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Movement Abnormalities in Youth at Clinical and Genetic Risk for Psychosis

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Abstract

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The link between movement abnormalities and psychotic disorders is presumed to reflect a common neural mechanism that influences both motor function and vulnerability to psychosis. However, it remains unclear how these movement abnormalities manifest in indivdiuals at clinical or genetic risk for schizophrenia-spectrum disorders. Examining movement abnormalities in at-risk populations enhances the potential to identify neural substrates that may be linked to etiology. The present study examined the nature and occurrence of movement abnormalties, as well as their associaton with prodromal symptoms, in youth at clinical risk for psychosis and patients with 22q11.2 deletion syndrome. The Structured Interview for Prodromal Symptoms (Miller et al., 2002) and the Dyskinesia Identification System (Kalachnik & Sprague, 1993) were used to assess prodromal symptoms and movement abnormalities in normal controls (NC; n=27), youth at clinical-risk (Prodromal; n=49), 22q11.2 deletion syndrome patients (22q11DS; n=31), and psyhiatric controls (OPD; n=30). Results showed that the 22q11 DS and Prodromal groups had elevated rates of movement abnormalities compared to the NC and OPD groups, with 22q11 DS exhibiting the most severe movment abnormalities. Results also revealed differing associations between movement abnormalities and prodromal symptoms. In the Prodromal group, movement abnormalities were positively correlated with negative symptoms, while in the 22q11 DS group movement abnormalties were positively correlated with positive symptoms. These findings suggest that movement abnormalities are elevated in at-risk populations and that both unique and shared neural mechanisms give rise to a partially overlapping phenotype.

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Movement abnormalities have long been observed in individuals with schizophrenia-spectrum disorders (Boks, Liddle, Burgerhof, Knegtering, & van den Bosch, 2004; King, 1954; Fish, 1997; Woods, Kinney, & Yurgelun-Todd, 1986). While the defining characteristics of the illness include deficits in cognitive and socioemotional functioning, movement abnormalities appear across the lifespan at an increased rate in a subgroup of the patient population. This rate is significantly elevated even in comparison to mood disorder patients, suggesting a diagnostic specificity that may relate to the pathophysiology of the illness itself (Kennard 1960; Woods et al. 1986). It is presumed that the presentation of both movement abnormalities and psychotic symptoms reflects a common neural mechanism that influences both motor function and vulnerability to psychosis (Cassidy 1998; Graybiel, 1997; Mittal & Walker, 2007; Walker, 1994). Movement abnormalities thus serve as external markers for underlying neural processes that may be linked to etiology. The examination of these abnormalities, particularly in at-risk populations, has the potential to provide insights into the neuropathophysiology of schizophrenia-spectrum disorders.

Recent studies have focused on movement abnormalities in individuals at clinical risk for schizophrenia and other Axis I psychotic disorders, in part because this minimizes the confound of antipsychotic medication and enhances the potential for identifying neural substrates. In particular, investigators have shown that movement abnormalities are observed in youth who meet criteria for schizotypal personality disorder and the ‘prodromal’ syndrome, both of which are associated with elevated risk for subsequent psychosis (Mittal, Dhruv, Tessner, Walder, & Walker, 2007; Mittal et al., 2007). Further, some recent reports have documented motor dysfunction in youth with 22q Deletion Syndrome (22q11 DS), a well-characterized genetic

disorder that confers heightened risk for schizophrenia (Bassett, Chow, Abdel-Malik, Gheorghiu, Husted, & Weksberg, 2003; Murphy & Owen, 2001).

The present study extends these lines of investigation, and examines the nature and occurrence of movement abnormalities in both 22q11 DS and youth at clinical risk for psychosis. The primary goals are to determine 1) whether 22q11 DS patients manifest an elevated rate of movement abnormalities when compared to healthy controls and those with other personality disorders, 2) whether 22q11 DS and youth at clinical risk for psychosis differ in the severity or nature of movement abnormalities, and 3) how movement abnormalities are linked with prodromal symptoms in these two groups.

