the expression of neurological soft signs is so large that it is seen even with unreliable subdomains. Research employing more reliable composites is needed to clarify this issue in a sample of psychometrically identified positive and negative schizotypy.

Scoring system modalities. This study also compared the original, ordinal scoring system (Buchanan & Heinrichs, 1989) with a recently proposed continuous scoring system (Sanders, 1998; Sanders et al., 2006) that recorded errors and latency. Note that both methods produced good to excellent interrater reliability. Although the results from

the regression analyses were comparable across both systems, the continuous system captured more variance and had higher interrater reliability values compared to the ordinal system. Therefore, the continuous scoring method appears to be superior to the ordinal system and is recommended for use with nonclinical samples who are expected to display a milder expression of neurological soft signs.

Bilateral tasks. Contrary to the way bilateral tasks are traditionally treated in the NES literature, this study demonstrated that there was little support to combine or collapse bilateral task scores for ordinal or error count tasks (although there was support for latency tasks). Thus, future research should examine this association empirically before deciding how to treat bilateral tasks. Note handedness was unrelated to schizotypy, although the findings are mixed in the literature.

It is also recommended that handedness is coded as dominant/nondominant rather than right/left. This will allow researchers to understand the relation between neurological soft signs and cerebral lateralization – two phenomena proposed to underlie the etiology of schizophrenia. Although examining this association was beyond the scope of this project, we plan to assess the relation of performance disparity between hands on bilateral tasks with positive and negative schizotypy. Crow (e.g., Crow, 1989) suggested that hemispheric asymmetry is reduced in patients with schizophrenia. Therefore, one hypothesis may be that less performance disparity across hands is related to negative schizotypy.

In summary, the majority of individual tasks of the NES appear to be useful measures of neurological soft signs. However, modifications are needed in order to strengthen the overall utility of the NES battery within a nonclinical sample.

Implications

Given that neurological soft signs may be conceptualized as a phenotypic expression of neural dysmaturation that is intermediate between genetic expression and the clinical disorder, the results from this study support schizotypy as an expression of neurodevelopmental vulnerability for schizophrenia. Moreover, the results corroborate the notion that neural dysmaturation predates the appearance of schizophrenia and can be detected across the schizotypy continuum. In addition, the differential relation between neurological soft signs and positive and negative schizotypy supports the multidimensional construct of schizotypy. This does not mean, however, that schizotypy is limited to only two factors. Although the positive and negative symptom dimensions are the most widely reported factors of schizotypy and schizophrenia, the focus on and identification of these factors admittedly reflects the nature of the measures administered.

There is considerable controversy regarding the underlying nature of schizotypy. The predominately European notion, as espoused by Claridge (1984), considers schizotypy to be a normal dimension of personality (fully dimensional model), while the predominately North American conceptualization, as set forth by Meehl (1962), considers schizotypy to represent the expression of a pathological process of neurodevelopment that is taxonic in nature. Taxometric methods and finite mixture modeling have been used to support the notion of a schizotypic taxon (Lenzenweger & Korfine, 1992;

Lenzenweger, McLachlan, & Rubin, 2007). However, both the North American and European conceptualizations are consistent with a multifactorial structure for schizotypy in which schizotypic traits are distributed across continua of increasing severity. The models differ on whether these dimensions are continuous or discontinuous with the general population. It is important to note that the present study focused on further validating the multidimensional structure of schizotypy, not resolving the issue of whether schizotypy is fully dimensional or taxonic in nature. However, the reliable identification of these underlying dimensions should facilitate the resolution of this larger issue.

The current findings also support the use of psychometric screening inventories for detecting meaningful variation related to schizotypy and neurological soft signs. Future studies should employ the psychometric method to assess the relation between schizotypy and multiple domains of risk including biobehavioral, cognitive, and affective features to reliably indentify people along the schizotypy continuum. This will provide a platform for longitudinal study, which will aid in our understanding of the development and expression of schizotypy and will ultimately contribute to the development of prophylactic interventions.

