MULTIVARIATE PREDICTION OF SCHIZOPHRENIA IN ADULTHOOD

UTILIZING CHILDHOOD NEUROLOGICAL DATA

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Abstract

Research has highlighted numerous benefits of identifying at-risk individuals before they develop schizophrenia. Longitudinal studies have elucidated a number of neurological deficits present in people with schizophrenia that can be measured premorbidly. Most of these studies, however, have suffered from methodological limitations, including only incorporating a single neurological variable, small sample size, and truncated follow-up assessment period. The objective of the current study was to examine the ability of multiple neurological variables to predict adult psychiatric status in high risk individuals and healthy controls. Data were derived from a longitudinal dataset of a large Danish cohort study begun in 1959, and included information on offspring of parents hospitalized with schizophrenia as well as age-matched controls. In adulthood, 32 offspring were diagnosed with a schizophrenia-spectrum disorder, 79 with a non-psychotic diagnosis and 133 with no diagnosable mental illness. The most accurate prediction model correctly classified 65.6% of schizophrenia-spectrum outcomes based on risk status and neurological data. Minor physical anomalies, a marker of pre- or perinatal complications, were the single most significant neurological predictor of schizophrenia-spectrum outcomes, followed by neuromotor dysfunction. Ocular alignment deficits, abnormal cerebral lateralization, and delayed developmental milestones contributed the least to predicting outcome diagnoses relative to other proxies of neurological dysfunction. Results are discussed with respect to the two-hit model of schizophrenia etiology.

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CHAPTER 1: INTRODUCTION

An Overview of Schizophrenia

Schizophrenia continues to be one of the most costly and debilitating mental disorders, disturbing an individual's social, cognitive, neurological, and psychological functioning. Although prevalence estimates vary, it is believed the disease affects 1% of the population in any given year (American Psychiatric Association, 2000). Schizophrenia is characterized by positive symptoms, involving exaggeration or distortion of normal thoughts, emotions, and behavior; negative symptoms, which consist of deficit features such as blunted affect and passive social withdrawal; as well as neurological and cognitive abnormalities, such as deficits in coordination and intellectual functioning.

In addition to symptoms, schizophrenia is correlated with a host of additional life concerns. For instance, people with schizophrenia are estimated to be at 13 times greater risk of committing suicide compared to the general population (Saha et al., 2007). People with schizophrenia are also at increased risk of suffering from a multitude of medical problems, including cardiovascular, digestive, endocrine, neurological, genitourinary, and respiratory problems, all of which contribute to a life expectancy approximately 20% shorter than age-matched controls (Newman & Bland, 1991; Brown et al., 2000). Additionally, many individuals with schizophrenia report trouble achieving a satisfactory quality of life. Quality of life indicators, such as the ability to obtain competitive employment, live in the community, reach financial independence, and establish stable romantic relationships are often impaired in populations with schizophrenia (e.g., Savilla et al., 2008; Rosenheck et al., 2006; Tulloch et al., 2006).

Although a relatively small percentage of the population suffers from schizophrenia, the disease creates enormous social and economic concerns. Economic costs of schizophrenia include each patient's salary loss, costs covered by relatives, the price of care providers and treatment, research costs, and the social encumbrance (Moscarelli, 1994). The costs of schizophrenia are disproportionate compared to the prevalence rates. In 1990, for example, the economic burden was estimated at $32.5 billion for schizophrenia and $30.4 billion for affective disorders, though affective disorders are nearly ten times more prevalent than schizophrenia (Rice, 1999). Despite the fact that billions of dollars are spent each year to address the physical, mental, emotional, and neurological impairments associated with schizophrenia, some research suggests incidence and suicide rates may be on the rise (Bray et al., 2006; Healy et al., 2006). Much effort, therefore, has been exerted to investigate methods for early identification and treatment for people at risk for developing schizophrenia.

The Development of Schizophrenia

The "two-hit" model of schizophrenia integrates evidence for the roles of genetic vulnerability, pre- and perinatal environmental events, and environmental events later in life contributing to the development of schizophrenia. The two-hit model purports that schizophrenia is caused by genetically preprogrammed or exogenous prenatal insults acting as a "first hit" that disrupt the normal development of the central nervous system (CNS). If a vulnerable CNS is exposed to an environmental stressor, or "second hit," later in life, the preexisting comprome might prevent successful buffering of the second hit, leading to the development of schizophrenia (Bayer et al., 1999).

A related theory on the development of schizophrenia is the neurodevelopmental model which posits that the brain anomalies associated with schizophrenia are caused by prenatal insults that interrupt typical neurodevelopment. These insults are sometimes characterized as the second "hit," following genetic predisposition, however, they might also play the role of a first hit, followed by a later exogenous environmental stressor (Schiffman et al., 2001). It is hypothesized that early neurodevelopmental anomalies interact with the typical maturational brain processes throughout childhood and adolescence, causing a range of subthreshold issues for the individual. Not until late adolescence or early adulthood, however, does the interaction between early neurodevelopmental disruption and typical brain maturation ultimately lead to the manifestation of the characteristic positive, negative, and cognitive symptoms of schizophrenia (Weinberger, 1987). Some of these abnormalities appear to be related to prenatal problems in neurogenesis, neural and synaptic pruning, and neural migration (Keshavan, 1999; Flagstad et al., 2004). Though the clinical symptomatology resulting from this brain maldevelopment remains relatively dormant until full-blown psychosis, studies suggest that it is possible to recognize some of these neuropathological signs premorbidly. Premorbid neurological indicators might serve as viable markers to portend schizophrenia.

There are a number of theories behind the causes of schizophrenia-relevant early neurodevelopmental disruption. There is a wealth of behavioral genetic literature documenting a strong heritable component to schizophrenia (e.g., Gottesman, 1994; Tsuang, 2000; Chang et al., 2002). More recently, attention has focused on combinations of specific genes (as well as gene by environment interactions) that might be involved in

the development of schizophrenia. It is believed that a combination of relatively high-risk genes can lead to neural maldevelopment, cognitive deficits, as well as positive symptoms. Specific genes, or deletions within genes, in combination with environmental factors, affect the development of proteins and enzymes, neuroanatomy, and neurotransmitter activity. These malformations are sometimes evidenced in neurological and cognitive problems. Genes implicated in psychosis vulnerability include *DTNBP1, DAOA, TAAR6, NRG1, COMT, ZDHHC8,* and DISC1 (see Lakhan & Vieira, 2009 for a review).

Neurological Dysfunction in Schizophrenia

Although schizophrenia is well-known for, and in fact defined by, its positive and negative symptoms (American Psychiatric Association, 2000), many contend that the neurological problems that accompany schizophrenia may represent the "true" underlying pathophysiology that eventually manifests in psychotic symptoms (e.g., Andreasen et al., 1999; Mittal et al., 2007). Early leaders in the field such as Kraeplin and Blueler conceptualized hallucinations and delusions as "downstream effects" of fundamental neurological deficits (e.g., Ho et al., 2004). More recently, Andreasen and colleagues characterized the relationship between neurological abnormalities and psychotic symptoms as a function of "cognitive dysmetria," referring to a dysfunction related to moderation of mental activities. According to this theory, schizophrenia is primarily a cognitive disorder in which neurodevelopmental problems result in abnormalities in the cortical-cerebellar-thalamic-cortical-circuit (CCTCC). This deficit manifests in difficulty "coordinating the processing, prioritization, retrieval, and expression of information." These cognitive and perceptual dysfunctions are posited to lead to a misinterpretation of

stimuli, which can be seen in measurable neurological and cognitive problems as well as hallmark psychotic symptoms such as delusions, hallucinations, negative symptoms, and disordered thought processes (Andreasen at el., 1998; Andreasen at el., 1999).

This neurological impairment is thought to be relatively stable over time and generally remains even when an individual's other symptoms have abated (Albus et al., 2002). Many researchers have now targeted the neurological dysfunctions as not only a main feature of schizophrenia, but "the primary expression of the schizophrenic brain" (Heinrichs, 2005). Post-mortem and imaging studies of individuals with schizophrenia typically demonstrate neural structural and functional abnormalities (e.g., Shenton et al., 2001; Harrison et al., 2003; Davidson & Heinrichs, 2003). Formal neurological assessments administered to people with schizophrenia often reveal neurological "hard signs," which indicate localized brain abnormalities, and neurological "soft signs" which suggest global, non-specific, cerebral dysfunction (Lane et al., 1996). Neurological soft signs in particular appear to be highly associated with schizophrenia (e.g., Biswas et al., 2007; Flyckt et al., 1999; Venkatasubramanian et al., 2003). The majority of work examining neurological impairment and schizophrenia, however, has been conducted with individuals already diagnosed with the disorder.

Consequences of neurological impairment. Neurological impairment is extremely relevant with respect to real-world functioning. For example, neurological impairment correlates with decreased ability to gain employment (Beiser et al., 1994; Brekke et al., 1997, Velligan et al., 2000), lower quality of life (Fujii & Wylie, 2003), higher rates of relapse (Jarboe & Schwartz, 1999), increased medication mismanagement (Jeste et al., 2003), higher medical comorbidity (Friedman et al., 2002), and higher indirect and direct

costs to care for the individual (Sevy & Davidson, 1995). Further, early neurological deficits are predictive of later impaired functional outcomes (Milev et al., 2005).

Proxies for Neurological Dysfunction Observed in Adults with Schizophrenia.

Although imaging and postmortem assessments highlight neurological dysfunction in people with schizophrenia, proxies are often used in research as indicators of abnormal neurodevelopment, without *in vivo* assessment of the brain. These proxies, or indicator variables, are "quite valuable in etiologic research; for example, such a variable may be more directly or reliably assessed than the causal factor or process that it marks" (Cannon & Rosso, 2002).

Morphological proxies. Both the central nervous system and the skin form concurrently from the same structural origins. As a result, insults during pregnancy that interrupt neurodevelopment and potentially lead to the development of schizophrenia can leave accompanying irregularities in the development of the epidermis and other external features. These skin "fossils" of abnormal brain development are external and therefore can be more easily measured than direct assessment of the brain (Lobato et al., 2001). These external features point both to neurodevelopmental disruption as well as to the timing of the prenatal disruption. Some morphological features, for example, are formed during the second trimester, so an aberration in one of these features is indicative of an early insult between months three and six of *in utero* life. Furthermore, the features of the abnormalities can inform as to the type of prenatal insult, such as ischemia, or a restriction in blood supply, as opposed to chromosomal aberration (Green et al., 1994).

One frequently studied external indicator of neurodevelopmental disruption are minor physical anomalies (MPAs), which are slight malformations of the head and limbs

that are clinically and cosmetically insignificant, but can be used as markers of disturbed development. These anomalies include hair anomalies (two or more hair whorls, fine electric hair), abnormal head circumference, epicanthus (skin fold at inner corner of eye), hyperteliorism (wide-set eyes), ear abnormalities (low-seated ears, adherent ear lobes, malformed ears, asymmetrical ears, soft pliable ears), high-steepled palate, furrowed tongue, tongue with smooth-rough spots, curved fifth finger, single transverse palmar crease, third toe longer than second, and partial syndactylia (webbing) of toes (e.g., Ismail et al., 1998; McNeil et al., 2000; Gourion et al., 2004).

Studies suggest that MPAs are largely due to environmental, rather than genetic, influences. Although not entirely understood, prenatal insults are purported to lead to morphological abnormalities through the disruption of neural migration (Green et al, 1994). Additionally, intrauterine growth retardation and edema are both associated with development of schizophrenia (Bracha et al., 1995) as well as irregular skin development (Bracha et al., 1992). Retinoic acid (a Vitamin A derivative implicated in embryonic growth) excess or deficit, too, can influence epidermal ridges as well as neuronal migration (Goodman, 1996). Prenatal exposure to anticonvulsants can restrict blood flow to the developing epidermal arteries which in turn affects skin formation (Daniellsson et al., 1995). Simultaneously, exposure to anticonvulsants is purported to alter the number of benzodiazepine binding sites in the growing brain (Gallager & Mallorga, 1980). Although a number of studies implicate environmental factors in the development of MPAs, some research also demonstrates an increase in MPAs in healthy first-degree relatives of individuals with schizophrenia. It is possible that genetic risk decreases an individual's ability to defend against environmental stressors supporting the contribution

of genetics in concert with extragenetic influences in the development of MPAs (Ismail et al., 1998).

MPAs are consistently shown to be elevated in schizophrenia and schizophrenia-spectrum disorders relative to control populations, with a meta-analysis reporting an effect size of d=1.13 in a sample of 1,120 people with schizophrenia (Weinberg et al., 2007). Sivkov and Akabaliev (2004) found the positive predictive value of MPAs for predicting diagnosis of schizophrenia versus no diagnosis was 71.6%. MPAs appear to be elevated both in children who later develop schizophrenia in adulthood (Schiffman et al., 2002) and people in their first episode of schizophrenia (e.g., Dean et al., 2006; Dean et al., 2007).

Neuropsychological functioning. A host of studies demonstrate that people with schizophrenia demonstrate deficits in neuropsychological performance, which are thought to reflect neurological abnormalities. Some of the more consistently documented neuropsychological deficits in people with schizophrenia are those of executive functioning, sustained attention, set-shifting or cognitive flexibility, processing speed, working memory, and overall intelligence quotient (e.g., David et al., 1997; Heinrichs & Zakzanis, 1998; Laurent et al., 2000; Liu et al., 2002; Fioravanti et al., 2005; Dickinson et al., 2007; Forbes et al., 2009). Additionally, people with schizophrenia underperform healthy controls on a number of specific verbal tasks including semantic and phonemic fluency, verbal learning, and verbal memory (e.g., Bagner et al., 2003; Henry & Crawford, 2005).

Neuropsychological deficits have been demonstrated in healthy first-degree relatives of individuals with schizophrenia, in premorbid individuals who have yet to

develop schizophrenia, and in individuals with schizophrenia-spectrum disorders (e.g., Mitropoulou et al., 2005; Kuha et al., 2007; Seidman et al., 2010). This suggests that neuropsychological impairment is related to an underlying vulnerability towards developing schizophrenia, rather than specifically to the illness course itself. The severity of many of these deficits increases with earlier age of schizophrenia onset, with earlier age of onset being associated with more severe forms of schizophrenia (e.g., Hoff et al., 1996; Bellino et al., 2004; White et al., 2006; Biswas et al., 2006). Although there appears to be a decline in neuropsychological performance after illness onset, research indicates that functional decline stabilizes following first psychotic break (e.g., Gold et al., 1999; Hoff et al., 1999).

Neuromotor functioning. In addition to general neurological and neuropsychological deficits, adults with schizophrenia demonstrate specific neuromotor abnormalities. These dysfunctions include problems with motor coordination (e.g., Walker, 1981), motor control (e.g., Manschreck et al., 2004), motor sequencing (e.g., Delevoye-Turrell et al., 2003), and extrapyramidal signs (parkinsonism, dyskinesia) in neuroleptic-naïve individuals (Torrey, 2002). In particular, people with schizophrenia have elevated rates of oculomotor abnormalities (e.g., Ross et al., 1997, Clementz & Sweeney, 1990). Research suggests these neuromotor dysfunctions are correlated with global neurological and neuroanatomical abnormalities (Mohr et al., 1986).

Neuromotor dysfunction in adults with schizophrenia is associated with prenatal neurodevelopmental disruption and subsequent maldevelopment of the CCTCC. Animal studies suggest that even mild prenatal stress is linked to neuromotor abnormalities in primates (Schneider, 1992). Subcortical pathways associated with these neuromotor

deficits (i.e., striatal and hypothalamic-pituitary-adrenal dysfunction) are also associated with positive psychotic symptoms. Related to this neuroanatomical vulnerability, healthy relatives of individuals with schizophrenia manifest neuromotor dysfunction at higher rates than healthy controls, indicating a genetic component (McNeil & Cantor-Graae, 2000; Huttunen et al., 2008; Lee et al., 2008).

Laterality. Abnormal cerebral lateralization, specifically manifested by left- and mixed-handedness, is hypothesized to be caused by some of the same prenatal insults that are associated with MPAs and is often used as a proxy for neurological dysfunction. Although not consistently replicated, researchers have observed decreased rates of right-handedness in people with schizophrenia compared to control populations (Sommer et al., 2001; Dragovic & Hammond, 2005). In addition to aberrant handedness, adults with schizophrenia appear to have higher rates of left-eye dominance than healthy control populations (Giotakos, 2002). Further studies have found increased rates of abnormal lateralization in relatives of individuals with schizophrenia (Grosh et al., 1995; Orr et al., 1999; Sommer et al., 2001) and groups with psychometrically-identified psychosis-proneness (Kim et al., 1992; Richardson, 1994; Chapman & Chapman, 1997), which supports the notion that these anomalies may be related to inherited pathophysiology (Keshavan et al., 2008).

Crow has posited that cerebral asymmetry has been fundamental to the development of language in human evolution and that "asymmetry is the defining feature of the human brain" (Crow et al., 1996; Crow, 2004). A failure to develop normal asymmetry may be a core feature of schizophrenia that affects normal cerebral hemispheric communication and surfaces as neurological deficits. Exposure to sex

hormones during pregnancy, specifically testosterone, is hypothesized to cause the abnormal lateralization seen in schizophrenia (Arató et al., 2004; Cohen-Bendahan et al., 2005). This disruption in normal hemispheric lateralization appears to affect the planum temporale, in particular, which has less leftward asymmetry in people with schizophrenia compared to control populations and is implicated in handedness (Falkai et al., 1995).

Ocular alignment. A number of studies have established abnormal eye movements in populations of people with schizophrenia, including pursuit eye movement abnormalities and ocular alignment deficits, such as strabismus (e.g., Brownstein et al., 2003; Toyota et al., 2004). These eye movement deficits are thought, in part, to be associated with neurobiological deficits, including disturbances in the frontal areas, posterior hippocampus, and right fusiform gyrus (Tregellas et al., 2004). Other researchers have suggested that ocular alignment dysfunction may actually be a type of minor physical anomaly (Toyota et al., 2004).