Background

Movement abnormalities associated with schizophrenia have been apparent since the inception of the diagnosis. Kraeplin and other prominent clinicians of the late 19th and early 20th centuries frequently described abnormalities in movement among the patients they observed. Kraepelin (1919) detailed a "spasmodic phenomenon in the musculature of the face, distortions of the corners of the mouth, irregular movements of the tongue and lips, peculiar sprawling, and irregular choreiform movements." Meanwhile, Bleuler (1950) documented the presence of "tremors, quite similar to the coarse shivering of the feverish, which in the chronic patients arise quite independently of agitations, excitements and strains." The prevalence of such movement abnormalities led some early schools of psychopathology to create a "parakinetic" schizophrenia subtype characterized by unnatural and awkward movements. This subgroup was believed to have a distinct neuropathology that affected both motor and mental systems (Waddington, 1998). While motor research has not become a major line of investigation in the field, movement abnormalities remain an important clinical characteristic. Dyskinesias are the most common

category of movement abnormalities observed in the schizophrenia-spectrum. Although dsykinetic movements show some overlap with the motor dysfunction associated with Parkinsons and Huntingtons disease, these abnormalities are relatively unique to schizophrenia (Boks, Liddle, Burgerhof, Knegteng & van den Bosh, 2004; Woods et al., 1986). Table 1 provides descriptions of the most commonly observed movement abnormalities that have been documented in unmedicated patients with schizophrenia or other psychoses (Feen, Moussaoui, Hoffman, Kadri, Bentoousnssi, Tilane et al., 1996; Fenton, Wyatt, McGlashan, 1994; McCreadie, Thara, Kamath, Padmavathy, Latha, & Mathrubootham, 1996; Owens, Johnstone, Firth, 1982; Waddington, Youssef, 1990).

The most informative studies on movement abnormalities in schizophrenia come from unmedicated patients, as antipsychotics have a range of motor side effects. Numerous studies have reported elevated rates of movement abnormalities among unmedicated schizophrenia patients relative to the general population (Caligirui & Lohr, 1994; Casey et al. 1984; Dewey et al. 1997; Fenton 2000; Gervin et al., 1998; Ismail et al., 1998; Khor & Wyatt 1991; Puri et al., 1999). The rate of spontaneous dyskinesias in the general population is less than 1% (Chorfi & Moussaoui, 1985) while the rate is estimated to be between 14-15% in schizophrenia populations (Caligiuri et al., 1994; Cassady et al., 1998 Fenton et al., 1994; Hoffman et al., 1995). This is consistent with case records from the preneurolpetic era in which the rate of movement abnormalities in schizophrenia populations ranged from 15-28% (Fenton et al., 1994; Turner et al., 1989). In a review of neuromotor abnormalities, Marsden (1982) found that hyperkinesias seemed to be the most prevalent motor disturbance in schizophrenia patients. Hyperkinesias are of particular interest as they are associated with increased dopamine activity, which has been consistently implicated in psychotic symptoms. More specifically, the oral-facial region and

upper extremities have been reported to be the most affected by spontaneous dyskinesias (Gervin, Browne, Lane, Clarke, Waddington, Larkin, & O'Callaghan, 1998). Given that motor sub-circuits in the brain are topographically organized for different body regions, it is possible for movement abnormalities to be limited to specific areas. Spontaneous dyskinesias are present throughout the course of illness and have been found to increase with age in schizophrenia populations (Chorfi & Moussaoui, 1985; McCreadie & Ohaeri 1994; Owens, Johnston, & Firth, 1982). While there is a typical increase in the spontaneous movements that accompanies old age in normal populations, the increase is significantly more pronounced in elderly schizophrenia populations (Waddington & Youssef, 1990). Studies have also found that greater movement abnormalities are associated with a more severe illness course, including earlier onset of illness and poorer premorbid functioning (Walker, 1994). The consistent documentation of these movements in unmedicated patients suggests that these abnormalities are part of, or at least associated with, the schizophrenia syndrome in a subgroup of patients.