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APPENDIX. TABLES AND FIGURES

Table 1. Description of NES subscales and subtests

Subscale	Subtest	Subtest Description
Sensory Integration	Audio-visual integration	Matches auditory tapping sounds with visually presented dots.
	Stereognosis*#	Identifies an object in hand with eyes closed.
	Graphesthesia*#	Identifies a number written on the tip of forefinger with eyes closed.
	Extinction	Identifies if touched on either right/left cheek, hand, or both.
	Right/left confusion	Points to right or left body parts of self or examiner.
Motor Coordination	Tandem walk	Walks in a straight line for 12 feet, heel to toe.
	Rapid alternating movements*#	Alternates slapping leg with palm and back of hand.
	Finger-thumb opposition*#	Touches the tip of fingers (from forefinger to pinky) with the tip of thumb.
	Finger-nose test*#	Touches tip of nose with tip of index finger with eyes closed.
Motor Sequencing	Fist-ring*#	Alternates hand position between fist and ring.
	Fist-edge-palm*#	Alternates hand position between fist, edge of hand, and palm.
	Ozeretski	Simultaneously alternates both hands between fist and palm-down positions.
	Tap Production	Produces a series of taps.
Other	Romberg test	Stands with arms held parallel to the floor with eyes closed for one minute.
	Adventitious overflow#	Examiner assesses fluttering movement in fingers, hands, arms during Romberg.
	Tremor#	Examiner assesses hand tremor during Romberg.
	Memory	Recalls four words at 5 and 10 minute intervals.
	Tap Reproduction	Reproduces a series of auditory taps.
	Mirror Movements*#	Examiner assesses parallel movements of fingers during finger-thumb opposition.
	Synkinesis#	Follows a pen cap with eyes only between right and left horizontal visual field.
	Convergence#	Follows a pen cap with eyes only as cap is moved toward nose.

	Gaze impersistence*#	Fixes gaze on pen cap at a 45 degree angle in right and left horizontal visual fields.
	Glabellar reflex	Examiner assesses blinking when glabllelar region is tapped.
	Snout and Suck reflexes	Tongue depressor is placed against philtrum to assess puckering and pursing of lips.
	Grasp reflex*#	Examiner assesses flexion of fingers when palm is stroked.

*Indicates right and left side assessed separately, #Indicates right and left side scored separately

Table 2. Relation between dominant and nondominant hand for bilateral tasks.

NES Task	Ordinal[1]	Error[1]	Latency[2]
Stereognosis	-.01	.03	
Graphesthesia	.53***	.49***	
Rapid Alternating Movements	-.01	.11	.93***
Finger-Thumb Opposition	.50**	.39***	.90***
Finger-Nose Test	.37***		
Fist-Ring	.79***	.47***	.91***
Fist-Edge-Palm	.45***	.45***	.92***
Adventitious Overflow	.97***		
Tremor	.96***		
Mirror Movements	.58***		
Synkinesis	.55***		
Convergence	.95***		
Gaze Impersistence	.51***		.23**
Grasp Reflex	.80***		
Palmomental Reflex		.39***	

[1]Polychoric correlation
[2]Pearson correlation
**p<.01 ***p<.001

Table 3. Descriptive Statistics.