The causes of ocular alignment abnormalities are not wholly understood. There is evidence that the ocular alignment abnormalities seen in many people with schizophrenia are related to various genes that regulate dopamine. Therefore, it is possible that both strabismus and psychotic symptoms may relate to disruption in the development of dopaminergic pathways (Schiffman et al., 2006). First-degree unaffected relatives of people with schizophrenia also demonstrate eye movement abnormalities, supporting the notion of some genetic basis for ocular abnormalities (Paul, 1994; Toyota et al., 2004).

Neurological Dysfunction: Precursor to or Byproduct of Schizophrenia?

As described above, there is ample literature linking an array of neurological abnormalities to schizophrenia. Most studies that examine neurological dysfunction and

schizophrenia employ neurological assessments of adults after they have developed schizophrenia or post-mortem studies of the brain. It is difficult to ascertain, therefore, whether the dysfunctions observed are present before the onset of the disease or are a byproduct of the illness. Hospitalization, substance use, social isolation, long-term pharmaceutical treatment, and the potential neurotoxic effects of schizophrenia itself may, in part, be responsible for the neurological dysfunction manifested by individuals with chronic schizophrenia (e.g., Madsen et al., 1999; van Haren et al., 2008). Another key consideration with respect to the literature on adults with schizophrenia and neurological signs is blinding of raters. Comparing individuals with full schizophrenia to controls can unwittingly bias raters towards the study hypothesis during their assessment (Watt et al., 1984).

Arguing against the notion that neurological abnormalities are a function of the onset of schizophrenic illness, there is some evidence that individuals who are neuroleptic-naïve and/or are experiencing first-episode schizophrenia also manifest neurological impairment and neuroanatomical abnormalities (e.g., Chatterjee & Lieberman, 1999; Dazzan & Murray, 2002; Pantelis et al., 2003). Studying individuals during their first psychotic break diminishes confounds of psychiatric treatment and substance abuse on neurological abnormalities. Nevertheless, it has been suggested that individuals with schizophrenia seeking first treatment may have already experienced events (biological or environmental) that might have implications for neurological functioning (Sanders et al., 1994; Gupta et al., 1995; Browne et al., 2000). Additionally, the issue of blinded ratings is not adequately addressed in studies of individuals in their first episode of psychosis. Given these limitations, studies of adults already with

psychotic symptoms cannot completely elucidate whether neurological dysfunction precedes the onset of schizophrenia or is a byproduct of psychosis.

Premorbid Neurological Dysfunction

Studies suggest that the deteriorative process of schizophrenia begins years before the first psychotic break. Subtle neurological, social, and affective anomalies are evident in many children who later develop schizophrenia. Prospective studies involving individuals before they develop schizophrenia offer substantiation for neurological dysfunction preceding schizophrenia onset. In addition to surmounting the issue of treatment or course of illness effects that might play a role in neurological functioning, assessments prior to illness have the advantage of more effectively blinding raters as future psychiatric outcome remains unknown.

Prospective studies of neurological dysfunction and schizophrenia: Birth cohort studies of neurological dysfunction and schizophrenia. One methodology used to study children who go on to develop schizophrenia is the large-scale longitudinal assessment of birth cohorts. Longitudinal cohort studies follow large groups of people from a time and location over many years. They have the benefit of increased power to detect findings due to their size and can provide a window into developmental progression.

A longitudinal cohort study by Cannon and colleagues (2002) compared neurological functioning in a one-year birth cohort of 1,037 children enrolled in the Dunedin Multidisciplinary Health and Development Study. At age 26, participants underwent assessments that yielded four diagnostic groups: schizophreniform disorder (n=36), anxiety or depressive disorder (n=278), mania (n=20), or did not meet criteria for a psychiatric diagnosis (n=642). Results indicated that the children who went on to

develop schizophrenia-spectrum disorders in adulthood were significantly more impaired on biennial evaluations conducted between ages 3 and 11 years on cognitive development (f^2=.49), neuromotor functioning (f^2=.64), and receptive language skills (f^2=.45) and had significantly more internalizing (f^2=.37) and interpersonal problems (f^2=.85) compared to all other outcome groups (F^2 is an effect size measure used in the context of regression analyses with an effect of .02 considered small, .15 as medium, and .35 as large; Cohen, 1992). These results indicate that there are measurable differences between children who go on to develop schizophrenia-spectrum disorders later in life and children who do not (Cannon et al., 2002).

There are, however, several limitations to this study that should be considered when interpreting the results. As is the case in many birth cohort studies, the sample size of participants who went on to develop a schizophrenia-spectrum disorder is small. Additionally, at the time of publication, not enough time had necessarily elapsed to consider the participants in the control groups to have truly passed the age of risk for developing psychosis. Moreover, the use of schizophreniform disorder as the primary psychiatric outcome poses questions about the stability of these diagnoses.

Several studies have used a subset of data from the Philadelphia cohort of the Philadelphia National Collaborative Perinatal Project (NCPP) to identify childhood variables associated with adult schizophrenia. This cohort included 9,138 offspring born at two obstetric wards between 1959 and 1966. These children were given behavioral and speech/language evaluations at 8 months, 4 years, and 7 years. A citywide database was later screened for outcome diagnoses in adulthood. By 1996, 72 cohort individuals had developed a schizophrenia diagnosis and 7,941 had no known psychiatric diagnosis.

Participants with adulthood diagnoses of schizophrenia had significantly more motor coordination deficits (OR=2.4, 95% CI:1.1-5.5), social maladjustment (OR=2.54, 95% CI:1.33-4.86), and abnormal speech (OR=12.70, 95% CI:2.46-65.66) in childhood than participants with no psychiatric diagnosis (Rosso et al., 2000; Bearden et al., 2000).

It is important to note, however, that reliance on the citywide database for adulthood diagnoses may have led to misclassification of outcome psychiatric status. Participants with schizophrenia were only identified as such if they were still living in the Philadelphia area, had been treated at a public mental health facility between 1985 and 1995, and still had their childhood name. There remains the possibility that participants misidentified as control cases had systematically different childhood behavioral and language functioning than those who were correctly identified. Additionally, participants with non-psychotic disorders were excluded so it is possible that any differences found were due to psychopathology in general and are not exclusive to schizophrenia-spectrum disorders.

The Northern Finland 1966 Birth Cohort is comprised of 12,058 offspring who were prospectively evaluated for developmental milestones. Adulthood diagnoses were determined using the Finnish Hospital Discharge Registry which maintains records of all mental and general hospitals in addition to beds in local health centers throughout the country. Children who developed psychotic disorders in adulthood (n=155) were more delayed in one-year developmental milestones (age of standing, walking, day/night wetting, spoken words, gross neurological deviations) compared to participants who developed non-psychotic disorders (n=315) and control participants (n=10,457), with risk

ratios for developing psychotic disorders related to late developmental ranging from .99 (daytime wetting) to 1.60 (never being potty trained) (Isohanni et al., 2001).

As with other studies, it is possible that not all cases of people with schizophrenia were correctly identified, as the registry does not include people who did not receive treatment or were treated at private hospitals. Diagnoses were only coded through 1997, so cases that developed after age 31 may have been misclassified as controls. In addition, some variance in developmental milestones was potentially lost as many participants met these milestones after the age one assessment.

Cannon and colleagues (1997) examined participants enrolled in the Medical Research Council National Survey of Health and Development, a stratified random sample of 13,687 British people born during six weeks in 1946. At age 11, participants were given an examination of hand and eye dominance. Adulthood diagnoses were identified using a national registry of hospital admissions when the cohort was 43-years-old. Of the participants available for follow-up, those who developed schizophrenia (n=24) had significantly higher rates of left- mixed-eye dominance (OR=2.5, 95% CI:1.0-5.8) than control participants (n=4,024).

In a design related to cohort studies, Davidson et al. (1999) ran analyses incorporating data from the Israeli Draft Board Registry with the Israeli National Psychiatric Hospitalization Case Registry. All Israeli citizens between the ages of 16 and 17 are required by law to undergo an assessment to determine their fitness for military service. This examination includes an assessment of psychiatric history, a cognitive test battery, and an interview of behavior and personality traits. The Israeli National Psychiatric Hospitalization Case Registry includes diagnostic information on all patients

that are treated in inpatient psychiatric facilities across the nation. Cross-referencing information gathered from these two sources, Davidson and colleagues analyzed all adolescents who were examined by the draft board between 1985 and 1991 and who were also listed on the National Psychiatric Hospitalization Case Registry between 1970 and 1995. Using data from the draft assessment as predictor variables for case registry diagnoses, Davidson et al. were able to achieve a sensitivity of 75% and a specificity above 99% in distinguishing future individuals who would develop schizophrenia (n=509) from those with no future psychiatric diagnosis (n=9,125) using a combination of scores on social functioning (OR=4.37, 95% CI:3.39–5.75), organizational ability (OR=2.03, 95% CI:1.66–2.49), and intellectual functioning (OR=1.62, 95% CI:1.39–1.72).

Although this combination of predictor variables yielded results with particularly high specificity, there are a number of notable limitations. Similar to the NCPP and Northern Finland 1966 Birth Cohort studies, adult diagnoses were based on a case registry that may have misclassified people with schizophrenia as being control participants if they did not receive treatment in an inpatient psychiatric facility in Israel. Additionally, this study only included adolescent males, who are more likely to suffer from a more severe form of schizophrenia and to be hospitalized (Munk-Jorgensen, 1985; Meltzer et al., 1997). Based on these participant demographics, this study may not have included individuals with less severe forms of schizophrenia who did not necessitate inpatient treatment, nor did it include any women. As an outcome of schizophrenia was only compared to adults with no diagnosis, it is possible that these early predictor variables are associated with a vulnerability to psychopathology in general and are not

specific to schizophrenia. Again, the follow-up period did not extend through the entire period of risk for developing schizophrenia so it is possible that some participants classified as controls may go on to develop psychopathology.

Prospective studies of neurological dysfunction and schizophrenia: Longitudinal high-risk studies of neurological dysfunction and schizophrenia. Another powerful design in evaluating the precursors of schizophrenia is through the genetic high-risk method. Genetic high-risk designs take advantage of the fact that individuals with a parent with schizophrenia are at a ten- or more fold risk for developing schizophrenia than individuals in the general population. Through the high-risk design, because more individuals will eventually develop schizophrenia, researchers can follow fewer individuals (often at a greater level of detail) than in cohort studies. Similar to cohort studies, high-risk longitudinal studies have the advantages of blindness to future psychiatric status and analysis of risk factors prior to the emergence of psychotic symptoms. Additionally, high-risk studies allow for finer-grained analysis of the genetic components of vulnerability towards schizophrenia.

The Swedish High-Risk Study began in 1973 with 103 pregnant women with a psychosis diagnosis and 103 control pregnant women. The focus of this study was on pre- and perinatal complications as well as early childhood development, and included longitudinal offspring assessment at birth, 3 weeks, 6 weeks, 3.5 months, 6 months, 12 months, 24 months, 48 months, and 72 months. These assessments included evaluations of neurological functioning, temperament, behavior, and physical health (McNeil & Kaij, 1987). At mean age 22, 38 offspring of mothers with schizophrenia, 36 offspring of mothers with affective psychosis, and 88 control offspring were assessed for psychiatric

status. At that time, six offspring of mothers with schizophrenia were diagnosed with a schizophrenia-spectrum or Cluster A personality disorder (schizotypal personality disorder, n=3; schizoid personality disorder, n=1; schizophrenia, n=1; schizoaffective psychosis, n=1), two offspring of mothers with affective psychosis were diagnosed with a Cluster A personality disorder (paranoid personality disorder, schizoid personality disorder), and two control offspring were diagnosed with schizotypal personality disorder. Examination of early childhood data revealed that, among high-risk participants, dysfunction in verbal memory (d=0.83), attention (d=0.80), and complex executive function (d=0.99), were specifically related to schizophrenia-spectrum and Cluster A personality disorder diagnoses (Schubert & McNeil, 2007). Premorbid neuropsychological deficits, therefore, appear to be associated with later risk for developing schizophrenia-related illnesses.

The Jerusalem Infant Development Study recruited pregnant women with and without schizophrenia from 1973 to 1977. Offspring were subsequently given psychiatric and neurobehavioral assessments at mean ages 10.3 and 17.56. Significantly more offspring of mother's with schizophrenia (n=10, 42%) demonstrated neurobehavioral deficits compared to offspring of control mothers (n=9, 22%). In addition, although the sample size was small, the four genetically-at risk subjects who developed schizophrenia-spectrum disorders significantly underperformed the other outcomes groups on a composite neuromotor and neuropsychological score of tests administered prior to onset (x^2=11.43, p<.0005). This study provides some evidence to suggest that early neurobehavioral dysfunction is both a marker of genetic risk for schizophrenia as well as a premorbid predictor of poor psychiatric outcome (Hans et al., 1999).

Both the Swedish High-Risk study and the Jerusalem Infant Development Study, however, had very small sample sizes yielding relatively small numbers of people with schizophrenia. Such small samples raise issues regarding reliability of findings. It is also possible that some control participants may have developed schizophrenia after the assessment time period.

The New York Infant Study, begun in 1952, was the earliest longitudinal high-risk study of maternal schizophrenia, offspring development, and offspring adult psychiatric outcome. Fish et al. conducted neurological, psychiatric, and psychological assessments of high-risk (n=12) and control (n=12) offspring starting at birth. Offspring were assessed 10 times between birth and age 2, with follow-up psychiatric interviews and psychological testing at ages 10, 15, 22, and 27-35. They computed a gross index of infant neurointegrative maldevelopment, or "pandysmaturation," based on offspring scores of motor/visual development, functional deficits, and retardation of skeletal growth. Results indicated that, at last publication, seven high-risk participants had developed a schizophrenia-spectrum disorder in adulthood and all had pandysmaturation in infancy (OR=106.33, 95% CI:3.72-3023.9) (Fish et al., 1992).

The New York High-Risk Project is a prospective, longitudinal study of offspring born in the 1970s to parents both with and without schizophrenia. The children were given a series of attention and information processing, neuromotor, psychophysiological, psychiatric and clinical, social, cognitive, and personality evaluations approximately every three years from mean age 9.29 to mean age 27.30. Participants with schizophrenia-spectrum disorders in adulthood (n=17) had significantly lower IQ scores, more behavioral problems, and more impairments in attention, memory and gross motor

skills in childhood (Ott et al., 1998; Amminger et al., 1999). Notably, they also found that a combination of childhood gross motor scores, attentional, and memory measures was more accurate (sensitivity=83%) than individual scores in identifying the offspring who had developed schizophrenia-spectrum disorders by approximately age 30 (false positive rate =10%, positive predictive value = 46%) (Erlenmeyer-Kimling et al., 2000). Although ultimately, the number of individuals with schizophrenia is small, results from the New York Infant Study and the New York High-Risk Project indicate that combining neurological and non-neurological predictor variables into an index score may be a promising route towards more sensitive prediction of adulthood schizophrenia.

The Perinatal Project is a longitudinal high-risk study of schizophrenia. Participants are part of a major perinatal cohort of 9,182 deliveries in Copenhagen, Denmark between September 1, 1959, and December 31, 1961. A subset of this cohort was recruited to participate in the Obstetric (OB) Project, which was originally designed to examine obstetric complications and later development of schizophrenia. As part of the OB Project, the offspring of high-risk parents (i.e., mothers with schizophrenia), parents with non-psychotic mental illness diagnoses, and healthy control parents were given childhood assessments of MPAs, neurological functioning, sociability, laterality, and ocular alignment. Offspring have been followed through 2007. Offspring who went on to develop schizophrenia-spectrum disorders in adulthood (n=32) were determined to have significantly higher rates of MPAs (Schiffman et al., 2002), more sociability deficits (Schiffman et al., 2004), more motor coordination problems (Schiffman et al., 2009), more left-footedness and left eye-dominance (Schiffman et al., 2005), and more strabismus (Schiffman et al., 2006) during childhood assessment than offspring with a

non-psychotic diagnosis (n=79) or no diagnosis in adulthood (n=133). Although the OB project has yielded valuable data on childhood precursors to schizophrenia, these predictor variables were studied individually and have not been examined in concert with one another.

The Need for Additional Research

Although great strides have been made in the study of schizophrenia-spectrum disorder prediction, much work remains. Though several studies conduct their own confirmation of adulthood diagnoses (e.g., Cannon et al., 2002; Ott et al., 1998; Hans et al., 1999), others rely solely on mental health databases or psychiatric admission records (e.g., Isohanni et al., 2001; Cannon et al., 1997; Davidson et al., 1999). Although diagnostic assessment through database likely identifies many individuals with schizophrenia, it excludes individuals who have emigrated or who have not sought professional help, potentially subsets that systematically differ from individuals with schizophrenia who have stayed in the country or who have been hospitalized. Moreover, several studies have reported findings before the cohorts had passed the age of primary risk for developing psychosis (e.g., Cannon et al., 2002; Hans et al., 1999), potentially including individuals who later develop psychosis in the comparison condition. Other studies only compare individuals with adulthood schizophrenia diagnoses to individuals with no diagnosable mental illness in adulthood, which does not clarify whether the results are specific to schizophrenia-spectrum disorders or represent an underlying vulnerability towards all psychopathology (e.g., Davidson et al. 1999).

Additionally, given the time frame necessary to conduct prospective studies, the number of studies completed to date is small. Within completed studies, there are

relatively few participants who develop schizophrenia-spectrum disorders in adulthood. In the Jerusalem Infant Development Study, for example, four participants developed psychotic disorders at follow-up, one with schizophrenia, one with schizotypal personality disorder, and two participants with paranoid personality disorder. Small conversion rates may in part be related to the reduced follow-up time in some studies. Replicating these results would strengthen the confidence in the link between premorbid neurological dysfunction and adult schizophrenia.

Combining neurological predictors. Although some longitudinal studies have combined premorbid variables, with only a few exceptions, specific studies of neurological functioning have been univariate by design. Studies that have examined multiple premorbid predictor variables have combined a single neurological variable with one or more non-neurological variables. Studying one neurological variable at a time with respect to future schizophrenia prohibits the ability to evaluate relative contribution and potential overlap in variance accounted for by different predictors. Combining multiple neurological indices (e.g., laterality, neuromotor impairment, neuropsychological functioning, formal neurological evaluations, MPAs) has the potential of elucidating the origins and mechanisms of specific types of neurological dysfunction in schizophrenia as well as increasing predictive power. Although each of these neurological indices has demonstrated some individual predictive power, using a variety of neurological measures allows for the comparison of such markers, with the potential of demonstrating which variables have the most robust predictive power. Should premorbid markers contribute independently to the prediction of schizophrenia,

combining these markers of neurological dysfunction identified prospectively may lead to more precise early identification of individuals destined to develop schizophrenia.