Premorbid Motor Abnormalities

Infancy and Childhood. While the studies described above indicate that movement abnormalities are present early in the course of illness, other research suggests they may precede the onset of clinical symptoms. Premorbid movement abnormalities have been documented as early as infancy, as well as in middle childhood, and adolescence (Walker, 1999). Walker et al.'s (1994) home video study revealed a higher rate of movement abnormalities in pre-schizophrenia infants and children when compared to their healthy siblings, with significant group differences in the first two years of life. Choreoathethoid movements and dystonic posturing were the most common abnormalities observed (Walker et al., 1994). High-risk infant offspring of biological

parents with schizophrenia have also been found to show developmental delays in motor function (Fish, Marcus, Hans, Auerbach, & Perdue, 1992; Hans & Marcus 1991). In fact, impaired motor coordination and delayed motor development have consistently discriminated between children at high and low "genetic risk" for schizophrenia (Hans & Marcus, 1991; Mednick & Silverton, 1988). Fish (1992) followed a group of infants born to mothers with schizophrenia, and found that those with greater delays in motor development during the first two years of life were more likely to be diagnosed with schizophrenia-spectrum disorders in adulthood. Subsequent longitudinal and prospective studies have shown that children who later develop psychotic disorders manifest a higher frequency of movement abnormalities beyond infancy (Bornblatt & Obuchowki, 1997; Schiffman, Walker, Ekstrom, Schulsinger, Sorensen, & Mednick, 2004). Though observable signs of motor dysfunction tend to be less pronounced in middle childhood Schiffamn and colleagues (2004) found a higher occurrence of movement abnormalities distinguished pre-schizophrenia children from normal controls at 11-13 years old. Taken together these studies suggest that movement abnormalities may reflect a constitutional vulnerability to schizophrenia that is present at birth.

Adolescence. In the past decade, systematic studies have examined the course of movement abnormalities in adolescents at risk for psychotic disorders. Adolescence is a particularly important developmental period because the prodromal signs of behavioral dysfunction that precede the onset of psychosis typically arise during this time (Niendam, Jalbrzikowski, & Bearden, 2009). Prodromal signs have been defined as subclinical manifestations of the perceptual, ideational, and behavioral symptoms of psychosis, and they are usually observed for months to several years before the clinical onset of psychotic symptoms (Yung & McGorry, 1996). Schizotypal personality disorder (SPD) is among the syndromes

included in standardized measures of prodromal syndromes. SPD is a DSM-IV-TR Axis II personality disorders with diagnostic criteria that range from suspiciousness, unusual perceptual experiences, social deficits, and eccentricies in behavior (Neumann et al., 1995). It is believed that SPD is on the spectrum and has been linked both genetically and developmentally to schizophrenia (Siever, Silverman, Horvath, Klar, Coccaro, Keefe, Pinkham, Rinaldi, Mohs, & Davis, 1990; Siever, Kalus & Keefe, 1993). Studies have shown that individuals with SPD manifest cognitive deficits (Raine & Mednick, 1995) and brain abnormalities (Cazzulo, Vita, Giobbio, Dieci, & Sacchetti, 1991) similar to those observed in schizophrenia patients. It is estimated that between 25-45% of individuals diagnosed with SPD in adolescence go on to develop schizophrenia in early adulthood (Miller et al., 2002; Yung, Phillips, Yuen, Francey, McFarlane, & Hallgren, 2003).