Task	Mean	SD	Min	Max	Skew	IRR	Analysis Plan
Audivisual Integration							
Error count	.42	.74	0	3	1.85	.97	Negative Binomial Regression
Ordinal	.39	.65	0	2	1.43	.96	Categorical Regression
Stereognosis							
Dominant - Error count	.04	.20	0	1	4.77	.85	Drop
Nondominant - Error count	.27	.47	0	2	1.40	.92	Negative Binomial Regression
Dominant - Ordinal	.05	.21	0	1	4.42	.85	Drop
Nondominant - Ordinal	.26	.46	0	2	1.44	.92	Categorical Regression
Graphesthesia							
Dominant - Error count	.83	1.01	0	4	1.27	1.00	Negative Binomial Regression
Nondominant - Error count	.63	.84	0	4	1.37	1.00	Negative Binomial Regression
Dominant - Ordinal	.74	.79	0	2	.50	1.00	Categorical Regression
Nondominant - Ordinal	.57	.72	0	2	.86	1.00	Categorical Regression
Face-Hand Test							
Error count	.04	.22	0	2	6.23	.66	Drop
Ordinal	.04	.22	0	2	6.23	.66	Drop
Right-Left Confusion							
Error count	.86	.97	0	4	.82	.98	Negative Binomial Regression
Ordinal	.79	.84	0	2	.41	.99	Categorical Regression
Tandem Walk							
Error count	.16	.45	0	2	2.94	.96	Negative Binomial Regression
Ordinal	.19	.52	0	2	2.75	.98	Categorical Regression
Rapid Alternating Movements							
Dominant - Error count	.06	.29	0	2	5.03	1.00	Drop
Nondominant - Error count	.15	.45	0	3	3.41	1.00	Negative Binomial Regression
Dominant - Latency	14.12	3.07	7.58	35.00	2.49	.99	Linear Regression
Nondominant - Latency	14.02	3.10	8.49	36.00	2.68	.97	Linear Regression
Average Latency	14.06	3.03	8.04	35.50	2.71	.99	Linear Regression
Dominant - Ordinal	.05	.22	0	1	4.12	.79	Drop

Nondominant - Ordinal	.12	.34	0	2	2.80	.95	Categorical Regression
Finger-Thumb Opposition							
Dominant - Error count	.31	.68	0	4	2.99	.79	Negative Binomial Regression
Nondominant - Error count	.32	.67	0	3	2.29	.76	Negative Binomial Regression
Dominant - Latency	12.40	2.85	6.09	23.72	1.04	.98	Linear Regression
Nondominant - Latency	12.37	2.77	7.00	23.06	1.09	.98	Linear Regression
Average Latency	12.39	2.74	7.06	23.39	1.07	.99	Linear Regression
Dominant - Ordinal	.07	.31	0	2	4.98	*	Drop
Nondominant - Ordinal	.08	.30	0	2	3.63	.86	Drop
Finger-Nose Test							
Dominant - Ordinal	.60	.68	0	2	.69	.87	Categorical Regression
Nondominant - Ordinal	.66	.70	0	2	.58	.84	Categorical Regression
Fist-Ring							
Dominant - Error count	1.09	1.47	0	9	2.21	.94	Negative Binomial Regression
Nondominant - Error count	.66	1.21	0	7	2.53	.95	Negative Binomial Regression
Dominant - Latency	30.26	7.42	14.42	67.00	1.42	.96	Linear Regression
Nondominant - Latency	29.41	7.14	14.67	62.87	1.27	.99	Linear Regression
Average Latency	29.84	7.12	14.55	59.33	1.27	.99	Linear Regression
Dominant - Ordinal	.20	.50	0	2	2.48	.83	Categorical Regression
Nondominant - Ordinal	.15	.40	0	2	2.78	.89	Categorical Regression
Fist-Edge-Palm							
Dominant - Error count	1.85	1.79	0	12	1.77	.97	Negative Binomial Regression
Nondominant - Error count	1.07	1.24	0	5	1.22	.92	Negative Binomial Regression
Dominant - Latency	42.02	8.54	23.84	70.53	.57	.94	Linear Regression
Nondominant - Latency	41.02	9.14	23.39	87.06	1.33	.99	Linear Regression
Average Latency	41.52	8.67	23.62	78.69	.94	.98	Linear Regression
Dominant - Ordinal	.47	.64	0	2	1.02	.88	Categorical Regression
Nondominant - Ordinal	.21	.45	0	2	2.00	.71	Categorical Regression
Ozeretski							
Error count	3.91	5.25	0	30	2.57	.98	Negative Binomial Regression
Latency	18.48	5.39	8.69	42.00	1.19	.96	Linear Regression
Ordinal	.79	.85	0	2	.42	.96	Categorical Regression
Tap Production							