Obstetric Project. As noted above, a subset of the Danish Perinatal Project participants were recruited to participate in the Obstetric (OB) Project. Offspring of parents hospitalized with schizophrenia (n=94), offspring of parents hospitalized with a non-psychotic mental illness (n= 84), and offspring of parents without a psychiatric hospitalization history (n=66) were recruited for participation. Data incorporate baseline psychiatric diagnoses of parents; offspring neurological assessment at one year of age; assessments of offspring neurological functioning, laterality, neuromotor functioning, minor physical anomalies, and neuropsychological functioning at ages 10-13; and psychiatric diagnoses of offspring through age 47. When offspring psychiatric diagnoses were most recently assessed, 32 participants were identified as having a schizophrenia-spectrum disorder, 79 were diagnosed with a non-psychotic disorder, and 133 were determined to have no diagnosable mental illness (Schiffman et al., 2009). Compared to previous studies, this dataset has the advantage of prospective data, raters blind to risk status and psychiatric outcome, both a healthy control group and a non-psychotic psychiatric control group, and a relatively high number of participants with a schizophrenia-spectrum disorder outcome diagnosis.

Current Study

This study involved a reanalysis and extension of this large, longitudinal dataset aggregated by Dr. Sarnoff Mednick and colleagues. The primary goal was to analyze a number of proxies for neurological maldevelopment to assess their combined power in predicting adulthood schizophrenia-spectrum disorders in a high-risk population.

Although neurological proxies have been studied univariately, this is the first longitudinal high-risk of schizophrenia-spectrum disorders with multiple neurological predictor variables. Additionally, this study compared the predictive power of individual neurological predictors.

IRB Considerations. This study met criteria for a University of Hawai‘i Institutional Review Board review exemption based on category (4), “Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.” All study participants completed consent forms prior to data collection and all collected data have been deidentified.

CHAPTER II. METHOD

Dataset Methodology

Given the benefits of utilizing high-risk, longitudinal data in studying schizophrenia predictor variables, data from the Obstetric Project was obtained for the current analyses. Recruitment, psychiatric evaluations, and neurological assessments were carried out by researchers and clinicians associated with University of Copenhagen as well as the Rigshospitalet, Psykologisk Institute, and the Kommunehospitalet in Copenhagen, Denmark.

Determination of risk status: Parental diagnosis. In 1969, the lifetime record of psychiatric admissions for the parents of the birth cohort was checked through face-to-face interviews and a scan of the Danish psychiatric record registry. In 1993, the parental diagnoses of offspring still participating in the study were rechecked and updated with

any changes in parental diagnostic information. Offspring of parents with a face-to-face interview or psychiatric registry diagnosis of schizophrenia were considered to be at higher risk of developing schizophrenia-spectrum disorders themselves (n=94, "high-risk"). A second group was chosen, comprised of 84 gender-matched control children whose parents had a non-psychotic disorder diagnosis ("other risk"). A third group consisted of 66 offspring whose parents had no record of psychiatric hospitalization ("low-risk") (Mednick et al., 1971).Originally, parental risk status groups were established with an effort to match all groups on demographic variables. Over time, as some parents changed in diagnostic status, risk group status changed for some offspring.

One-year neurological examination. When the cohort was one-year-old, they were administered a neurological assessment by a neurologist associated with the research project. This neurological examination included the assessment of timing of developmental milestones including smiling, lifting head, holding head, sitting, crawling, reaching for objects, standing with support, standing without support, walking with support, and walking without support. Data were recorded as mean age at which the milestones were each achieved, according to parent report.

Follow-up neurological and neuromotor examination. In 1972, when the cohort was between 10- and 13-years-old, they participated in a one-day examination at a laboratory at the Kommunehospitalet in Copenhagen (n=265). All children were given a comprehensive 90-minute neurological assessment by an experienced pediatric neurologist blind to parental diagnosis. Items for the examination were chosen to reflect three neurological domains, deficits in which have been found at increased rates in populations of individuals with schizophrenia and those at genetic risk for schizophrenia:

sensory integration, motor coordination, and sequencing of complex motor acts (Heinrichs & Buchanan, 1988; Dazzan & Murray, 2002). Dysfunction in these areas may reflect both specific and general neurological dysfunction (e.g., Tosato & Dazzan, 2005; Heinrichs & Buchanan, 1988; Dazzan & Murray, 2002; Schubert & McNeil, 2004). The assessment included a test of left diadochokinesia, right diadochokinesia, left finger opposition test, right finger opposition test, left speeded finger opposition test, right speeded finger opposition test, right index finger and right foot tap, right and left index finger and right foot tap, and right hand-left hand opens-closes.

Naturalistic neuromotor assessment. Following the neurological examination, participants took part in a naturalistic neuromotor assessment. Children were randomly grouped into pairs, except in the case of 41 children for whom no partners were available. The same-age pairs did not know each other beforehand. The participants were provided with a typical Danish lunchtime meal of an open-face sandwich which requires motor skills to deconstruct and eat. They were sat in a specially designated room on either side of a corner of a table facing a tri-pod mounted Akai VT-100R, black and white, reel-to-reel video recorder. The position of the camera and lighting remained consistent for all subject dyads. For the first three minutes of the meal, the initial camera angle focused on both children. The camera then focused on a close-up of the subject sitting on the left for one minute and then a close-up on the subject sitting on the right for one minute. The camera focused on both children again for the final minute.

The reel-to-reel was converted to videotapes and raters blind to psychiatric risk status coded the tapes for the following neurological variables for each child: 1) number of times elbows were raised, 2) number of nystagmus-like eye movements (rapidly

shifting eyes around three places), 3) number of involuntary facial movements (e.g., tics, orofacial dyskinesia), and 4) number of other abnormal movements. Scores were combined into a summary neuromotor score. Two coders evaluated one third of the subjects.

Laterality assessment. On the same day as the neurological and neuromotor assessments, participants underwent a thorough laterality assessment. The examination included assessment of eye, and foot dominance, and provided a scaled score indicating the degree of left or right dominance. Footedness was assessed by asking subjects to kick a ball, balance, and hop on one foot. The foot used for each task was noted and scored (1=left, 0=right), and scores were summed to give a footedness score for each subject.. Crider's Ring, Crider's Card, and Crider's Box (Crider, 1944) were employed to measure eye dominance. Subjects' choice of eye was observed for each task. Responses for tasks were scored (1=left, 0=right) and scores were summed to give a total eye dominance score for each subject.

Neuropsychological examination. On the 1972 assessment day, participants also underwent a neuropsychological assessment consisting of the Wechsler Intelligence Scale of Children (WISC; Wechsler, 1949). The WISC provides a measure of verbal, performance, and general intelligence quotient, with a mean of 100 and a standard deviation of 15. Subscales included in this assessment were Similarities, Vocabulary, Block Design, and Maze. Each subscale provides a scale score based on normative data, with a 10 indicating the 50th percentile. Subscale scores can range from 1 to 19.

Minor physical anomalies (MPAs). Participants were also examined for minor physical anomalies by an experienced Danish pediatric neurologist. The MPA

examination was conducted using the Waldrop Scale (Waldrop & Halverson, 1971) and measures included: epicanthus, hyperteliorism, adherent ear lobes, low-seated ears, malformed ears, asymmetrical ears, soft pliable ears, single transverse palmar crease, high-steepled palate, third toe longer than second, partial syndactylia of two middle toes, fundus abnormalities, fine electric hair or two or more hair whorls, and furrowed tongue or tongue with smooth-rough spots.. The Waldrop scale has been found to be a valid measure of developmental instability and scores on the Waldrop scale are associated with neuroanatomical abnormalities (Euler et al., 2009).

Ocular alignment. Lastly in the series of examinations, participants were administered several tests of ocular alignment functioning, including monocular covering/uncovering, the Worth 4-Dot Test, and the Titmus Fly Test. In monocular covering/uncovering, participants used both eyes, then with each eye individually covered, to focus on a visual target at differing distances. Presence of ocular alignment dysfunction was determined by movement in the uncovered eye when that eye took up fixation originally held by the covered eye. The Worth 4-Dot Test presented participants with a panel with a red light at the top, a white light at the bottom, and green lights on the left- and right-hand sides. Participants wore glasses with one green and one red lens and were asked to report on the number of color of lights they saw. Ocular alignment dysfunction was present when the participant reported seeing only two or three lights, indicating an inability to fuse two retinal images together into a single image. The Titmus Fly test presented participants with a series of pairs of identical or slightly different images. Participants viewed the images through a Polaroid visor. Ocular alignment dysfunction was present when participants perceived the images to be two-dimensional

rather than three-dimensional. A general ocular alignment score was calculated by summing the scores from the three tests.

Diagnostic methods: The offspring. Two-hundred and forty-four cohort members (92% successful follow-up from 1972) were available for follow-up examinations in 1992 when they were 31-33 years of age. A psychiatrist ascertained DSM-III-R diagnoses for each participant based on two structured diagnostic interviews, the Structured Clinical Interview for DSM-III-R (SCID; Spitzer, Williams, & Gibbon, 1990) and the psychosis section of the Present State Examination 16 (PSE; Wing, Cooper, & Sartorious, 1974). In addition, Danish hospital registries were scanned through 2007. Based on this diagnostic process, eighteen participants were identified as having schizophrenia and fourteen participants with another schizophrenia-spectrum disorder (see Table 3). Of the thirty-two subjects with a schizophrenia-spectrum diagnosis, twenty-two had a parent with schizophrenia, eight had a parent with a non-psychotic diagnosis, and two had a parent without a diagnosed mental illness. Additionally, 79 participants were determined to have a non-psychotic diagnosis and 133 to have no diagnosable mental illness (Schiffman, et al., 2009).

CHAPTER III: RESULTS

The Mednick et al., dataset contained the raw data for all of the variables of interest. A data computation procedure was employed to calculate variables of interest for the current study and to address missing data. Next, multinomial and binary regression analyses were conducted to examine the variables' ability to predict outcome diagnoses. Subsequently, discriminant function analyses were employed to determine what variable weightings best discriminated between outcome groups. Lastly, receiver operating

characteristic (ROC) analyses were used to determine variable accuracy in predicting schizophrenia-spectrum outcomes.

Abnormal lateralization was calculated by summing the standardized scores of foot lateralization and eye lateralization. Higher scores indicated more left-sided lateralization. Although the OB dataset included information on handedness as well, this element of lateralization was excluded a priori given its relatively low predictive power, potentially related to the culture-boundedness of hand dominance (Schiffman et al., 2005).

Minor physical anomalies (MPAs) was a sum score of 16 measures of abnormal morphology (presence or absence of each abnormality), including epicanthus, hyperteliorism, adherent ear lobes, low-seated ears, malformed ears, asymmetrical ears, soft pliable ears, single transverse palmar crease, high-steepled palate, third toe longer than second, partial syndactylia of two middle toes, fundus abnormalities, fine electric hair or two or more hair whorls, and furrowed tongue or tongue with smooth-rough spots. Each MPA was scored as either present or absent. Higher scores indicated more MPAs.

Ocular alignment dysfunction was the sum of the standardized scores on three ocular tests: Monocular covering/uncovering, the Worth 4-Light Test, the Titmus Fly Test. Higher scores indicated more ocular alignment dysfunction.

Intelligence quotient (IQ) scores were the total score from the Wechsler Intelligence Scale of Children. Scores were reversed (multiplied by negative 1) in an attempt to make this variable comparable to the other variables in this study in which higher scores represented more dysfunction.

Coordination scores were the sum of the standardized scores of coordination tests including left diadochokinesia, right diadochokinesia, left finger opposition test, right finger opposition test, left speeded finger opposition test, right speeded finger opposition test, right index finger and right foot tap, right and left index finger and right foot tap, and right hand-left hand opens-closes. Higher scores indicated more coordination dysfunction.

Neuromotor dysfunction, obtained from the video recording of the participants eating lunch, was based on the sum of standardized scores of the following neuromotor variables: number of times elbows were raised, number of nystagmus-like eye movements (rapidly shifting eyes around three places), number of involuntary facial movements (e.g., tics, orofacial dyskinesia), and number of other abnormal movements. Higher scores represented more neuromotor dysfunction.

Developmental milestone scores were calculated from taking the mean of the standardized scores of ten milestone variables, measured in number of months taken to acquire each skill. The milestone variables included age at which participant lifted head, held head up, reached for objects, smiled, sat, crawled, stood with support, stood without support, walked with support, and walked without support. Higher scores indicated later development and therefore more dysfunction.

Missing Data. There was no missing data for MPAs or IQ. See Table 1 for specific information regarding missing data for laterality, ocular alignment, coordination, neuromotor functioning, and delayed developmental milestones.

In the case of neuromotor functioning and developmental milestones, there were a significant number of missing values. Some neuromotor recordings were lost when the

reel-to-reel tapes the sessions were recorded on were converted to videotapes. Additionally, the study paradigm consisted of partnered lunch sessions. Occasionally, one partner would miss the appointment, therefore invalidating the data from the other partner (Schiffman et al., 2004). With respect to developmental milestones, data collection relied on parents making note of when offspring attained specific abilities. Information missing in this domain could be related to memory failure or the fact that some of these milestones may have gone unnoticed by the parents (Sørensen et al., 2001).

Table 1. *Summary of Neurological Variables' Missing Data*

Neurological Variable	Subcomponent	Missing from SZ (Total N=32)	Missing from OPD (Total N=79)	Missing from NMI (Total N=133)
Laterality	Eye Lateralization	0	0	0
	Foot Lateralization	3 (9.38%)	1 (1.27%)	3 (2.26%)
Ocular Alignment	Monocular	0	0	3 (2.26%)
	Worth 4-Light Test	1 (3.13%)	3 (3.80%)	0
	Titmus Fly Test	0	0	0
Coordination	Right Diadochokinesia	1 (3.13%)	3 (3.80%)	1 (.75%)
	Left Diadochokinesia	1 (3.13%)	3 (3.80%)	1 (.75%)
	Right Hand-Left Hand Opens-Closes	1 (3.13%)	0	0
Neuromotor	Total Neuromotor Score	10 (31.25%)	30 (37.97%)	52 (39.10%)
Milestones	Lifted Head	14 (43.75%)	45 (56.96%)	37 (27.82%)
	Smiled	10 (31.25%)	39 (49.37%)	50 (37.59%)
	Held Head Up	16 (50%)	45 (56.96%)	59 (44.36%)
	Reached for Objects	19 (59.38%)	46 (58.23%)	61 (45.86%)
	Sat	11 (34.38%)	27 (34.18%)	42 (31.58%)
	Crawled	20 (62.5%)	38 (48.10%)	55 (41.35%)
	Stood with Support	4 (12.5%)	20 (25.32%)	18 (13.53%)
	Stood without Support	22 (68.75%)	38 (48.10%)	78 (58.65%)
	Walked with Support	7 (21.88%)	17 (53.13%)	24 (18.05%)
	Walked without Support	18 (56.25%)	17 (53.13%)	82 (61.65%)

Note: SZ=Schizophrenia-Spectrum outcome, OPD=Other Psychopathology Diagnosis outcome, NMI=No Mental Illness outcome

Table 2. *Summary of Comparisons Between Participants with and without Missing Milestone and Neuromotor Data with Respect to Diagnostic Outcome, Sex, and Risk Status*

Neurological Variable	Chi Square For Diagnostic Outcome	Chi Square For Sex	Chi Square For Psychiatric Risk Status
Milestones	x^2_2=3.47, p=.11	x^2_2=.99, p=.32	x^2_2=3.24, p=.20
Neuromotor	x^2_2=3.37, p=.19	x^2_2=.99, p=.32	x^2_2=1.25, p=.54

Due to the large number of missing variables, particularly within the neuromotor functioning and developmental milestone areas, an analysis of missing data was undertaken for missing values from all domains. First, Little's chi square statistic tested whether the values were missing completely at random (MCAR), which informed what method of imputation was appropriate. In Little's chi-square test, the null hypothesis is that the data is MCAR. In this case, the chi-square statistic was not significant (x^2_{943} = 987.80, p=.16), suggesting MCAR, and indicating that the Expectation-Maximization (EM) algorithm is appropriate. The EM algorithm is a relatively new iterative process that finds maximum likelihood estimates for missing data that are unbiased estimates (Schafer, 1997; SPSS, Inc., 2009). Each iteration employs an expectation step, which computes an expected value for the missing data, given the available means and covariances from each particular participant. Next, in the maximization step, these expectations are substituted for the missing data. For example, if a participant has missing data for neuromotor functioning, but has complete data for the remaining variables, the EM method uses the available data from the covariance matrix to get the regression of neuromotor functioning on all of the other variables. The resulting regression coefficients are used to generate imputed neuromotor values, based on the observed values. This expectation and maximization process starts over and continues

until the estimates converge and do not change significantly from one iteration to the next (Allison, 2001; Schlomer et al., 2010). The EM algorithm has been employed in prior research using this dataset to obtain adequate sample size (Sorenson et al., 2010) as well as other schizophrenia research (e.g., Lenzenweger et al., 2003; Guo et al., 2007). The EM analysis was employed to create a new data set with imputed values for data missing for all predictor variables with any missing values (neuromotor dysfunction, milestones, ocular alignment, coordination, and laterality) based on the EM algorithm estimates. Thus for the remaining analyses, there was no missing data, however, analyses were run with and without the developmental milestone and neuromotor data to examine whether this data imputation procedure influenced their degree of contribution to predicting psychiatric outcome.

Descriptive Results. Participants with no outcome data were removed, leaving a final sample size of 244 (92% of the original sample). As noted above, in adulthood, eighteen participants were identified as having schizophrenia and fourteen participants with another schizophrenia-spectrum disorder. Of the thirty-two subjects with a schizophrenia-spectrum diagnosis, twenty-two had a parent with schizophrenia, eleven had a parent with a non-psychotic diagnosis, and four had a parent without a diagnosed mental illness. Additionally, 79 participants were determined to have a non-psychotic diagnosis and 133 to have no diagnosable mental illness (Schiffman, et al., 2009; see Table 3).