One of the most common measures of prodormal syndromes, the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan, 2001), also includes a syndrome labeled "Attenuated Positive Symptoms" (APS). APS is characterized by moderate severity of one or more of the following: unusual thought content/delusions, suspiciousness, grandiosity, perceptual abnormalities/hallucinations, and disorganized speech. It is the most common prodromal syndrome, and overlaps significantly with SPD, which is also considered a prodromal syndrome in youth. Studies of individuals who meet prodromal criteria manifest a rate of conversion to psychosis that ranges from 30%-40% within 2 years (Yung & McGorry, 1996; Yung et al., 1998). Thus, the prodromal period is a crucial developmental period that may shed light on the etiology of schizophrenia. The prodrome is also important for prospective studies, as prodromal symptoms increase in severity and frequency in a subgroup of high-risk individuals (Mittal et al., 2007). It is assumed that the heightened risk associated with this developmental period results,

in part, from neuromaturational processes that trigger the behavioral manifestations of latent vulnerability (Walker & Diforio, 1997).

Because the adolescent period is viewed as pivotal in the neuropathological process, researchers have begun to examine movement abnormalities in youth who manifest prodromal syndromes. In a study by Walker and colleagues (1999), raters coded movements from videotaped interviews with adolescents diagnosed with SPD. Movements were coded as involuntary if they occurred with no apparent intent (e.g. facial grimacing, writhing and alternating extensions, flexing or fingers or wrist) and as voluntary if the movement conveyed meaning or achieved a purpose (e.g., scratching, repositioning, gesturing). These movements were assessed in the head/face, trunk, arms, hands, fingers, legs, and feet. Compared with age-matched healthy controls, the SPD groups showed significantly higher frequencies of involuntary movements in the face, upper limbs, and trunk. In contrast, there were no diagnostic group differences in the rate of voluntary movements. This is consistent with previous literature on movement abnormalities in schizophrenia populations and suggests that involuntary movements may possess a diagnostic specificity (Marsden, 1982; Whitty, Owoeye, and Waddington, 2009).

In a similar study, Mittal and colleagues (2007) looked at movement abnormalities in adolescents with SPD. The Dyskinesia Identification System, a 15- item observational measure of abnormal movements, was used to code movement during videotaped clinical interviews. The SPD group exhibited significantly more movement abnormalities compared to the healthy control and other personality disorder group (which comprised adolescents with other personality disorders or conduct disorder). Specifically, movement abnormalities in the face and upper body regions were most prevalent. A longitudinal study of this sample found that, when controlling for baseline symptoms, baseline movement abnormalities predicated severity of prodromal

symptoms one year later, as well as conversion to Axis I psychotic disorders over a 3 to 4 year period (Mittal et al., 2007). Movement abnormalities in the face and upper body region were again the most significantly elevated and increased in frequency/ severity over time.

The mechanisms underlying the relationship between movement abnormalities and psychosis are of interest as the hypothesized neurocircuitry is implicated in both psychotic symptoms and dyskinetic movements (Gray, Kumari, Lawrence, & Young, 1999; Graybiel, 1997; Walker, 1994). Previous research suggests that movement abnormalities are associated with basal ganglia dysfunction and over activation of dopamine systems. More specifically, hyperkinetic movements have been found to reflect over activation of ascending dopamine pathways in the striatal pathways mediated by D2 receptors (Alexander, Crutcher, Delong, 1990; Smith, Devan, Shink & Bolam, 1998). Interestingly, striatal D2 receptor over activation has also been implicated in Axis I psychosis (Alexander at al., 1990). A striatal dopamine receptor abnormality, or disruption of the basal ganglia pathway, could result in the manifestation of both movement abnormalities and psychotic symptoms. Given the overlap in neural circuitry, it seems that movement abnormalities may originate from the same neural substrate or may be a consequence of the same etiologic agent (Walker et al. 1994)