Error count	.40	.82	0	5	2.82	.88	Negative Binomial Regression
Ordinal	.34	.61	0	2	1.59	.96	Categorical Regression
Romberg							
Ordinal	.06	.26	0	2	4.87	*	Drop
Adventitious overflow							
Dominant - Ordinal	.49	.65	0	2	1.00	.89	Categorical Regression
Nondominant - Ordinal	.46	.65	0	2	1.11	.92	Categorical Regression
Tremor							
Dominant - Ordinal	.14	.41	0	2	3.02	.74	Categorical Regression
Nondominant - Ordinal	.12	.38	0	2	3.32	.61	Categorical Regression
Memory - 5 minute delay							
Error count	.33	.61	0	3	1.81	1.00	Negative Binomial Regression
Ordinal	.33	.59	0	2	1.63	1.00	Categorical Regression
Memory - 10 minute delay							
Error count	.40	.63	0	3	1.49	1.00	Negative Binomial Regression
Ordinal	.39	.61	0	2	1.33	1.00	Categorical Regression
Tap Reproduction							
Error count	1.05	1.05	0	5	.99	.90	Negative Binomial Regression
Ordinal	.95	.85	0	2	.09	.94	Categorical Regression
Mirror Movements							
Dominant – Ordinal	.82	.56	0	2	.05	.91	Categorical Regression
Nondominant - Ordinal	.67	.55	0	2	.03	.74	Categorical Regression
Synkinesis							
Dominant – Ordinal	.29	.55	0	2	1.76	.95	Categorical Regression
Nondominant - Ordinal	.28	.50	0	2	1.56	.93	Categorical Regression
Convergence							
Dominant – Ordinal	.40	.57	0	2	1.09	.88	Categorical Regression
Nondominant - Ordinal	.46	.64	0	2	1.06	.79	Categorical Regression
Gase Impersistence							
Dominant - Latency	1.28	4.63	0	24.12	3.72	1.00	Censored Regression
Nondominant - Latency	1.31	4.64	0	26.23	3.91	1.00	Censored Regression
Dominant - Ordinal	.11	.36	0	2	3.58	.96	Categorical Regression
Nondominant - Ordinal	.13	.41	0	2	3.34	1.00	Categorical Regression

Glabellar Reflex							
Error count	1.29	1.43	0	10	2.05	.76	Negative Binomial Regression
Ordinal	.08	.30	0	2	3.63	.65	Drop
Snout Reflex							
Ordinal	.00	.00	0	0		**	Drop
Grasp Reflex							
Dominant - Ordinal	.16	.45	0	2	2.85	1.00	Categorical Regression
Nondominant - Ordinal	.10	.35	0	2	3.73	.89	Categorical Regression
Suck Reflex							
Ordinal	.02	.22	0	2	9.11	1.00	Drop
Palmomental Reflex							
Dominant - Error count	.31	.93	0	7	4.67	.38	Drop
Nondominant - Error count	.32	1.42	0	15	7.71	.59	Drop
Go-No-Go Task							
Error count	.71	1.16	0	7	2.38	.97	Negative Binomial Regression

*Negative average covariance

**No variance

Table 4. NES Subtests

	Ordinal			Error			Average Latency[1]		
	Step 1		Step 2	Step 1		Step 2	Step 1		Step 2
	Positive Schizotypy	Negative Schizotypy	PXN	Positive Schizotypy	Negative Schizotypy	PXN	Positive Schizotypy	Negative Schizotypy	PXN
NES Criterion	**β**	**β**	**β**	**B**	**B**	**B**	**β**	**β**	**B**
Audiovisual Integration	.01	-.07	0	.03	.01	.03			
Stereognosis									
Nondominant	-.03	.13	-.10	-.01	**.17@**	-.01			
Graphesthesia									
Dominant	.02	.02	**-.16@**	.01	.08	**-.15***			
Nondominant	**.17***	-.03	-.09	**.12@**	-.03	-.05			
Right Left Confusion	**.16***	.09	.06	**.14****	.07	0			
Tandem Walk	-.21	**.27***	-.03	-.26	**.38***	-.13			
Rapid Movements							-.12	-.02	.14
Nondominant	.11	.06	-.03	.02	.08	.01			
Finger-Nose									
Dominant	.08	.03	-.06						
Nondominant	.13	.09	**-.15@**						
Fist-Ring							.03	.07	**.15@**
Dominant	-.13	.15	-.01	-.06	**.16@**	0			
Nondominant	-.04	.14	-.19	-.04	.10	**-.16@**			
Fist-Edge-Palm							-.01	.10	**.17@**
Dominant	.11	**.22****	-.01	.04	**.16****	0			
Nondominant	.02	.08	-.05	.03	.04	-.06			
Ozeretski	.03	**.16***	0	.02	**.16@**	-.03	-.02	.06	.06
Tapping Production	.02	0	-.11	-.05	.04	-.08			
Adventitious Overflow									
Dominant	-.09	**.18***	.12						
Nondominant	0	**.16***	.06						
Tremor									