Table 3. *Offspring Diagnoses as of 2007*

Diagnosis		N
Schizophrenia spectrum		32
	Schizophrenia	18
	Any psychosis or delusional disorder	8
	Schizotypal personality disorder	4
	Paranoid personality disorder	2
Non-psychotic diagnoses		79
	Mood or anxiety disorder	27
	Alcohol/Drug abuse	34
	Other personality disorder	18
No diagnosis		133
Total		244

Means and standard deviations for the seven neurological proxy variables with respect to outcome group are presented in Table 4. Cronbach's alpha for each was determined as a gauge of scale reliability, with the results as follows: laterality, Cronbach's α=.22; MPA, Cronbach's α=.28; ocular alignment, Cronbach's α=*.48; neuromotor dysfunction,* Cronbach's α=.52; coordination, Cronbach's α=.89; and milestones, Cronbach's α=.80. Raw data for IQ was unavailable for an item analysis.

Sex. In the final sample, there were 120 male participants and 124 female participants. To examine whether there was a significant relationship between sex and outcome, a chi square analysis was employed. There was not a significant association between sex and adult psychiatric outcome (x^2_2 = .36, p=.84). Similarly, there was no significant relationship between sex and parental risk status (x^2_2 = .59, p=.74).

Table 4. *Means and Standard Deviations of Neurological Proxy Variables*

Variable	SZ Outcome Mean (SD)	OPD Outcome Mean (SD)	NMI Outcome Mean (SD)
Laterality	-.05 (1.57)	-.06 (1.54)	-.01 (1.51)
MPA	3.42 (1.54)	2.77 (1.48)	2.57 (1.59)
Ocular Alignment	.01 (1.92)	-.20 (1.61)	.08 (2.31)
IQ	-102.78 (18.20)	-104.15 (15.05)	-109.39 (13.85)
Neuromotor Dysfunction	.08 (1.84)	-.72 (1.05)	-.45 (1.49)
Coordination	1.55 (7.91)	-.53 (6.64)	-.33 (6.10)
Milestones	.12 (.44)	-.09 (.53)	.02 (.52)

T-tests, adjusted using a Bonferroni correction, demonstrated several significant differences on dependent variables between male and female participants. Male participants had significantly lower IQ scores (M=-111.33, SD=14.31) than female participants (M=-102.48, SD=14.56; t_{242}=-4.79, p<.001). Since IQ scores were reverse scored, this indicates that male participants were higher functioning on this domain. Additionally, male participants scored significantly higher (M=-.22, SD=1.55) on neuromotor functioning (t_{242}=2.71, p<.01) than female participants (M=-.71, SD=1.26). Given this potential influence of sex differences, sex was examined within the subsequent analyses as a predictor variable.

Risk and Outcome. A chi square analysis was employed to examine the relationship between parental risk and adult psychiatric outcome, two nominal variables. There was a significant association between parental risk and adult psychiatric outcome (x^2_4= 21.04, p<.001). See Table 5. The odds of a schizophrenia-spectrum diagnosis outcome was 4.29 times higher if the parent had schizophrenia ("high-risk") than if the parent did not have a schizophrenia-spectrum diagnosis (other psychopathology or nor

mental illness). The odds of a schizophrenia-spectrum diagnosis outcome were 3.5 times higher if the parent had another psychopathology diagnosis ("other risk") than if the parent had no diagnosis ("low-risk"). The odds of a schizophrenia-spectrum diagnosis outcome were 2.9 times higher if the parent had a schizophrenia-spectrum diagnosis ("high-risk") than if the parent had another diagnosis ("other risk").

Table 5. *Chi Square Analysis of Parental Risk and Offspring Psychiatric Outcome*

	High-Risk	Other Risk	Low-Risk	Total N
Schizophrenia-Spectrum Outcome	22 (23.4%)	8 (9.5%)	2 (3%)	32
Other Outcome	28 (29.8%)	34 (40.5%)	17 (25.8%)	79
No Mental Illness Outcome	44 (46.8%)	42 (50%)	47 (71.2%)	133
Total	94	84	66	244

Few longitudinal high-risk studies have had the benefit of being able to compare high-risk offspring who developed schizophrenia directly with low-risk offspring who developed schizophrenia and explore the differences in schizophrenia etiology between those with and without known genetic loading. Thus, in addition, to assess whether there were significant differences on the neurological variables between those who developed schizophrenia-spectrum disorders from different risk groups, an analysis of variance was employed to explore neurological differences between high-risk offspring who developed schizophrenia-spectrum disorders (N=22) and relatively lower risk offspring who developed schizophrenia-spectrum disorders (N=10). No significant differences were found between the two groups for any of the neurological variables (laterality: F=.05, p=.83; MPAs: F=.63, p=.44; ocular alignment: F=.62, p=.44; IQ: F=.15, p=.70; coordination: F=.01, p=.92; neuromotor functioning: F=2.77, p=.12; milestones: F=.28,

p=.60). Although limited in power, the results suggest that there are not significant differences in the dependent variables within the schizophrenia-spectrum group as a function of their genetic risk.

In addition, this dataset had the capacity to compare "pure" schizophrenia diagnoses with other spectrum diagnoses (psychosis or delusional disorders, schizotypal personality disorder, paranoid personality disorder). An analysis of variance was employed to explore neurological differences between those who developed schizophrenia in adulthood (N=18) and those who developed another spectrum diagnosis (N=14). There were no significant differences with respect to neurological variables between schizophrenia and schizophrenia-spectrum outcomes (laterality: F=.2.56, p=.12; MPAs: F=.02, p=.90; ocular alignment: F=3.21, p=.08; IQ: F=1.87, p=.18; coordination: F=.68, p=.42; neuromotor functioning: F=.31, p=.58; milestones: F=2.03, p=.16). Moreover, chi square analyses were employed to compare the schizophrenia and schizophrenia-spectrum groups in terms of the categorical variables of sex and parental risk. No systematic differences were found between schizophrenia and schizophrenia-spectrum groups with respect to sex (x^2_1= 1.25, p=.26) or parental risk status (x^2_2= 4.48, p=12).

Correlations. Pearson correlations were conducted to examine the correlations between the individual neurological variables (see Table 6). There was a significant positive correlation between laterality and IQ (r=.14, p<.05), coordination and ocular alignment (r=.15, p<.05), and coordination and milestones (r=.13, p<.05). There was also a significant negative correlation between IQ and ocular alignment (r=-.15, p<.05), coordination and neuromotor dysfunction (r=-.13, p<.05), and milestones and neuromotor

dysfunction (r=-.14, p<.05). Given the potential assumption violations for the planned analyses of regression and discriminant function analysis, multicollinearity was examined (See Multinomial Logistic Regression).

Table 6. *Neurological Variable Pearson Correlations*

	MPAs	Ocular	IQ	Coordination	Neuromotor	Milestones
Laterality	.10	.10	.14*	.09	.07	-.03
MPAs	1	-.03	-.02	.03	.06	.02
Ocular		1	-.15*	.15*	-.07	-.02
IQ			1	.09	-.03	.12
Coordination				1	-.13*	.13*
Neuromotor					1	-.14*

*p<.05

Multinomial Logistic Regression. Multinomial (polychotomous) logistic regression was performed to assess the ability of the previously collected premorbid variables (sex, parental risk status, laterality, MPAs, ocular alignment, intelligence quotient scores, neuromotor evaluation results, coordination examination score, and developmental milestones) to predict adult diagnostic outcome (schizophrenia-spectrum, other psychopathology, or no mental illness). Parental risk was categorized as parent with a schizophrenia-spectrum diagnosis, parent with another psychopathology diagnosis, or parent with no mental illness. Multinomial logistic regression is appropriate when there are multiple predictor variables and multiple, categorical outcome variables. The data was first examined for independence of errors and multicollinearity, particularly given the presence of significant correlations between predictor variables, as these concerns violate the assumptions of multinomial logistic regression. Independence of errors means

that the cases of data are not related; if they are related, for example, if the same person is measured at different points in time, overdispersion is created. The assumption of independence of errors was met in that the dispersion parameter (the ratio of the chi-square goodness-of-fit statistic, 479.99; to its degrees of freedom, 470=1.02) was not greater than two.

Multicollinearity exists when there is a perfect linear relationship between predictor variables, which makes it difficult to examine the individual power of each predictor. Multicollinearity was examined by using the data to run a linear regression analysis, which produces collinearity diagnostics, since collinearity diagnostics are not available in logistic regression. Multicollinearity was ruled out in this case as no predictor variables had high proportions on the same small eigenvalues, indicating that there was not a perfect linear relationship between predictor variables (Field, 2009). In addition, parental risk (parental schizophrenia-spectrum diagnosis, parental diagnosis other than schizophrenia, parent with no diagnosis) was dummy coded as it was a nominal variable with more than two categories.

For the multinomial regression analysis, an outcome of a schizophrenia-spectrum diagnosis was used as the reference category as this was the primary outcome of interest. Although the sample size was not large enough to examine the interaction of parental risk with all neurological variables, the interactions of parental risk x coordination, parental risk x ocular alignment, and parental risk x IQ were chosen based on the literature suggesting they have relatively higher genetic components (e.g., Dazzan & Murray, 2002; Rosso et al., 2002; Missitzi et al., 2004; Toyota et al., 2004; Friedman et al., 2008). Backward elimination was employed in which all predictor variables were entered into

the model. At each step, the least significant stepwise term was eliminated from the model until all of the remaining variables had a statistically significant contribution to the model. In this case, sex, laterality, ocular alignment, parental risk x IQ, and parental risk x ocular alignment weakened the model and were therefore removed.

Log-likelihood is a measure of how much unexplained variability there is in the data, with the change in log-likelihood indicating how much new variance has been explained by the model. The decrease from the baseline model (-2 Log Likelihood, Intercept Only=469.61) to the final model (-2 Log Likelihood, Final Model=412.81) was significant which indicated that the final model explained a significant amount of the original variability and was a better fit than the original model (x^2_{16}=56.80, p<.001). The Pearson and deviance statistics test whether the predicted values from the model differ significantly from the observed values. They were both not significant, so the model was a good fit of the data.

The likelihood ratio tests can be used to ascertain the significance of predictors to the model. This test indicated that parental risk (x^2_4=22.56, p<.001), IQ (x^2_2= 9.19, p<.01), MPAs (x^2_2= 8.20, p<.05), and neuromotor dysfunction (x^2_2= 6.36, p<.05) had a significant main effect on schizophrenia-spectrum outcome diagnosis. In addition, parental risk status interacted with coordination to predict outcome diagnosis (x^2_4=10.05, p<.05).

In multinomial regression, parameter estimates are displayed for differences between the reference group (schizophrenia-spectrum outcome) and every other possible outcome (other psychopathology, no mental illness) individually. In this case

schizophrenia-spectrum outcome was first compared to other psychopathology outcome and then to no mental illness outcome.

Schizophrenia-spectrum and Other Psychopathology. Neuromotor dysfunction significantly predicted whether outcome diagnosis was schizophrenia-spectrum or another psychopathology (b=.39, Wald x^2_1= 5.51, p<.05). The odds ratio indicated that as the neuromotor dysfunction increased by one unit, the change in odds of outcome of other diagnosis rather than schizophrenia is 1.39. Thus, the odds of a schizophrenia-spectrum outcome rather than another diagnosis increased 1.39times for every one unit increase on the neuromotor dysfunction scale, all other things being equal.

MPAs also significantly predicted whether the outcome diagnosis was schizophrenia-spectrum or another psychopathology (b=.33, Wald x^2_1=4.62, p<.05). The odds ratio indicated that as MPAs increased by one unit, the change in odds of outcome of other diagnosis rather than schizophrenia is 1.39. In other words, participants were 1.39 times more likely to develop a schizophrenia-spectrum disorder than another psychopathology for every one unit increase on the MPA scale.

Schizophrenia-spectrum and No Mental Illness. MPAs significantly predicted whether outcome diagnosis was a schizophrenia-spectrum diagnosis or no mental illness (b=.41, Wald x^2_1=7.85, p<.01). Participants were 1.51 times more likelihood to develop a schizophrenia-spectrum disorder rather than no mental illness for every one unit increase in MPAs.

IQ also significantly predicted whether outcome diagnosis was a schizophrenia-spectrum diagnosis rather than no mental illness (b=.04, Wald x^2_1= 5.31, p<.05). The odds ratio indicated that as IQ increased by one unit, the change in odds of outcome of a

schizophrenia-spectrum disorder rather than mental illness was 1.03. Lastly, having a parent with schizophrenia significantly predicted whether outcome diagnosis was a schizophrenia-spectrum diagnosis rather than no mental illness (b=2.84, Wald x^2_1= 5.52, p<.05). The odds ratio indicated that as risk changed from having a parent with schizophrenia to having a parent with no mental illness, the change in odds of the offspring developing a schizophrenia-spectrum disorder was 10.92. Parameter estimates compare pairs of outcome categories and specify what the effect of the predictor variables is. See Table 7. Table 8 presents the correlation matrix for the analysis. The multinomial regression was also run without interaction terms and there were no significant differences between the two multinomial regression analyses. In addition, given the possible instability that could arise from the number of missing milestone data points in the original dataset, the analyses were rerun without milestones data. There were no significant differences between those two multinomial regression analyses.

Overall, the model successfully categorized 58.6% of participants' outcomes. See Table 9.

Table 7. *Summary of Multinomial Logistic Regression Analysis for all Participants*

	Wald x^2	df	*B (SE)*	*Exp(B)* (95% CI)
SZ vs. OPD Outcome				
Intercept	3.38	1	3.93 (2.14)	
Parent with SZ vs NMI	3.09	1	2.16 (1.23)	8.68 (.78-96.87)
Parent with SZ vs OPD	.21	1	.59 (1.30)	1.80 (.14-22.79)
IQ	.37	1	.01 (.06)	1.01 (.98-1.04)
Coordination	.51	1	-.17 (.23)	.85 (.54-1.33)
MPAs	4.62*	1	.33 (.15)	1.39 (1.03-1.88)
Neuromotor	5.51*	1	.39 (.17)	1.47 (1.07-2.04)
Parent with SZ vs NMI x Coordination	.40	1	.15 (.28)	1.16 (.73-1.85)
Parent with SZ vs OPD x Coordination	1.94	1	.33 (.28)	1.39 (.87-2.21)
SZ vs. NMI Outcome				
Intercept	.25	1	1.04 (2.06)	
Parent with SZ vs NMI	5.52*	1	2.84 (1.21)	10.92 (2.36-50.56)
Parent with SZ vs OPD	1.28	1	1.45 (1.28)	2.82 (1.10-7.25)
IQ	5.31*	1	.04 (.02)	1.03 (1.01-1.07)
Coordination	.59	1	-.18 (.23)	.84 (.54-1.31)
MPAs	7.85**	1	.41 (.15)	1.51 (1.13-2.02)
Neuromotor	1.69	1	.19 (.15)	1.21 (.91-1.60)
Parent with SZ vs NMI x Coordination	.37	1	.14 (.26)	1.15 (.73-1.83)
Parent with OPD x Coordination	1.96	1	.33 (.26)	1.39 (.88-2.20)

Note: R^2=.21 (Cox & Snell), .24 (Nagelkerke). Model x^2_{16}=56.80, p<.001; *p<.05, **p<.01

Note: SZ=Schizophrenia-Spectrum, OPD=Other Psychopathology Diagnosis, NMI=No Mental Illness

Table 8. *Multinomial Regression Analysis Correlation Matrix for all Participants*

		MPAs	IQ	Neuromotor	Parent with SZ vs OPD	Parent with SZ vs NMI
SZ vs OPD		-.29	.81	.08	-.27	-.48
	MPAs		1	.04	.03	.03
	IQ			1	.02	.08
	Neuromotor				1	.21
	Parent with SZ vs OPD					1
	Parent with SZ vs NMI					-.48
SZ vs NMI						
	MPAs	1	.03	.05	.06	.04
	IQ		1	.04	.04	.01
	Neuromotor	.		1	.02	.08
	Parent with SZ vs OPD	.			1	.20
	Parent with SZ vs NMI					1

Table 9. *Multinomial Regression Analysis Classification Summary for all Participants*

	Predicted Group Membership			
Observed	SZ	OPD	NMI	Percent Correct
SZ	12	3	17	37.5%
OPD	6	16	57	20.3%
NMI	6	12	115	86.5%
Overall Percentage	9.8%	12.7%	77.5%	58.6%

Note: The cut value is .500
Note: SZ=Schizophrenia-Spectrum, OPD=Other Psychopathology Diagnosis, NMI=No Mental Illness

A second multinomial regression analysis was employed using parental risk, MPAs, and neuromotor dysfunction, and IQ as predictors to examine whether these variables alone would classify outcomes more accurately. This final model was also a better fit of the data than the original model (χ^2_8=36.81, p<.001). Likelihood ratio tests indicated parental risk (χ^2_2=12.88, p<.01), IQ (χ^2_2=9.31, p<.01), and MPAs (χ^2_2=7.90 p<.05) had significant main effects on schizophrenia-spectrum outcome diagnosis, with neuromotor dysfunction approaching significance (χ^2_2=5.75, p=.06), In terms of distinguishing schizophrenia-spectrum outcomes from other psychopathology, parental risk (b=1.33, Wald χ^2_1= 8.41, p<.01) and neuromotor dysfunction (b=.36, Wald χ^2_1= 5.38,

p<.05) were significant contributors with MPAs approaching significance (b=.28 Wald χ^2_1= 3.82, p=.051). In terms of distinguishing schizophrenia-spectrum outcomes from no mental illness, parental risk (b=1.50, Wald χ^2_1= 11.74, p<.01), MPAs (b=.38, Wald χ^2_1= 7.60, p<.01), and IQ (b=-03, Wald χ^2_1= 5.56, p<.05) were significant contributors. This multinomial regression model successfully classified 56.3% of outcome diagnoses overall and 28.1% of schizophrenia-spectrum outcome diagnoses.