Symptoms and Motor Abnormalities

Knowledge of the relation between movement abnormalities and clinical characteristics may help us better understand the biological underpinnings of the schizophrenia-spectrum. Positive and negative symptoms may be differentially associated with movement abnormalities, however the findings are not consistent. Negative symptoms and motor abnormalities have been associated in several studies. Fenton et al. (1994) reported higher rates of motor disturbances in

a sub-group of schizophrenia patients characterized by persistent, stable negative symptoms. In this subgroup 32% of the patients demonstrated spontaneous oral-facial dyskinesia, compared with only 8% in patients with a mixed symptom presentation. Patients with oral-facial dyskinesias had more severe negative symptom scores on the Positive and Negative Symptom Scale (PANSS). They were also more symptomatic at follow up 23 years later. Similarly, McCreadie et al. (1996) found that dyskinesia in elderly schizophrenic patients was associated with greater negative symptoms scores on the PANSS. Neumann and Walker (2003) found that motor functioning was associated with negative symptoms in adolescents with SPD. Specifically, greater motor force and force instability, both of which appear to be sensitive and specific characteristics of schizophrenia, were significantly associated with negative symptoms. Interestingly, in a previous study Neumann and Walker (1995) found that neuromotor dysfunction in preschizophrenia children was significantly related to early childhood withdrawal behavior, and less related to thought problems.

However, a number of studies have reported an association between movement abnormalities and positive symptoms (Caligiuri, 1994; Caligiuri, 1993; Cassady et al. 1998; McCreadie, 1994). Cassady et al. (1998) found that global dsykinetic scores were significantly associated with positive symptoms scores derived from the Structured Interview for DSM-III Personality Disorders. The association remained significant even after age, gender, and history of depression were entered as covariates. Caligiuri et al. (1993) found a positive association between severity of motor rigidity and severity of positive symptom subscale scores on the Brief Psychiatric Rating Scale (BPRS). It is possible that the differences in study findings reflect developmental changes in the nature of the associations between movement abnormalities and

symptoms. Further research is needed to better understand the association, particularly in high-risk populations.

Genetic High-Risk Group

22q11.2 Deletion Syndrome. As noted above, the 22q11.2 deletion syndrome is a genetic disorder that confers heightened risk to schizophrenia. The syndrome is caused by a deletion of approximately three million base pairs (30 to 40 genes) on one copy of chromosome 22. While 22q11 DS is autosomal dominant, meaning the phenotype is expressed in those who have inherited only one copy of a particular gene mutation. However, the majority of cases are a result of spontaneous genetic mutations. The disorder occurs in 1 out of every 4,000 births, making it the most common chromosomal deletion syndrome in humans (Devriend, Fryns, Mortier, van Thienen, & Keymolen, 1998; Wilson, 2004). The clinical manifestations are highly variable but typically include congential heart defects, palate malformations, immune deficiency, learning disabilities, and range of psychiatric phenotypes (Antshel, Aneja, Strunge, Peebles, Fremont, & Stallone, 2007; Gothelf, Feinstein, Thompson, Gu, Penniman, & van Stone, 2007). Schizophrenia is the most prevalent psychiatric disorder in adults with 22q11 DS. Studies have reported that 30% of adults with 22q11 DS meet criteria for schizophrenia (Bassett et al., 2005; Murphy et al., 1999). Given the genetic risk, symptoms of psychosis have been assessed in individuals with 22q11 DS, and it is reported that 14-48% of adolescents with 22q11 DS experience positive psychotic symptoms (Baker & Skuse, 2005; Debbane, Glaser, & David, 2006; Feinstein, Eliez, Blasey, & Reiss, 2002; Vortsman, Morus, Duijff, Klaassen, Heinemen-de Boer, & Beemer, 2006). In a recent report by Stoddard and colleagues (2010), adolescents with 22q11 DS were assessed for sub-clinical psychotic symptoms using the Structured Interview for

Prodromal Symtoms (SIPS). The SIPS directly assesses attenuated symptoms that are reliably associated with increased clinical risk for schizophrenia. In the sample of 22q11 DS, 45% of the individuals experienced positive symptoms that rated in the "moderate" to "severe and psychotic" range and almost all presented with moderate to severe symptoms in the negative, disorganized, and general symptom categories. Additionally, 35% reported motor disturbances.