Dominant	.16	**.21**[@]	0						
Nondominant	.10	**.36*** **	-.06						
Memory - 5 min delay	-.05	**.24****	-.11	-.04	**.26****	-.11			
Memory - 10 min delay	-.14	**.26*** **	-.17	-.13	**.26*** **	**-.15**[@]			
Tapping Reproduction	-.04	.03	-.07	-.03	.01	-.05			
Finger-Thumb Opposition							-.10	.08	.14
Dominant				-.06	.06	-.01			
Nondominant				-.22	.18	-.01			
Mirror Movements									
Dominant	**.16**[@]	.06	-.07						
Nondominant	**.17***	-.03	.01						
Synkinesis									
Dominant	.07	.13	**-.31***						
Nondominant	**-.17**[@]	**.32*** **	.07						
Convergence									
Dominant	-.09	.07	-.10						
Nondominant	-.03	**.17***	.05						
Gaze Impersistence									
Dominant	.01	.01	.03				.26	.73	.28
Nondominant	-.01	-.13	.15				-.37	-2.39	2.18
Glabellar Reflex				**-.11**[@]	.08	.02			
Grasp Reflex									
Dominant	-.03	**.29*** **	**-.34***						
Nondominant	.12	.01	-.14						
Go-No-Go Task				**.20***	.14	-.10			

PXN = Interaction [@]p<.10 *p<.05 **p<.01 ***p<.001

[1]Latency data for Gaze Impersistence was examined separately for dominant and nondominant hands.

Table 5. Exploratory factor analyses for NES composites.

NES Domain	Chi-Square Test of Model Fit	Chi-Square Test of Model Fit for the Baseline Model	CFI	TLI	RMSEA	SRMR	Minimum Rotation Value
Sensory Integration (all tasks)	X^2 = 51.41**, df= 14	X^2 = 120.42** , df = 21	.62	.44	.123	.126	2.159
Sensory Integration (no dropped tasks)	X^2 = 11.59*, df = 5	X^2 = 51.90** , df=10	.84	.69	.086	.083	1.171
Motor Coordination (all tasks)	X^2 = 89.22**, df = 21	X^2 = 89.22** , df=21	0	0	.135	.130	****
Motor Coordination (no dropped tasks)	X^2 = 24.36**, df = 6	X^2 = 24.36** , df=6	0	0	.131	.039	23181.92
Motor Sequencing (all tasks)	X^2 = 12.33, df = 9	X^2 = 286.32** , df=15	.99	.98	.046	.072	2.424
Other (no dropped tasks)	X^2 = 1790.56**, df=152	X^2 = 15300.95**, df=171	.89	.88	.247	.331	7.787
NES total (no dropped tasks)	X^2 = 2860.06**, df=527	X^2 = 16588.62**, df=561	.85	.85	.158	.239	8.502

*p<.05, **p<.001

Table 6. NES Composites Excluding Dropped Tasks.

	Ordinal		
	Step 1		**Step 2**
	Positive Schizotypy	**Negative Schizotypy**	**Interaction**
NES Criterion	**B**	**B**	**B**
Sensory Integration Dysfunction	.07*	03	-.04[@]
Motor Coordination	.05	.11*	-.07*
Motor Sequencing	.01	.16*	-.03
Others	.01	.11**	-.05[@]
Total	.02	.11***	-.05**

[@]p<.10 *p<.05 **p<.01
***p<.001

Figure 1. Simple slopes analysis exhibiting the interaction between the predictions of positive and negative schizotypy and motor coordination (excluding dropped tasks).