In an attempt to produce an analysis that was more easily comparable to case-control designed studies, another multinomial logistic regression was employed that only included those with parents with schizophrenia-spectrum diagnoses ("high-risk", N=94) to those with parents without schizophrenia-spectrum diagnoses ("low-risk", N=66). In this regression all neurological predictor variables, as well as sex, and dichotomous parental risk were entered in a backward elimination fashion. Offspring psychiatric diagnosis (schizophrenia-spectrum, other psychopathology, and no mental illness) was used as the dependent variable.

Coordination, ocular alignment, laterality, and milestones were eliminated from the model. The decrease from the baseline model (-2 Log Likelihood, Intercept Only=307.93) to the final model (-2 Log Likelihood, Final Model=263.00) was significant which indicated that the final model explained a significant amount of the original variability and was a better fit than the original model (x^2_{10}=44.93, p<.001). The Pearson and deviance statistics were both not significant, so the model was a good fit of the data. The likelihood ratio tests indicated that parental risk (x^2_2=14.80, p<.001), MPAs (x^2_2= 9.90, p<.01), and neuromotor dysfunction (x^2_2= 8.44, p<.05) had a significant main effect on schizophrenia-spectrum outcome diagnosis.

In predicting schizophrenia-spectrum versus other psychopathology, parental risk (b=1.69, Wald x^2_1=4.12, p<.05), neuromotor dysfunction (b=.57, Wald x^2_1=7.13, p<.01), and MPAs (b=.55, Wald x^2_1=8.75, p<.01) significantly distinguished between the two outcomes. With respect to predicting schizophrenia-spectrum versus no mental illness, parental risk (b=2.37, Wald x^2_1=8.98, p<.01) and MPAs (b=.46, Wald x^2_1=7.21, p<.01) significantly contributed to outcome prediction. See Table 10.

Overall, this model using dichotomous risk successfully categorized 61.9% of participants' outcomes. See Table 11.

Table 10. *Summary of Multinomial Logistic Regression Analysis for High-Risk and Low-Risk Participants*

	Wald x^2	Df	*B (SE)*	*Exp(B)* (95% CI)
SZ vs. OPD Outcome				
Intercept	1.70	1	2.77 (2.12)	
Parental Risk	4.12*	1	.169 (.83)	5.42 (1.06-27.72)
IQ	.04	1	.00 (.02)	1.00 (.97-1.04)
MPAs	8.75**	1	.55 (.19)	1.74 (1.21-2.51)
Neuromotor	7.13**	1	.57 (.22)	1.78 (1.17-2.71)
Sex	.87	1	56 (.60)	.57 (.18-1.85)
SZ vs. NMI Outcome				
Intercept	.45	1	1.37 (2.05)	
Parental Risk	8.98**	1	2.37 (.79)	10.72 (2.27-50.62) (.02-.44)
IQ	3.03	1	.03 (.02)	1.03 (1.00-1.07)
MPAs	7.21**	1	.46 (.17)	1.58 (1.13-2.20)
Neuromotor	3.35	1	.31 (.17)	1.37 (.98-1.92)
Sex	.38	1	.34 (.56)	1.41 (.47-4.20)

Note: R^2=.25 (Cox & Snell), .29 (Nagelkerke). Model x^2_{10}=44.93, p<.001;
*p<.05, **p<.01
Note: SZ=Schizophrenia-Spectrum, OPD=Other Psychopathology Diagnosis, NMI=No Mental Illness

Table 11. *Multinomial Regression Analysis Classification Summary for High-Risk and Low-Risk Participants*

	Predicted Group Membership			
Observed	SZ	OPD	NMI	Percent Correct
SZ	10	3	11	41.7%
OPD	2	12	31	26.7%
NMI	5	9	77	84.6%
Overall Percentage	10.6%	15.0%	74.4%	61.9%

Note: The cut value is .500
Note: SZ=Schizophrenia-Spectrum, OPD=Other Psychopathology Diagnosis, NMI=No Mental Illness

To explore the potential error introduced by data imputation, a multinomial regression analyses was performed in which neuromotor and milestone data, the variables with the highest number of missing values, were excluded. The final model continued to be a better fit of the data than the original model (χ^2_6=31.07, p<.001), and ocular alignment, laterality, coordination, and sex were all statistically removed from the model. Likelihood ratio tests indicated parental risk (χ^2_2=14.27, p<.001), MPAs (χ^2_2=7.83, p<.05), and IQ (χ^2_2=9.31, p<.01), had significant main effects on schizophrenia-spectrum outcome diagnosis. In terms of distinguishing schizophrenia-spectrum outcomes from other psychopathology, only parental risk (b=1.41, Wald χ^2_1= 9.68, p<.01) and MPAs (b=0.28, Wald χ^2_1= 3.91, p<.05) were significant contributors. In terms of distinguishing schizophrenia-spectrum outcomes from no mental illness, parental risk (b=1.56, Wald χ^2_1= 12.71, p<.001), MPAs (b=-.37, Wald χ^2_1= 7.55, p<.01), and IQ (b=-.03, Wald χ^2_1= 5.40, p<.05) were significant contributors. This multinomial regression model that did not include neuromotor and milestone variables successfully classified 55.7% of outcome diagnoses overall and 21.9% of schizophrenia-spectrum outcome diagnoses.

Further, an exploratory multinomial regression analysis was employed utilizing only high-risk offspring (N=94). Results did not differ significantly from the initial multinomial regression.

Binary Logistic Regression. A binary logistic regression analysis was performed to examine predictors in terms of distinguishing outcome diagnoses of schizophrenia versus non-schizophrenia (i.e., no mental illness or other psychopathology). This was employed in an effort to make results more comparable to other cohort studies that use this dichotomy (e.g., Davidson et al., 1999; Cannon et al., 2002). Additionally, presuming some homogeneity between the OPD and NMI outcome groups, combining these groups increases the total comparison N and subsequently statistical power. In this analysis, the dependent variable was schizophrenia-spectrum versus no schizophrenia-spectrum diagnostic outcome. The first set of predictor variables were sex and parental risk. Next, laterality, MPAs, ocular alignment, IQ scores, neuromotor evaluation results, coordination examination score, and developmental milestones were entered into the equation. A backward likelihood ratio model was employed because this analysis was primarily exploratory. This method starts with all of the predictors. At each step, predictors that contribute the least to the model, based on maximum partial likelihood estimates, are removed. Ultimately, the analysis finds the best combination of variables to explain the largest proportion of the variance in outcome.

Moving backward, as in the multinomial regression, sex was eliminated as a predictor terms because it weakened the model. At the next step, all neurological variables, plus parental risk, were retained. The result of the final model χ^2 remained significantly different from the constant-only model at 30.96 (df=8, p<.001) and successfully classified 86.9% of participants (see Table 12). The final model was also found to adequately fit the data using the robust Hosmer-Lemeshow statistic (χ^2_8=8.71, p=0.37).

Table 12. *Binary Logistic Regression Analysis Classification Summary for all Participants*

	Predicted Group Membership		
Observed	SZ	Not SZ	Percent Correct
SZ	4	28	12.5
Not SZ	4	208	98.1
Overall Percentage			86.9

Note: The cut value is .500
Note: SZ=Schizophrenia-Spectrum, OPD=Other Psychopathology Diagnosis, NMI=No Mental Illness

As in multinomial regression, the beta values, Wald statistics, and odds ratios can also be computed for all predictor variables to determine whether the addition of each respective variable adds to prediction. Parental risk (Wald χ^2_1=10.00, p< 0.01), MPAs (Wald χ^2_1=6.68, p< 0.01), and neuromotor dysfunction (Wald χ^2_1=5.31, p< 0.05) were significant predictors of schizophrenia-spectrum outcome. The parameter estimates, Wald χ^2, odds ratios, and confidence intervals of the variables that were retained in the model after steps one (parental risk) and two (neurological predictors) are presented in Table 13.

Table 13. *Summary of Binary Logistic Regression Analysis for all Participants*

	Wald x^2	Df	*B (SE)*	*Exp(B)* (95% CI)
Constant	.01	1	-.12 (1.51)	
Parental Risk	10.00**	1	1.36 (.43)	3.90 (1.68-0.05)
Coordination	1.93	1	-.04 (.03)	.94 (.76-1.15)
Ocular Alignment	.38	1	-.07 (.11)	.94 (.76-1.15)
Laterality	.81	1	.13 (.15)	1.14 (.86-1.53)
MPAs	6.68**	1	-.35 (.13)	.71 (.54-.92)
IQ	2.53	1	-.02 (.01)	.98 (.95-1.01)
Milestones	.47	1	-.28 (.40)	.76 (.35-1.66)
Neuromotor Dysfunction	5.31*	1	-.31 (.14)	.73 (.56-.96)

Note: Variable(s) entered on step 1: Coordination, Ocular Alignment, Laterality, MPA, IQ, Neuromotor Dysfunction, Milestones.
Note: Model χ^2_8= 30.96, p<.001; Hosmer-Lemeshow χ^2_8= 8.71, p=.37; R^2=.12 (Cox & Snell), .22 (Nagelkerke);
*p<.05; **p<.001

Table 14 presents the correlation matrix for the analysis.

Table 14. *Binary Regression Analysis Correlation Matrix for all Participants*

	Risk	MPAs	IQ	Neuromotor	Milestones	Coordination	Ocular	Laterality
Risk	1	.07	.00	.06	-.14	.05	.05	.00
MPAs		1	.09	.06	-.04	.07	.07	-.09
IQ			1	.10	-.16	.22	.22	-.26
Neuromotor				1	.13	.14	.14	-.14
Milestones					1	-.03	.03	.07
Coordination						-.15	.15	-.13
Ocular							1	-.22
Laterality								1

As parental risk, MPAs, and neuromotor dysfunction all significantly contributed to the model, an exploratory binary logistic regression analysis was conducted using only those three variables to predict the outcome of schizophrenia-spectrum diagnosis or not. This exploratory model (χ^2_3= 24.23, p<.001) successfully classified 88.1% of participants (See Table 15) and was also found to adequately fit the data using Hosmer-Lemeshow statistic (χ^2_8= 5.21, p=0.76).

Table 15. *Binary Regression Analysis Classification Summary for all Participants using Parental Risk, MPAs, and Neuromotor Dysfunction*

	Predicted Group Membership		
Observed	SZ	Not SZ	Percent Correct
SZ	3	29	9.4
Not SZ	0	212	100.0
Overall Percentage			88.1

Note: The cut value is .500
Note: SZ=Schizophrenia-Spectrum, OPD=Other Psychopathology Diagnosis, NMI=No Mental Illness

While all variables entered were retained for the final model, only parental risk (Wald χ^2_1=12.02, p< 0.01) and MPAs (Wald χ^2_1= 6.60, p< 0.01) were significant

predictors of schizophrenia-spectrum outcomes whereas neuromotor functioning approached significance (Wald χ^2_1= 3.59, p=.06).

Again, to explore the impact of neuromotor functioning and milestone predictors, the variables with a high degree of missing data, a binary regression analysis was run with those variables excluded. Ocular alignment, laterality, coordination, and IQ were removed from the model in a backward elimination manner. The result of the final model χ^2 remained significantly different from the constant-only model at 21.41 (df=3, p<.001) and successfully classified 86.9% of outcome diagnoses and 6.3% of schizophrenia-spectrum outcomes. Parental risk (Wald χ^2_1=13.18, p< 0.001) and MPAs (Wald χ^2_1=7.15, p< 0.01) were significant predictors of outcome diagnosis.

Finally, two additionally binary logistic regression analysis was performed: one including only "high-risk" (N=94) offspring and "low-risk" offspring" (N=66) and another including only high-risk offspring. There were no significant differences between these analyses and the initial binary logistic regression analysis that included all participants and all neurological variables.

Discriminant function analysis. A discriminant function analysis (DFA) was employed to augment the regression analyses. Both DFA and multinomial logistic regression use predictors to determine categorical outcomes, which must be mutually exclusive. Logistic regression, however, does not require the same assumptions as DFA, which dictate that the independent variables must be normally distributed, linearly related, and that the groups must have equal variance (Tabachnick & Fidell, 1996). On the other hand, DFA is more appropriate for sample sizes smaller than 50, particularly when there are many groups in the dependent variable, it may be more accurate in

classifying outcomes and hypothesis testing and is more sensitive to nominal variable such as sex (Grimm & Yarnold, 1995; Kinnear & Gray, 2011). In DFA, the first discriminant function provides the maximum or best separation between the outcome groups. The second will provide the next best which is unrelated (orthogonal) to the first discriminant function and so on. Therefore, a discriminant function is like a regression equation in which each predictor is weighted and there is a constant.

As noted above, discriminant function analyses require more assumptions than logistic regression, including multivariate normal distribution, Homogeneity of variance-covariance matrix, and absence of multicollinearity. Before the analysis was performed, skewness and kurtosis of each variable was assessed. Ocular alignment and neuromotor dysfunction were skewed and kurtotic in that they had skewness and kurtosis statistics greater than 2 (Field, 2009). A square root transformation was applied to the neuromotor variable, correcting the skewness and kurtosis by reducing them to below 2. Ocular alignment, however, remained skewed and kurtotic (skewness and kurtosis greater than 2) following all attempts at transformation. Due to the distribution of scores, with the majority of participants having an absence of ocular alignment dysfunction, transforming the scores into quartiles was not appropriate. Therefore, ocular alignment was recoded as a dichotomous variable with higher scores (above the mean, N=67) representing relatively high ocular alignment dysfunction and all other scores (N=177) representing relatively low ocular alignment dysfunction scores. Again, multicollinearity was assessed by running a linear regression to test for collinearity diagnostics. Multicollinearity was absent in that variables with high proportions were not on the same eigenvalues.

Like the regression analyses, the grouping variable was psychiatric outcome (schizophrenia-spectrum, other psychopathology, or no mental illness) and the predictor variables included sex, parental risk status, laterality, MPAs, ocular alignment, intelligence quotient scores, neuromotor evaluation results, coordination score, and developmental milestones. For the prediction to be robust, the assumption of homogeneity of the variance-covariance matrix was assessed using Box's M and was not in violation (*Box's M*=103.72, p=.33).

Two discriminant functions were calculated, explaining 69% (canonical R^2=.14) and 31% (canonical R^2=.07) of the variance, respectively. Wilks' lambda is the ratio of the within-groups to the total sum of squares and varies from 0 to 1. A lambda of 1 indicates that the means of the groups all have the same value and do not differ. In SPSS, Wilks' lambda is converted into a chi square which can be used to test significance level. Wilks' lambda was significant for the combined functions (χ^2_{18} =51.35, p<.001), and remained significant after removing the first function indicating that both functions significantly differentiated the diagnostic outcome groups (χ^2_8= 16.34, p=.04).

The canonical coefficients indicated the relative contribution of each predictor to group separation. The coefficients revealed that the first discriminant function maximally differentiated the schizophrenia-spectrum outcome group from the other two outcome and was most associated with parental risk (-.88) and MPAs (.31). The second function maximally differentiated the other psychopathology group from the other two groups and was most associated with milestones (1.16), sex, (.77), and neuromotor dysfunction (.49). Centroids of the three outcome groups can be seen in Table 16 and are represented graphically in Figure 1.

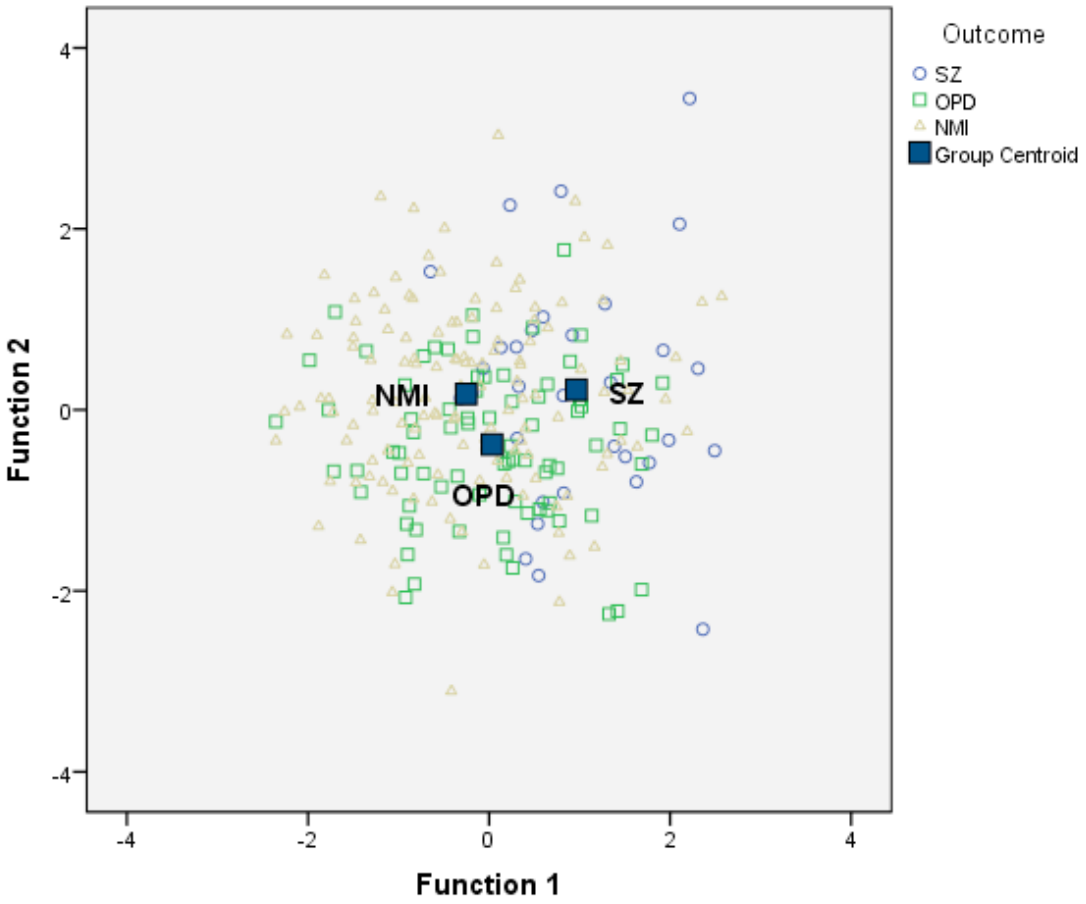


Figure 1. *Discriminant Function Analysis Canonical Discriminant Functions for all Participants*

Table 16. *Discriminant Function Analysis Functions at Group Centroids for all Participants*

	Function	
Outcome	1	2
SZ	.97	.22
OPD	.03	-.38
NMI	-.25	.17

Note: Unstandardized canonical discriminant functions evaluated at group means
Note: SZ=Schizophrenia-Spectrum, OPD=Other Psychopathology Diagnosis, NMI=No Mental Illness

About 50% of the cases were correctly classified. See Table 17.