22q11 DS appears to be more common in individuals with schizophrenia relative to the general population. While 22q11 DS tends to occur in 1 in 4000 live births in the general population, the deletion syndrome can be found in 1 in 100 individuals with schizophrenia, an 80-fold increase in prevalence (Bassett & Chow, 2008; Horowitz, Shifman, Rivlin, Pisante, & Darvasi, 2005; Karayiorgou, Morris, Morrow, Shprintzen, Goldberg, Borrow, Gos, Nestadt, Wolyniec, & Lasseter, 1995). Additionally, individuals with schizophrenia and 22q11 DS do not differ from idiopathic cases in age of onset, symptoms profiles, or medication responses (Basset et al. 2003). It is clear that there is a significant association present in the two clinical syndromes.

22q Deletion Syndrome and motor functions. Previous studies have reported deficits in the acquisitions of gross motor skills (e.g., crawling and walking independently) and problems with balance and coordination in 22q11 DS children (Gerdes et al., 2001; Oskarsdottir, Belfrage, Sandstedt, Viggedal, & Uvebrant, 2005; Swillen, Devriendt, Leguis, Vogels, Ghesquiere, & Frynes, 1999). Available studies have used a number of standardized testing measures to assess gross motor skills, dexterity and balance (Oskarsdottir et al., 2005; Sobin et al., 2006; Swillen et al., 2005). Swillen et al. (1999) found that children with 22q11 DS scored significantly lower than controls on the Peabody Developmental Motor Scales. The greatest motor deficits were on the locomotion and stationary subtests, which measure the ability to sustain balance and coordinate movements. Van Aken and colleagues (2007) found that children with 22q11 DS

scored significantly lower on the motor coordination and manual dexterity subtests of the Beery-Buktenica Visual-Motor Integration Test (Beery VMI). The Beery VMI assesses balance, bilateral coordination, upper limb coordination, reaction speed, and dexterity. When given the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP), a directly administered measure of fine and gross motor skills, the 22q11 DS youth once again showed significant deficits in motor functioning (Van Aken et al., 2007). While motor deficit seems to be associated with the 22q11 DS neuropychological profile, to our knowledge no studies of 22q11 DS patients have assessed the types of dsykinetic movement abnormalities commonly observed in schizophrenia (e.g., hyperkinsesias, choreoathoid movements, dystonic posturing).

Goals of the Present Study

Available evidence suggests that populations at risk for schizophrenia have increased rates of motor abnormalities. Both prodromal and 22q11 DS patients are at heightened risk for schizophrenia and other psychotic disorders, suggesting a shared neural vulnerability. Although it is well established that movement abnormalities are associated with risk for psychotic disorders, they have not been examined in patients with 22q11 DS. The present study will test the following hypotheses: 1) using a standardized measure of movement abnormalities, 22q11 DS patients will manifest an elevated rate of movement abnormalities in the upper limbs and oral-facial region when compared to healthy controls, and 2) in both 22q11 DS and youth with prodromal syndromes, the rate/severity of movement abnormalities will be positively correlated with negative symptom severity. In addition to testing these hypotheses, the diagnostic group differences in the severity and nature of movement abnormalities will be examined.

Method

Participants

Prodromal sample. The Prodromal sample consisted of 49 individuals ranging from 11 to 18 years of age. Participants were recruited for a longitudinal study of at-risk adolescents conducted at Emory University. Recruitment announcements described prodromal symptoms in lay terminology and were published in Atlanta newspapers and parenting magazines.

22q11 DS sample. The 22q11 DS sample consisted of 31 individuals ranging from 8 to 29 years of age. Participants were obtained from a case registry of Fluorescence In Situ Hybridization (FISH) confirmed cases maintained at Children's Healthcare of Atlanta. Each individual had previously been referred as either a child or adolescent, due to a presence of heart defect, speech and language difficulties, and/or immunological problems.