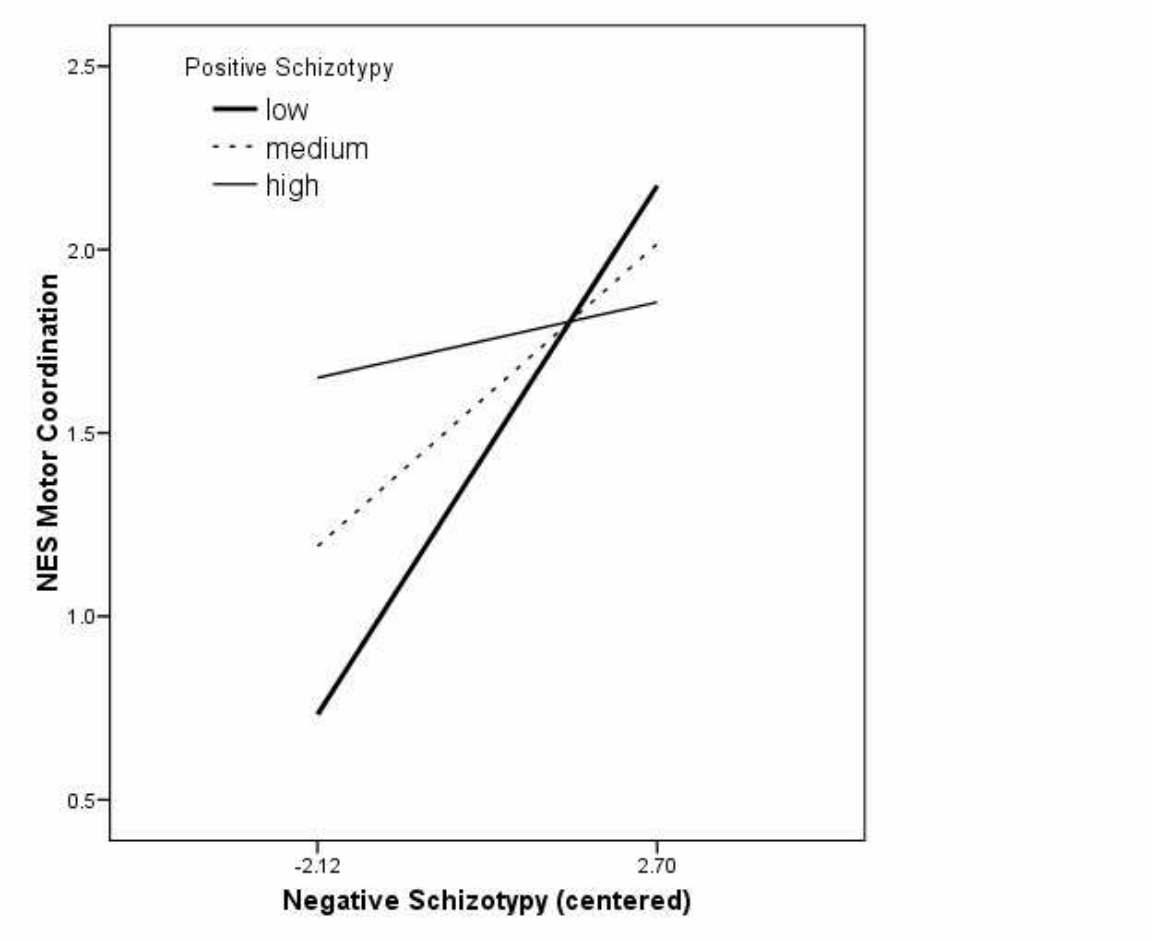

Figure 2. Simple slopes analysis exhibiting the interaction between the predictions of positive and negative schizotypy and NES total (excluding dropped tasks).