Table 17. *Discriminant Function Analysis Classification Summary for all Participants*

			Predicted Group Membership			
		Outcome	SZ	OPD	NMI	Total
Original	Count	SZ	18	6	8	32
		OPD	17	36	26	79
		NMI	27	38	68	133
	%	SZ	56.3	18.8	25.0	100.0
		OPD	21.5	45.6	32.9	100.0
		NMI	20.3	28.6	51.1	100.0

Note: 50.0% of original grouped cases correctly classified.
Note: SZ=Schizophrenia-Spectrum, OPD=Other Psychopathology Diagnosis, NMI=No Mental Illness

A second DFA was run wherein the grouping variable of psychiatric outcome was analyzed dichotomously, as schizophrenia-spectrum outcomes versus all other outcomes. Again, the predictor variables included sex, parental risk status, laterality, MPAs, ocular alignment, intelligence quotient scores, neuromotor evaluation results, coordination score, and developmental milestones. For this analysis as well, Box's M was not in violation *Box's M*=59.99, p=.35). In this case, only one discriminant function was produced, which accounted for 100% of the variance (canonical R^2=.13). The variables that contributed the most to group separation, based on their canonical discriminant

function coefficients, were parental risk (-.63), MPAs (.46), and neuromotor dysfunction (.44). Centroids of the three outcome groups can be seen in Table 18. Wilks' lambda was significant for the discriminant function (χ^2_7 =33.04, p<.001) and the function correctly classified approximately 70% of cases. See Table 19.

Table 18. *Dichotomous Discriminant Function Analysis Functions at Group Centroids for all Participants*

	Function
Outcome	1
SZ	.99
Not SZ	-.15

Note: Unstandardized canonical discriminant functions evaluated at group means

Table 19**.** *Dichotomous Discriminant Function Analysis Classification Summary for all Participants*

			Predicted Group Membership		
Original	Count	Outcome	SZ	Not SZ	Total
		SZ	21	11	32
		Not SZ	60	152	212
	%	SZ	65.6	34.4	100.0
		Not SZ	28.3	71.7	100.0

Note: 70.9% of original grouped cases correctly classified.

In another attempt to produce an analysis that was more easily comparable to case-control designed studies, a third discriminant function analysis was employed that only included those with parents with schizophrenia-spectrum diagnoses ("high-risk", N=94) to those with parents without schizophrenia-spectrum diagnoses ("low-risk", N=66). The assumption of homogeneity of the variance-covariance matrix was assessed using Box's M and was not in violation (Box's M=116.31, p=.17). Two discriminant functions were calculated, explaining 70.8% (canonical R^2=.19) and 29.2% (canonical R^2=.09) of the variance, respectively. Wilks' lambda was significant for the combined functions (χ^2_{18} =47.10, p<.001), but was no longer significant after removing the first

function, indicating that only the first function significantly differentiated the diagnostic outcome groups.

The canonical coefficients indicated the relative contribution of each predictor to group separation. The coefficients revealed that the first discriminant function maximally differentiated the schizophrenia-spectrum outcome group from the other two outcome and was most associated with parental risk (-.63), neuromotor dysfunction (.51), MPAs (.51), and coordination (-.06). Centroids of the three outcome groups can be seen in Table 20 and are represented graphically in Figure 2.

Table 20. *Discriminant Function Analysis Functions at Group Centroids for High-Risk and Low-Risk Participants*

	Function	
Outcome	1	2
SZ	1.14	.09
OPD	-.11	-.49
NMI	-.25	.22

Note: Unstandardized canonical discriminant functions evaluated at group means
Note: SZ=Schizophrenia-Spectrum, OPD=Other Psychopathology Diagnosis, NMI=No Mental Illness

About 55% of the cases were correctly classified. See Table 21.

Table 21. *Dichotomous Discriminant Function Analysis Classification Summary for High-Risk and Low-Risk Participants*

			Predicted Group Membership			
		Outcome	SZ	OPD	NMI	Total
Original	Count	SZ	16	4	4	24
		OPD	10	24	11	45
		NMI	22	21	48	91
	%	SZ	66.7	16.7	16.7	100.0
		OPD	22.2	53.3	24.4	100.0
		NMI	24.2	23.1	52.7	100.0

Note: 55.0% of original grouped cases correctly classified.
Note: SZ=Schizophrenia-Spectrum, OPD=Other Psychopathology Diagnosis, NMI=No Mental Illness

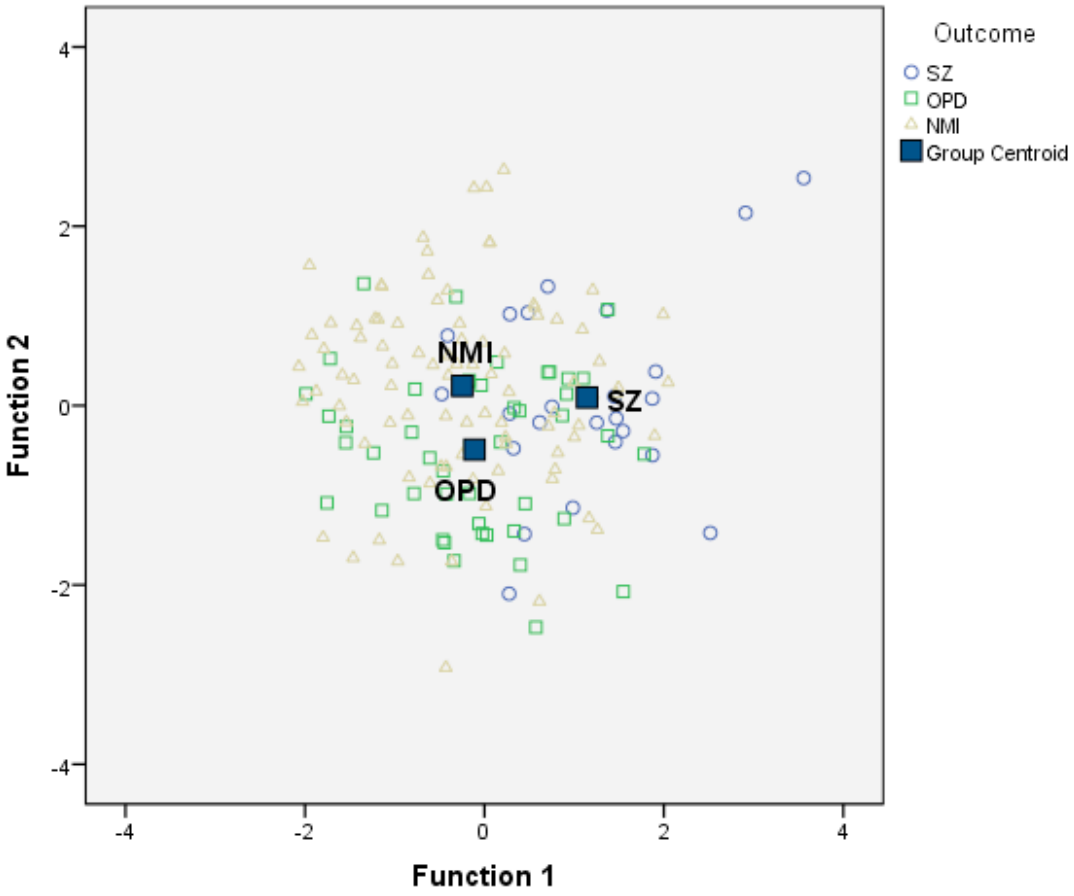


Figure 2. *Discriminant Function Analysis Canonical Discriminant Functions for High-Risk and Low-Risk Participants*

As in the regression analyses, a DFA was employed excluding neuromotor and milestone data altogether, as their contribution may have been impacted by data imputation. In this analysis the assumption of homogeneity of the variance-covariance matrix was assessed using Box's M and was not in violation (*Box's M*=54.37, *p*=.66). In this case, two discriminant functions were produced that accounted for 83% (canonical R^2=.12) and 17% (canonical R^2=.03) of the variance, respectively. Wilks' lambda was significant for the combined functions (χ^2_{14} =35.79, *p*<.001), but was not significant after the first function was removed (χ^2_6 =6.35, *p*=.36), indicating that only the first function significantly differentiated the diagnostic outcome groups. The variables that were most strongly associated with the significant discriminant function were parental risk (.69) and MPAs (.55), with 48.4% of psychiatric outcome successfully classified and 62.5% of schizophrenia-spectrum outcomes correctly classified.

Further, an additional exploratory DFA was employed utilizing only high-risk offspring (N=94). Results did not differ significantly from the initial DFA.

Receiver operating characteristics (ROC) analysis. Receiver operating characteristic (ROC) curves were first developed for use in electronic signal-detection theory. More recently, however, this methodology has been adapted by medical and psychology communities to indicate the presence of a disease or condition (positive) or the absence of the disease or condition (negative). A ROC curve, thus, is a plot of a test's false-positive rate, with the "test" in this case being scores on the neurological and other predictors (Swets et al., 2000; Obuchowski, 2005). The curve is plotted by determining the sensitivity and specificity of every observed data value (or neurological predictor) and plotting sensitivity against 1-specificity and is a visual index of the accuracy of the

predictor variables (Altman & Bland, 1994). In this study, a ROC curve was plotted to evaluate the combined sensitivity and specificity of the predictor variables in ascertaining adulthood schizophrenia-spectrum status (positive or negative). On the graph of the curves themselves, there is a straight diagonal reference line. The further the curve of the predictor variable lies above the reference line (the more separation there is between the reference line and the dashed predictor line), the stronger the predictive power of the model.

For each curve, in addition to the graphical representation, the area under curve (AUC) was determined. The AUC is the probability that randomly selected cases from each outcome category will be accurately classified and it allows researchers to examine the sensitivity and specificity for an array of cut-off points. The AUC score can vary from .5 to 1.0 and can be interpreted as 50–.70, poor; .70–.80, fair; .80–.90, good; .90–1.00, excellent (Hosmer & Lemeshow, 2000; Swets et al., 2000; Rice & Harris, 2005). Different AUC values for different ROC curves can thus be used to compare the accuracy of different predictor variables. In addition to each ROC curve having both a graphical representation and a specific AUC value, ROC analyses also compute sensitivity and specificity for a list of different cut-off values, with the challenge being to select a cut-off that properly balances the needs of sensitivity and specificity. The ROC analysis, in other words, "represents all possible discrimination rules that can be obtained from applying different cutpoints" (Olin et al., 1995, p. 60).

First a ROC curve was plotted using a neurological composite score (the summed z-scores of all of the neurological variables) as the predictor. Next a ROC curve was plotted based on combining the significant neurological predictors from the binary

logistic regression analysis (MPAs, neuromotor dysfunction). Third, a ROC curve was plotted weighing more heavily the neurological predictors that most discriminated schizophrenia-spectrum disorders from the other outcome groups based on the discriminant function analysis (MPAs and coordination). Finally, individual ROC curves were plotted using each neurological variable separately.

Using the neurological composite score, the AUC was .62 (95% C.I. =.51-.73, $p<.05$). The significant AUC indicates that this neurological composite is better than guessing when it comes to classifying psychiatric outcome. Next, a logistic regression-based ROC curve was plotted using a composite the sum of standardized MPAs and standardized neuromotor dysfunction scores. Using this logistic regression-based composite, the AUC was .67 (95% C.I. =.58-.76, $p<.05$). Again, this composite score was better than guessing in terms of predicting psychiatric outcome. A DFA-based composite was then computed by summing the standardized scores of MPAs, neuromotor dysfunction, the variables that most significantly distinguished outcome groups in the dichotomous DFA, as well as IQ which outperformed the other nonsignificant variables. This composite, too, had a significant AUC of .69 (95% C.I.=.57-.77, $p<.01$). The degree greater than the other two composites suggests that this DFA-based composite performs slightly better than the overall neurological composite and the regression-based composite. Subsequently, the seven neurological variables were analyzed separately. MPAs was the only neurological variable with a significant AUC (.64, 95% C.I.=.54-.74, $p<.05$), although neuromotor dysfunction approached significance (.61, 95% C.I.=.50-.71, $p=.06$).

To analyze whether the robustness of MPAs was responsible for the significance of the composite scores, a final ROC curve was plotted with all neurological variables excluding MPAs. This AUC was significant as well (.67, 95% C.I.=.58-.77, p<.01), indicating that although in isolation these variables were not significant, in combination they are better than guessing when it comes to predicting outcome diagnoses.

Additionally, a second set of ROC analyses were run using the same predictor variables but only including "high-risk" (N=94) offspring and "low-risk" offspring" (N=66). When only these two groups were included, the regression-based composite (AUC=.72, 95% C.I.= .62-.82, p<.001), the neurological composite (AUC=.72, 95% C.I.= .62-.82, p<.001), the neurological composite excluding MPAs (AUC=.70, 95% C.I.= .60-.80 p<.01), MPAs (AUC=.71, 95% C.I.= .56-.83 p<.05), and neuromotor dysfunction (AUC=.67, 95% C.I.= .55-.80 p<.05) were all significant.

A summary of these results are presented in Table 22, presenting the AUC values with confidence limits of the analyses involving all participants in addition to the analyses including only high and low-risk participants. The ROC curve plots for all participants with significant AUCs can be seen in APPENDIX A.

The AUC scores for each of the analyses were standardized and compared to one another using using Analyse-It for Microsoft Excel version 2.12 (Analyse-It Software Ltd., 2008). There were no significant differences between the individual predictor variables or the individual predictor variables and the composite scales.

Many factors contribute to the selection of cut-off scores to maximize sensitivity and specificity. In detecting risk for schizophrenia-spectrum disorders, there is a need to balance the ability of a test to correctly categorize those at highest risk versus false-

positives. Some factors include the availability, effectiveness, and cost of available interventions; the costs associated with interventions for those who ultimately did not need it (i.e., true schizophrenia-spectrum-negative cases who are classified as positive); and the costs related to the lack of intervention for those in need (i.e., true schizophrenia-spectrum -positive cases who are classified as negative) (Olin et al., 1997). Each ROC analysis presents a variety of possible cut-off scores, along with their associated sensitivity and specificity values. There are several strategies for choosing predictor variables cut-off points. For medical diagnostic tests, the cut-off associated with 90% sensitivity, regardless of specificity, is often selected (Platt, et al., 2000). This strategy has been used in studies of schizophrenia-proneness (Avila et al., 2002). Within the current study, with respect to the neurological composite, a sensitivity of 90% is associated with a cut-off of -7.42 and a specificity of 18.4%. Alternatively, the neurological composite cut-off that has the highest sensitivity (75%), without sacrificing specificity (42.9%) is -3.65.

Table 22. *Summary of Results for Receiver Operating Characteristic Analyses*

Variable	Area Under Curve	95% C.I.	Area Under Curve†	95% C.I. †
Neurological Composite	.62*	.51 - .73	.72**	.62-.82
Regression-Based Composite	.67*	.58-.76	.72***	.62-.82
DFA-Based Composite	.69**	.57-.77	.62	.48-.75
Coordination	.57	.45-.68	.47	.33-.61
Ocular Alignment	.52	.41-.63	.50	.36-.64
Laterality	.50	.39-.61	.58	.42-.73
MPAs	.64*	.54-.74	.71**	.56-.83
IQ	.55	.44-.65	.51	.37-.65
Milestones	.59	.49-.69	.55	.42-.68
Neuromotor Dysfunction	.61	.50-.71	.67*	.55-.80
Neurological Composite Excluding MPAs	.67	.58-.77	.70**	.60-.80

Note: *p<.05, **p<.01

†Only high-risk and low-risk participants included

CHAPTER IV. DISCUSSION

Summary of Results

The goals of the current study were two-fold: 1) to determine how well a combination of neurological predictor variables can predict schizophrenia-spectrum disorders and 2) to compare predictive power of these neurological variables. The different statistical techniques employed ranged from 12.5% to 88.1% in terms of correctly classifying overall diagnostic outcomes when the outcomes were dichotomous (schizophrenia-spectrum or not) and from 37.5% to 56.3% when all three outcomes were examined. With respect to predicting schizophrenia-spectrum outcomes specifically, results ranged from 12.5% to 66.7 % in terms of correct classification when the outcomes were dichotomous (schizophrenia-spectrum or not) and from 37.5% to 56.3% when all three outcomes were examined. MPAs and neuromotor dysfunction emerged as the most significant neurological predictors of schizophrenia-spectrum outcomes, followed by IQ. The most accurate classification of schizophrenia-spectrum outcomes (67%) involved a DFA in which high- and low-risk participants were included and psychiatric outcomes were analyzed as "schizophrenia-spectrum" or "not schizophrenia-spectrum." This can be compared to an 83% sensitivity rate based on childhood gross motor scores, attentional, and memory measures found in a previous longitudinal high-risk study (Erlenmeyer-Kimling et al., 2000). It should be noted, however, that the Erlenmeyer-Kimling study only followed participants through age 30 and the high sensitivity rate is only associated with high-risk participants, sensitivity was lower for "other risk" and "low risk" subjects.

Schizophrenia-Spectrum Outcomes vs Not Schizophrenia-Spectrum Outcomes.

The binary logistic regression analysis, dichotomous DFA, and ROC analyses all examined the ability for demographic (sex, parental risk) and neurological (laterality, MPAs, IQ, milestones, coordination, neuromotor dysfunction, ocular alignment) predictor variables to distinguish between outcomes of schizophrenia-spectrum disorders compared to non-schizophrenia-spectrum disorder (other psychopathology or no mental illness) outcomes. All three of these analyses found MPAs to be a significant predictor of the presence or absence of a schizophrenia-spectrum outcome. The regression and DFA found neuromotor dysfunction to significantly predict outcome as well. Although the AUC of neuromotor dysfunction in the ROC analysis was not significant, it came closer to significance than any other neurological variable (p=.056) with the exception of MPAs. Additionally, the analyses that also examined parental risk, namely, binary logistic regression analysis and dichotomous DFA, found it to significantly contribute to outcome diagnosis. Moreover, parental high-risk status alone put participants at 4.29 times higher risk of developing a schizophrenia-spectrum disorder than if the parent had another diagnosis or not diagnosis. Overall, parental risk, MPAs, and neuromotor dysfunction were most significant in distinguishing schizophrenia-spectrum outcomes from all other diagnostic outcomes.