NC & OPD Controls. Participants for the normal control (NC) group and other personality control (OPD) group were recruited through the Emory University Research Participant Registry. These groups were selected to be comparable to the Prodromal group in age, educational level, ethnic composition, and sex ratio. The NC group consisted of 27 participants who had no Axis II diagnoses. The OPD group was composed of 30 participants, who met criteria for one or more Axis II diagnosis or conduct disorder (schizoid: n=3, antisocial: n=2, borderline: n=4, narcissistic: n=3, avoidant: n=1, obsessive compulsive: n=3, conduct disorder: n=14). Demographic and clinical characteristics for the four groups are presented in Table 2.

Written consent was obtained from all participants and a parent, in accordance with the guidelines of the Emory University Human Subjects Review Committee. Exclusion criteria were neurological disorders, mental retardation, substance abuse or addiction, or current Axis I

disorder as described in the *Diagnostic and Statistical Manual of Mental Disorders*, with the exception of learning disorders, attention-deficit hyperactivity disorder, and other disruptive behavior disorders. The latter disorders have a high rate of comorbidity with psychosis (Schaeffer & Ross, 2002).

Measures

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). The SCID-I (Spitzer, Williams, & Gibbon, 1994) is a comprehensive assessment of symptom criteria for DSM-IV Axis I disorders (APA, 2000). Shown to have a good interrater reliability when used with adolescents (Martin, Pollock, Bukstein, and Lynch, 2000).

Structured Interview for DSM-IV Personality Disorders (SIDP-IV). The SIDP-IV (Pfohl et al., 1997) is a semi-structured interview that assesses DSM-IV Axis II criteria using questions about relationships, interests, activities, and emotions. Interviewers rate personality disorder criteria on a scale from 0 (not present) to 3 (strongly present). This measure emphasizes trait functioning, states, moods, or behaviors induced by an external stimulus. The semi-structured interview, taking between 60 and 90 minutes to complete, includes a portion of the measure that allows interviewers to rate clinical observations of each participant. Because of the one-to-one correlation between the SIDP-IV and the DSM-IV criteria, it is assumed to be a valid measure of personality disorders.

Structured Interview for Prodromal Syndromes (SIPS). The SIPS (McGlashan et al., 2001) is a semi-structured diagnostic interview containing a severity scale designed to define and diagnose prodromal states. The SIPS is modeled after the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) and includes 29 items that are organized into four

symptom scales: positive, negative, disorganized, and general symptoms. The positive symptom scales include items that assess unusual thought content, delusional ideas, suspiciousness, persecutory ideas, and grandiosity. The negative symptom scale includes items measuring social isolation or withdrawal, avolition, decreased expression of emotion, decreased experience of emotions, decreased ideational richness, and deterioration of role functioning. The disorganized symptom scale includes items assessing odd behavior or appearance, bizarre thinking, trouble with focus and attention, and impairment in personal hygiene and social attentiveness. The general symptom scale includes ratings on sleep disturbance, dysphoric mood, motor disturbances, and impaired tolerance to stress. Scores range from 0 to 6, and scores of 0-2 are considered to be non-prodromal. Individuals with scores falling between 3 and 5 are in the prodromal category, and scores of 6 are in the psychotic category (Miller et al., 1999).

Dyskinesia Identification System: Condensed User Scale (DISCUS). The DISCUS was empirically developed and is used to code involuntary movements (Kalachnik & Sprague, 1993). The measure contains 15 items that are rated on a 0-4 scale ranging from absent to severe. Movements were coded as involuntary if they occurred with no apparent intent or goal. The DISCUS was chosen because it yields high interater reliability (>.90) for both mentally ill and non-psychiatric subjects. The measure also provides separate indexes for three different body regions: facial (tics; grimace; blinking; chewing or lip smacking; puckering, sucking, or thrusting out of the lower lip; tongue thrusts; tonic tongue; tongue tremor, athetoid, mykymic, or later tongue), upper body (retrocollis or torticollis, shoulder or hip torsion, athetoid or myokymic finger-wrist-arm movements, pill rolling, writhing, and alternating extensions and flexions of the fingers or write), and lower body (ankle flexion or foot tapping, toe movement).