Schizophrenia-Spectrum Outcomes vs Other Psychopathology Diagnoses. The multinomial logistic regression analysis specifically examined predictor variables' relationship to an outcome of schizophrenia versus another psychopathology outcome. This analysis revealed that MPAs and neuromotor dysfunction significantly contributed to distinguishing these different diagnostic outcomes. Additionally, the odds of a

schizophrenia-spectrum diagnosis outcome were 2.9 times higher if the participant's parent had a schizophrenia-spectrum diagnosis than if the parent had another diagnosis.

Schizophrenia-Spectrum Outcomes vs No Mental Illness Outcomes. The multinomial regression analysis also compared schizophrenia-spectrum outcomes to no mental illness outcomes. This analysis revealed that MPAs, IQ, and parental risk significantly contributed to a schizophrenia-spectrum diagnosis versus no diagnosis. Participants with a parent with a schizophrenia-spectrum diagnosis were 16.67% more likely to develop a schizophrenia-spectrum diagnosis themselves, compared to low-risk offspring.

Comparison of Neurological Variables. There was a significant positive correlation between laterality and IQ, coordination and ocular alignment, and coordination and milestones. There was also a significant negative correlation between IQ and ocular alignment, coordination and neuromotor dysfunction, and milestones and neuromotor dysfunction. Although the negative correlations were unexpected, each pair of significant correlations involved a variable that demonstrated relatively low predictive power with respect to psychiatric outcome (i.e., laterality, coordination, ocular alignment, milestones).

In addition to correlations, however, this study allowed for the assessment of relative contribution of each neurological variable to predicting offspring psychiatric outcome. Results indicated that MPAs and neuromotor dysfunction consistently contributed significantly prediction of adulthood diagnoses and ocular alignment, laterality, and milestones repeatedly contributed the least to diagnostic outcome. Table 23

summarizes the relative predictive strength of each neurological variable for each analysis.

Notably, however, the ROC composite scores (neurological, neurological excluding MPAs, regression-based, and DFA-based) also had significant AUCs, even when the single significant neurological variable was removed. In addition, the regression models remained significant even after removing neuromotor dysfunction (due to missing data). This indicates that the predictive power of the neurological variables when combined is higher than any single variable individually, though there were no statistically significant differences between the AUCs.

Table 23. *Relative Contribution of Neurological Variables to Offspring Outcome Diagnosis*

Outcome Comparison	Analysis	Basis for ranking	Most significant to least significant contributors
SZ vs Not SZ	Binary logistic regression	Wald statistics	MPAs Neuromotor Dysfunction IQ Coordination Laterality Milestones Ocular Alignment
	Dichotomous DFA*	Standardized discriminant function coefficients	MPAs Neuromotor Dysfunction IQ Coordination Laterality Ocular Alignment
	ROC	AUC	MPAs Neuromotor Dysfunction Milestones Coordination IQ Ocular Alignment Laterality
SZ vs OPD	Multinomial logistic Regression	Wald statistics	Neuromotor Dysfunction MPAs Coordination IQ
SZ vs OPD with only High-Risk and Low-Risk participants	Multinomial logistic Regression	Wald statistics	MPAs Neuromotor Dysfunction IQ
SZ vs NMI	Multinomial logistic Regression	Wald statistics	MPAs IQ Neuromotor Dysfunction Coordination
SZ vs NMI with only High-Risk and Low-Risk participants	Multinomial logistic Regression	Wald statistics	MPAs Neuromotor Dysfunction IQ

Note: *relative contribution rankings same as DFA using only High-Risk and Low-Risk participants
Note: SZ=Schizophrenia-Spectrum, OPD=Other Psychopathology Diagnosis, NMI=No Mental Illness

Summary of Outcome Comparisons. Throughout all of the analyses, MPAs emerged as a robust predictor of schizophrenia-spectrum outcomes, whether that was in comparison to all other outcomes, other psychopathology outcomes, or no mental illness outcomes. Between specific types of outcome pairs, however, there was some variability (See Table 24). The most distinct difference is between comparing schizophrenia-

spectrum disorder outcomes with other psychopathology and comparing schizophrenia-spectrum disorder outcomes with no mental illness. Neuromotor dysfunction plays a role in distinguishing schizophrenia-spectrum disorders from other psychopathology whereas parental risk and IQ contribute to distinguishing schizophrenia-spectrum disorder from no mental illness.

Table 24. *Significant Predictor Variables Associated with Each Outcome Comparison*

SZ vs All Other	SZ vs OPD	SZ vs NMI
MPAs	MPAs	MPAs
Parental Risk		Parental Risk
Neuromotor	Neuromotor	
		IQ

Possible Mechanisms for Results

Differences in Statistical Techniques. There were some differences observed as a function of statistical techniques employed to predict psychiatric outcome. With respect to comparing schizophrenia-spectrum outcomes to non-schizophrenia-spectrum outcomes, there were some slight disparities in the results obtained from the binary logistic regression, DFA, and the receiver operating curves analyses. In both binary logistic regression and the dichotomous DFA, risk status, MPAs, and neuromotor functioning significantly contributed to distinguishing outcomes groups. In the DFA that examined all three outcomes, however, only parental risk and MPAs were associated with the first discriminant function, the variate that best distinguished schizophrenia-spectrum outcomes from all other outcomes. Additionally, in the ROC analyses, though parental risk was not analyzed, only neuromotor functioning was found to be a significant neurological predictor.

Although these may appear to be contradictory findings, some of the differences may be explained by the analyses utilized. In the DFA that was associated with all three outcomes, there were two significant discriminant functions: one of which best distinguished schizophrenia-spectrum outcomes from all other outcomes and one of which best discriminated other psychopathology from all other outcomes. While this first discriminant function is most easily compared to the separate dichotomous DFA which also examined dichotomous outcomes, the method by which the data was treated was not identical. In the first DFA, the first discriminant function only accounted for 69% of the variance because all three outcomes were being analyzed separately whereas in the dichotomous DFA, other psychopathology and no mental illness outcomes were aggregated and the single discriminant function accounted for 100% of the variance. In other words, in the dichotomous DFA, all non-schizophrenia diagnoses were analyzed as though they were identical outcomes whereas in the first DFA, no mental illness was distinguished from other psychopathology.

Although overall these techniques were employed to determine neurological variables' contribution to predicting outcomes diagnoses, there were subtle contrasts between the way the data was treated in each case that led to slight differences in results. Specifically, in multinomial regression and DFA, outcome diagnoses were separated into three groups whereas in binary regression, dichotomous DFA, and ROC analyses, other psychopathology and no mental illness were clustered into a "non-schizophrenia" outcome group. Multinomial regression further examined differences between schizophrenia-spectrum and other psychopathology in addition to differences between schizophrenia-spectrum and no mental illness. DFA, both dichotomous and not, were

employed to examine underlying functions associated with distinguishing outcomes. ROC analyses, on the other hand, examined individual predictors. The aggregated neurological, DFA-based, and regression-based composites cannot be directly compared side-by-side with the DFA and regression analyses because the variables were combined into an index score, so individual variable contribution was not available.

Analyses Excluding Variables with Significant Missing Data. It is notable that although neuromotor functioning continuously emerged as a relatively powerful predictor of outcome diagnoses, the variables that remained after it was removed were able to significantly distinguish diagnoses even when neuromotor functioning was excluded from the analyses. This may speak to the robustness of parental risk and MPAs – and IQ, to a lesser degree – in predicting outcomes. It may also speak to variance shared by MPAs and neuromotor dysfunction. Although multicollinearity and overdispersion were assessed and ruled out, MPAs and neuromotor dysfunction may be tapping into similar, though not completely overlapping, pathways towards developing schizophrenia. MPAS, for example, may be more sensitive to perinatal complications whereas neuromotor dysfunction may more closely reflect earlier prenatal insults. That the models remained significant after removing the largest contributor to prediction also emphasizes the strength of the model; its ability to predict schizophrenia-spectrum outcomes did not rely solely on a single variable. Although the regression models were a good fit of the data and the DFA was able to distinguish outcomes, when neuromotor functioning was removed, they did not correctly classify outcome diagnoses or schizophrenia-spectrum outcomes as accurately as the models that included neuromotor functioning. These

effects, taken together with the composite variable results from the ROC analyses, underscores the heightened capacity for prediction when variables are combined.

Minor Physical Anomalies (MPAs). The fact that MPAs emerged as a significant predictor in all outcome comparisons (schizophrenia-spectrum versus all other outcomes, schizophrenia-spectrum versus other psychopathology, schizophrenia-spectrum versus no mental illness) is consistent with previous literature. Congruous with these results, there is robust literature supporting differences in MPAs between those with schizophrenia-spectrum disorders and individuals with no mental illness (e.g., Green, Satz, & Christenson, 1994; Ismail et al., 2000; Schiffman et al., 2002; Sivkov & Akabaliev, 2004; Weinberg et al., 2007). Perhaps more germane to the cause of predicting schizophrenia, however, is examining MPAs' capacity to predict schizophrenia compared to other psychopathology, to determine the specificity of MPAs in the etiology of schizophrenia. The current results do suggest that within this dataset, MPAs significantly contributed to distinguishing between schizophrenia-spectrum disorders and other types of psychopathology. Previous research, too, has found significant increases in MPAs in schizophrenia compared to other types of psychopathology, or nonsignificant differences between control populations and other types of psychopathology, including bipolar disorder, major depression, and Alzheimer's disease (Green, Satz, & Christenson, 1994; Trixler et al., 2001; Lohr & Flynn, 1993; Lohr, et al., 1997). Nevertheless, other studies have failed to find significant differences in MPAs between schizophrenia and other types of psychopathology, which may be related to the relative depth of research comparing schizophrenia and MPAs and the relative dearth of research on MPAs and other mental illnesses (Pine et al., 1997; Compton & Walker, 2009).

Research has suggested a combination of environmental and genetic factors that are implicated in the specific association between schizophrenia and MPAs. Consistent with the "two-hit" model of schizophrenia development, among individuals already at risk for schizophrenia (those with genetic loading), increased MPAs (a marker of pre- or perinatal complications) are related to schizophrenia-spectrum outcomes (Green, Satz, & Christenson, 1994; Schiffman et al., 2002). These findings support the notion of MPAs as an endophenotype of schizophrenia, a calculable feature of a disease, generally unnoticeable to the unaided eye, that lies along the course between disease and distal genotype (Gottesman & Gould, 2003). For a variable to be considered an endophenotype, they must be stable over time, sensitive (demonstrable in individuals at risk for schizophrenia), specific (must be less common in patients with other psychiatric disorders), heritable, and at increased rates in first-degree relatives of individuals with schizophrenia (Kremen et al., 1994; Compton & Walker, 2009). Although additional research is needed, particularly in examining the specificity of MPAs to schizophrenia, the support of MPAs as an endophenotype indicates "that MPAs are closer to etiologic pathways of schizophrenia than are psychotic symptoms" (Compton & Walker, 2009). Given the relative ease of measuring MPAs, future high-risk studies should include it as a relatively robust indicator of vulnerability for developing a schizophrenia-spectrum disorder.

Further, MPAs are useful in determining the timing of prenatal insult. Although timing interacts with severity (e.g., a specific MPA may be the result of an early mild insult or a later, more severe insult), they are generally thought to be produced during weeks of 14-22 of gestation (Nowakowski, 1987; Green et al., 1994). These gestational

weeks of purported higher vulnerability for developing MPAs overlaps with the time of neural migration, abnormalities of which are associated with schizophrenia development. Additionally, genes that are involved in neuronal migration have been implicated in schizophrenia, further supporting the notion of genetic (first hit) by extragenetic (second hit) interactions in the development of schizophrenia and markers of schizophrenia vulnerability (Green et al., 1994; Fatemi & Folson, 2009).

Parental Risk. Perhaps unsurprisingly, parental risk also emerged as a predictor for developing schizophrenia-spectrum disorders. As in the case of MPAs, there is a significant body of literature supporting the role of genetic risk in offspring schizophrenia (Gottesman & Shields, 1982; Tsuang, 2000). It is notable that parental risk was associated with distinguishing schizophrenia-spectrum outcomes from no mental illness or all other outcomes, but not with distinguishing schizophrenia-spectrum outcomes from other types of psychopathology. This suggests that having a parent with schizophrenia may put one at risk for developing mental illness in general, and perhaps not specifically schizophrenia. This is consistent with previous genetic research. It has been estimated that having a parent with schizophrenia puts one at about a 13% risk of developing schizophrenia, compared to about a 1% risk in the general population (Gottesman, 1991). Having a parent with a psychotic disorder, however, may also put one at risk for other types of psychopathology, including internalizing and externalizing disorders (Keshavan et al., 2008). These diagnostic transmissions are potentially related to instability in child-rearing environment caused directly by having a parent with a serious mental illness. Additionally, they could point to schizophrenia being on a continuum with other disorders, with shared symptoms such as attentional deficits and mood dysregulation

(Khouri, 1977; Keshavan et al., 2008). In Khouri's discussion (1977) of continuum versus dichotomous conceptualizations of psychopathology, he suggests that differences between schizophrenia and other types of mental illness are quantitative rather than qualitative; all disorders may follow the same two-hit model whereby genetics make one vulnerable for developing a disorder and subsequent environmental and individual factors lead to the specific disorder manifestation.

Neuromotor Dysfunction. Within this study, neuromotor dysfunction distinguished between participants with schizophrenia-spectrum disorders and participants with other types of psychopathology, pointing to a specificity of neuromotor dysfunction to schizophrenia. Again, previous literature supports the concept of differences in neuromotor functioning between individuals with schizophrenia-spectrum disorders and individuals with other psychopathology (Hans et al., 1999; Erlenmeyer-Kimling et al., 2000; Cannon et al., 2002). Neuromotor dysfunction, however, did not appear to distinguish between offspring with schizophrenia-spectrum outcomes and offspring with no mental illness outcomes. With regard to the multinomial logistic regression, although neuromotor dysfunction was not a significant predictor of schizophrenia-spectrum versus no mental illness outcome, the odds ratio was higher than the odds ratios of MPAs or parental risk, which were significant. This suggests the possibility that the non-significance of neuromotor dysfunction relates to a relatively higher standard error (Field, 2009). It is also possible that the significant role of parental risk had a suppressor effect on neuromotor dysfunction. Additionally, when those with no mental illness were combined with participants with other mental illness outcomes,

neuromotor dysfunction did distinguish them from offspring with schizophrenia-spectrum outcomes.

As discussed earlier, Andreasen posited a dysfunction in the cortical-cerebellar-thalamic-cortical-circuit (CCTCC) as leading to primary deficits associated with schizophrenia. As the CCTCC plays a role in coordinating motor and cognitive activities, much support for the relationship between CCTCC and schizophrenia comes from neuromotor dysfunction in individuals with schizophrenia (Andreasen, 1999). Kraeplin was describing abnormal movements in people with schizophrenia at least as early as 1919 (Kraeplin et al., 1919); neuromotor dysfunction continues to be associated with schizophrenia in more recent studies as well (Walker & Green, 1982; Gupta et al., 1995; Flashman et al., 1996). Neuroanatomically, the CCTCC involves the basal ganglia, a structure that houses dopamine receptors, dysregulation of which are associated with symptoms of schizophrenia (Perez-Costas et al., 2010). Healthy first-degree relatives of individuals with schizophrenia also demonstrate dopamine dysregulation and neuromotor deficits to a higher degree than controls (McNeil & Cantor-Graae, 2000; Huttunen et al. 2008; Lee et al. 2008). Further, obstetric complications are related to increased neuromotor dysfunction in early childhood specifically in those who later developed schizophrenia (Rosso et al., 2000). Taken together, these studies may provide evidence that individuals with genetic risk are more likely to experience perinatal complications or are less able to successfully defend against such environmental stressors given their preexisting neural vulnerability.

Intelligence Quotient (IQ). The multinomial regression analysis revealed that IQ significantly contributed to a schizophrenia-spectrum diagnosis versus no diagnosis,

which is consistent with previous research on deficits in schizophrenia with regard to the domains measured on the WISC (Aleman et al., 1999; Hoff et al., 1999; Henry & Crawford, 2005). The lack of significant IQ differences between the schizophrenia-spectrum group and the other psychopathology group could be statistically or theoretically explained. As in the case of neuromotor dysfunction, the odds ratio of IQ in distinguishing between schizophrenia-spectrum group and the other psychopathology group was relatively high, and higher than either MPAs or neuromotor dysfunction, which were significant contributors. From a theoretical perspective, neuropsychological functioning, particularly when measured broadly as in the WISC, may be related to so many other types of psychopathology that it is not useful in specifying schizophrenia outcome (Zammit et al., 2004).

Relationships Between Variables. MPAs, followed by neuromotor dysfunction appearing to be the most significant predictors of schizophrenia-spectrum outcomes. Some correlations between variables, however, were not in the expected direction. Neuromotor dysfunction was significantly negatively correlated with developmental milestones, and coordination and IQ was significantly negatively correlated with ocular alignment. It is possible that this is an artifact of missing data and data imputation. Alternatively, these correlations may be related to the assumption of higher scores indicating more dysfunction. Potentially, the significant negative correlations may accurately reflect the relationships between variables, potentially pointing to related but distinct pathways to schizophrenia. Alternatively, the variables in question (developmental milestones, coordination, and ocular alignment) could be unrelated to a

schizophrenia development process within this population, as they all performed relatively poorly in predicting psychiatric outcomes.

Study Strengths

There are several methodological advantages to this dataset. Although many putative causes of schizophrenia have been studied individually, the advantage of this large dataset is that it allowed for an analysis of the predictive power of combined premorbid factors as well as insight into relative predictive strength among multiple predictors. Additionally, all measures for this study were prospective. Prospective studies eliminate the likelihood of adult clinical symptomatology or treatment influencing measurement of childhood neurological functioning and neural proxies. Prospective research also removes the biases associated with relying on personal or maternal recall of past events and ensured raters are blind to psychiatric outcomes, confounds which have been identified in retrospective research. Moreover, the average age of onset of schizophrenia and the relatively long time span of this study increases confidence that most participants who will develop schizophrenia have already done so and have not been misclassified as control participants (e.g., Räsänen et al., 1999; Tuulio-Henriksson, 2004). Lastly, compared to previous studies, this dataset has a large sample size, more thorough and systematic assessments, and a larger number of neurological variables than previous high-risk studies.

Study Limitations

Methodological Limitations. As is typical in longitudinal high-risk studies, generalization may be limited as the sample was selected for increased genetic risk for psychopathology. Not all individuals with schizophrenia have an identifiable positive

family history and those that do may not reflect typical pathways towards developing schizophrenia. Findings from this high-risk sample, however, likely generalize to many individuals with schizophrenia given the robust findings of parental genotypic risk transfer as well as the neurological deficits seen in healthy first-degree relatives (e.g., Cannon et al., 1995; Gourion et al., 2004; Sanders et al., 2006). The fact that all participants were Danish and Caucasian also limits generalizability. However, this limitation in external validity led to increased internal validity. Additionally, although the sample was small, there were no significant neurological differences between high-risk individuals who developed schizophrenia-spectrum disorders and relatively lower risk participants who developed schizophrenia-spectrum disorders, supporting the notion of common etiology.

There are also some limitations to the methodology used during data collection, particularly related to the assessment conducted when the participants were 10- to 13-years-old. Only one assessor administered the tests used in the 1972 evaluation. The assessor was, however, a leading Danish child neurologist with extensive training on all measures who was blind to risk status and to adult outcome. Additionally, the Waldrop scale, used in the assessment of MPAs, has been shown to have high inter-rater reliability (Gourion et al., 2004) although that was not directly measured for this study.

Additionally, diagnostic status for parents and offspring was based on lifetime prevalence of the disorder. Using this methodology did not distinguish between someone who was diagnosed with schizophrenia early in life and was successfully treated from someone who developed schizophrenia and was impaired throughout adulthood. Other differences related to illness severity including age-of-onset, diagnostic comorbidity,

level of impairment, and symptom count were also unavailable. It is possible, therefore, that heterogeneous outcomes (e.g., those with a single diagnosis of schizophrenia and those with comorbid schizophrenia and substance abuse diagnoses) were aggregated (in this example, both labeled as a "schizophrenia-spectrum outcome") in a way that conceals substantial outcome differences.

Despite advances in the understanding of neurological dysfunction and schizophrenia, localization of specific deficits is complicated and often inconsistent in schizophrenia due to the variety of brain regions and functions involved in even "relatively simple" tasks (e.g., Schubert & McNeil, 2004; Ismail et al., 1998). Motor coordination dysfunction, for example, could reflect basal ganglionic, pyramidal, and/or cerebellar dysfunction. Moreover, other factors (e.g., vision) might impact performance on a particular domain. Very few studies to date have examined actual brain correlates of neurological atypicalities (Dazzan et al., 2004). As a result, although this study tested the association, and relative strength of the association, between the neurological examination and other predictors in childhood and schizophrenia-spectrum in adulthood, specific mechanisms of these relationships are based on literature-derived conjecture.

Statistical Limitations. With respect to the 1972 assessment of neuromotor functioning, the level of inter-rater agreement and internal consistency was less than ideal for the neuromotor scale (ICC=0.65). Subtle distinctions between behaviors may have resulted in less agreement between raters. The neuromotor scale showed only moderate internal consistency (α=0.52). This low internal consistency may result from the small number of items in the scales and low behavioral frequencies of each item. Poorer

reliability indicates that a scale might not measure a single factor and might contribute to a failure to reject the null hypothesis, particularly when the sample size is small.

Raw data were standardized in order to create index scores. For example, scores on footedness and eyedness were standardized so that they could be combined into a single laterality score. Although standardization was necessary to aggregate scores, z-score transformations reduce data variability. As reliability is the ratio of the variance of the true score to the variance of the measure, reliability is impacted by changes in variability (Trochim & Donnelly, 2006). Related, there was a great deal of variability in the measures used, with Cronbach's α ranging from .22 for laterality to .89 for coordination.

As noted above, final number of participants with a schizophrenia-spectrum diagnosis was small, which limits the power of statistical analyses. Nevertheless, small sample size is a typical problem in longitudinal high-risk studies and the number of participants with an outcome of a schizophrenia-spectrum disorder actually exceeds that of previous longitudinal high-risk studies based on other cohorts (Fish et al., 1992; Amminger et al., 1999; Hans et al., 1999; Schubert & McNeil, 2007). While all schizophrenia-spectrum outcome diagnoses were grouped together, there is evidence of common etiology and impairment, between all such disorders (Adler & Strakowski, 2003). Additionally, unlike many cohort studies, this dataset did not group schizophrenia-spectrum disorders with other types of psychopathology, allowing for analyses of specificity to psychosis.

This study suffers from a significant number of missing data and relatively low internal consistency within measurement scales. It is further possible that the imputation

method used resulted in data that were not accurate reflections of premorbid neurological functioning. Nevertheless, there did not appear to be significant differences in terms of adult diagnostic outcome, sex, or psychiatric risk status between participants with and without missing data and the missing values analysis did not indicate systematic patterns of missing values. Additionally, the EM method is considered by many to yield more reliable and less biased data than other methods of data imputation (Enders, 2004; Schlomer, 2010).

Lastly, the statistical analyses are not explanatory, so it is possible that the variable that is most robust in its association with outcome status, MPAs, is simply the predictor variable with the least measurement errors, not the one that is best reflective of neural maldevelopment. Cronbach's alpha scores, however, do not suggest that the MPA scale had the highest reliability so internal consistency does not wholly account for why it outperformed other proxies. Measurement error nevertheless could potentially have been reduced by using established scales with known psychometric properties, using multiple raters for all scales, and increasing duration and intensity of rater training.

Implications

In recent years, the recognition of the effects of untreated psychosis as well as a focus on community-based interventions has led to increased efforts at identifying individuals before full-blown illness onset and the related more restrictive interventions (Lester et al., 2009). Longer duration of untreated psychosis is associated with more costly mental health services, more hospital readmissions, lower subjective quality of life, more impaired neurocognitive functioning, increased risk for depression and suicide, slower recovery, and more substance misuse (Helgason, 1990; Moscarelli et al., 1991;

Edwards & McGorry, 2002; Joyce et al., 2002). Therefore, there is a great deal of interest in focusing screening efforts towards the most vulnerable individuals and longitudinal high-risk studies such as this one are valuable in creating more targeted identification techniques, with the future goal of preventing schizophrenia (Compton, 2004).

Like most illnesses, prevention of schizophrenia, rather than treatment, would be ideal. Such methods are already being implemented in the area of relapse prevention, using techniques such as psychoeducation, active monitoring of symptoms, flexible clinical interventions, individual and family group therapy, and atypical antipsychotic treatment (e.g., Herz et al., 2000; Leucht et al., 2003). Putative causal factors for later schizophrenia, especially in high-risk individuals, could be managed prophylactically. Such contributing variables that could potentially be controlled in high-risk cases include mother/child Rhesus incompatibility (Wyatt, 1996) and reducing the risk of pregnancy and delivery complications (Warner, 2001). Other treatments targeted to people with a family history of schizophrenia might include genetic counseling (Compton et al., 2004), medication (Tsuang et al., 2000; Woo & Crowell, 2005), and psychosocial interventions (Morisson et al., 2004; Klosterkötter, 2008).

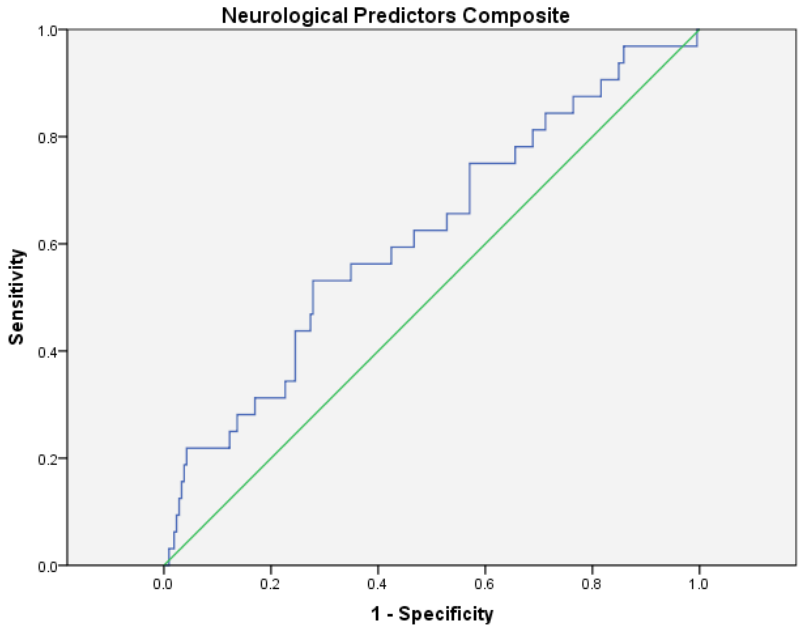
Although the benefits of early identification and intervention lead some researchers to sacrifice specificity for sensitivity, critics of treating at-risk youth point to such issues as medicating people who are not actually on a trajectory to develop schizophrenia as well as the stigma associated with a schizophrenia-spectrum diagnosis (Cornblatt et al., 2001). In addition, labeling one as mentally ill can frequently lead to adverse self-beliefs (Watson et al., 2007). These ethical issues, however, merely accentuate the importance of developing more accurate identification tools. The current

study highlights the importance of combining neurological variables to increase predictive power. In the ROC analysis, for example, the combination of neurological variables into a composite score outperformed any single predictor, drawing attention to the need for future screening tools that are more inclusive of many components of neurological dysfunction. Furthermore, this study demonstrated that the features used to distinguish schizophrenia from no mental illness are different from those used to differentiate between schizophrenia and other types of psychopathology, an issue that may have been obfuscated in studies that aggregated all psychopathology. In addition, future studies with larger sample sizes, may be able to better evaluate differences between "pure schizophrenia" development and those with schizophrenia-spectrum comorbid with other disorders, as comorbidity is associated with more impaired outcomes (Strakowski et al., 1993; Pallanti et al., 2004).

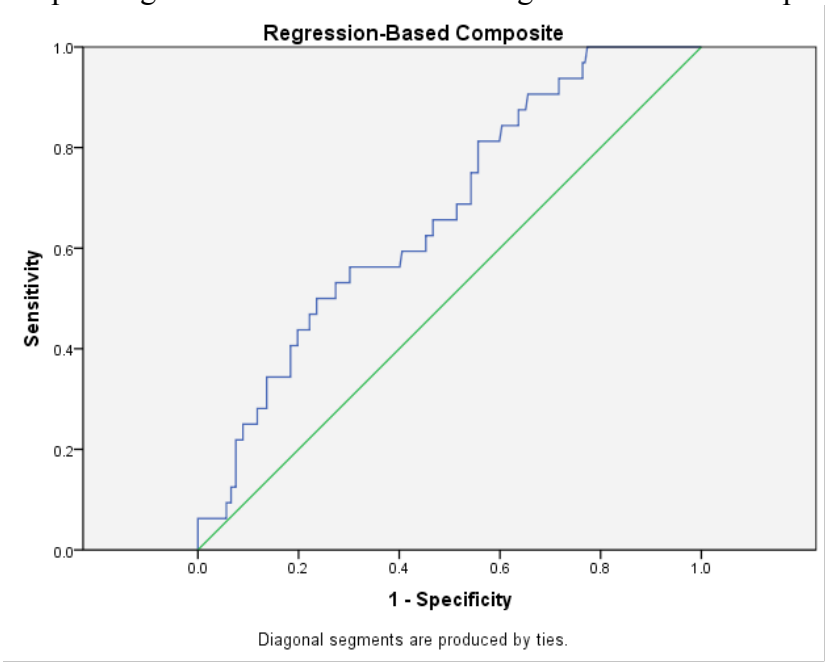
This study demonstrated the enhanced predictive power of combining genetic risk and neurological variables, yet even the most accurate analysis only correctly classified 65.6% of schizophrenia outcome cases. Notably, however, the neurological variables were most accurate in predicting outcome diagnoses when they were aggregated, rather than examined individually. As genetic and psychophysiological research methodology continues to develop, future studies will likely combine such findings with known neurological predictors to produce more concentrated identification and intervention.

APPENDIX A. Receiver Operating Characteristic Curves for Predicting Psychiatric Outcome based on Neurological Variables

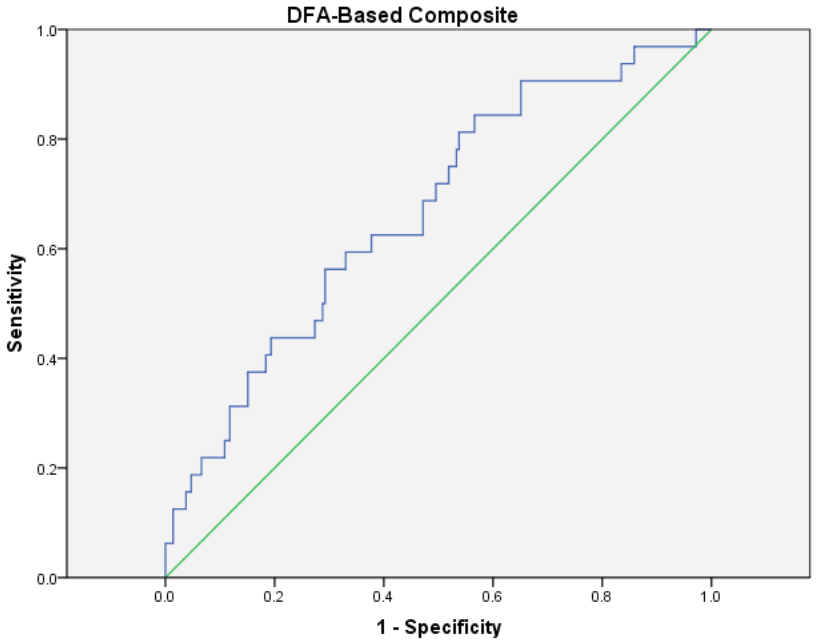
Receiver Operating Characteristic Curve for Neurological Predictors Composite Score



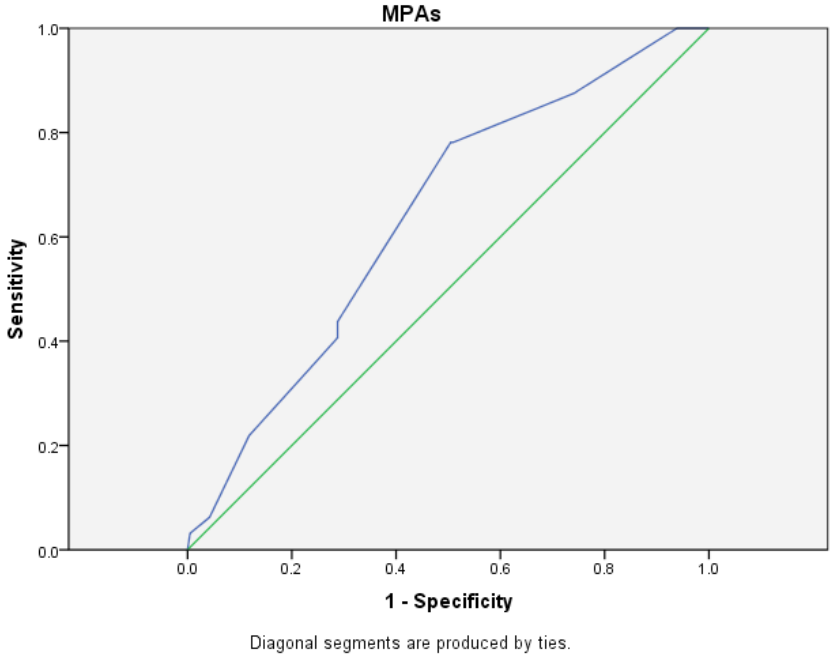
Receiver Operating Characteristic Curve for Regression-Based Composite Score



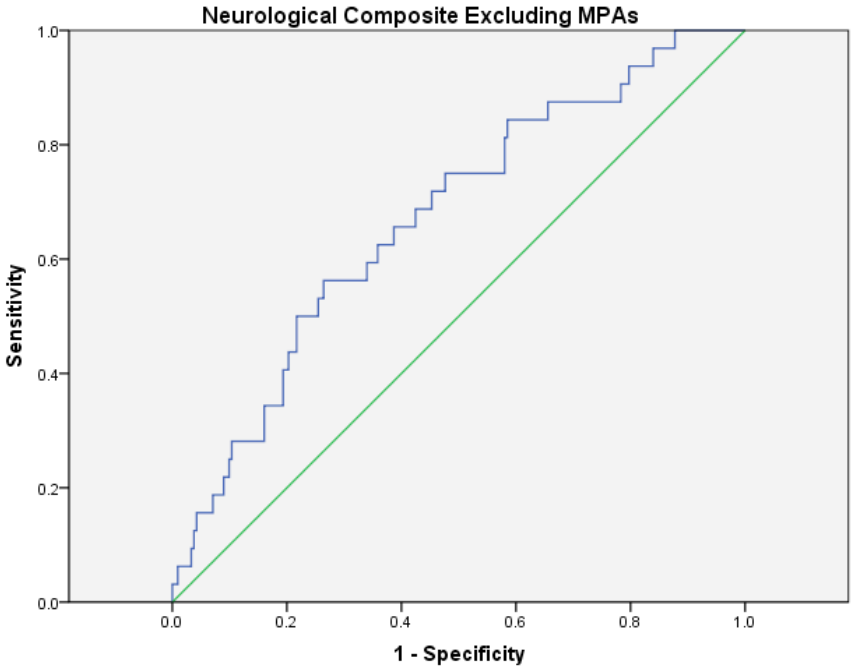
Receiver Operating Characteristic Curve for DFA-Based Composite Score



Receiver Operating Characteristic Curve for MPAs



Receiver Operating Characteristic Curve for Neurological Composite Score Excluding MPAs



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