Procedures

Diagnostic status. A battery of diagnostic measures was administered to all participants in a clinical interview. Interviews were conducted by advanced psychology doctoral students or licensed psychologists. Interviewer training was conducted over a 2-month period, and inter-rater reliabilities exceeded the minimum study criterion of kappa equal or greater than 0.80. All interviews were videotapes and reviewed to confirm diagnostic reliability.

Coding of movement abnormalities. Following the procedures used in previous motor research (Walker et al., 1999) raters coded motor behavior from videotapes of participants made during the clinical interview. Interviews were conducted in private rooms, and the participant was videotaped while sitting in a chair facing a wall-mounted camera. The chair was positioned so that the participant's entire body was visible on tape. A total of 45 minutes were coded from each videotape. Raters were blind to the participant's diagnostic status. Research assistants were trained in the application of the coding procedures over a one-month period using tapes of non-participants. Coding of the participant tapes began after all pairs of raters had achieved a minimum inter-rater reliability of .80 for coding each body region and movement types in a 6-min segment. The mean reliability at the end of the training period was .86, raging from .72 to .95 across body regions.

Statistical Analyses. All analyses were performed using SPSS 17.0 (Mac). Demographic and clinical variables were examined using basic descriptive statistics to determine central tendency and variability. Analysis of covariance (ANCOVA) was used to assess group differences in movement abnormalities and prodromal symptoms. To determine the association

between movement abnormalities and symptomology a Pearsons product moment correlation was conducted.

Results

Preliminary Analyses

Preliminary analyses were conducted to test for demographic differences among diagnostic groups and potential covariates. Demographic and clinical characteristics are presented in Table 2. There were no significant differences in sex or race distributions across the four diagnostic groups. One-way ANOVA showed that the diagnostic groups differed significantly on age [$F(3, 133) = 22.6$, $p < 0.001$], with the 22q11 DS participants being significantly older (there were no age differences between the NC, OPD, and Prodromal groups). Chi-squared analyses showed that the diagnostic groups differed significantly on medication status for stimulants ($\chi^2(1) = 60.9$, $p < 0.001$), antidepressants ($\chi^2(1) = 90.9$, $p < 0.001$), and antipsychotics ($\chi^2(1) = 106.6$, $p < 0.001$). Subsequent analyses were therefore conducted including age and medication status as a covariate

Analyses were also conducted to examine the distributions of the continuous variables to ensure that assumptions of parametric statistical procedures were satisfied. Box plot-graphs revealed significant positive skew across a number of clinical variables including symptom ratings of disorganized symptoms, and general symptoms as well as all five motor domains. It is expected that clinical variables of this nature tend to be positively skewed (i.e. more individuals fall within a normal range of scores, whereas fewer individuals fall within a more extreme range of scores). A log transformation was applied to each clinical variable to correct for the violation of normality. Box plot-graphs of the transformations showed that the new variables more closely approximated a normal distribution.

Diagnostic Group Differences in Movement Abnormalities

Table 3 presents means and standard deviations for movement abnormalities by body region for each diagnostic group; Figures 2 and 3 illustrate group mean differences. As expected, the Prodromal and 22q11 DS groups had significantly higher rates/severity of movement abnormalities across all body regions compared to the NC and OPD groups. Chi-squared analyses were used to examine diagnostic group differences in movement abnormalities by body region. The results supported an overall significant difference in movement abnormalities among the diagnostic groups (χ^2 (3) = 8.72, p = .033). Results showed significant differences in each body regions; oral-facial (χ^2 (8) = 670.1, p≤ 0.001), ocular (χ^2 (4) = 481.3, p≤ 0.001), lingual (χ^2 (3) = 384.2 , p≤ 0.001), head-neck-trunk (χ^2 (5) = 565.9, p≤ 0.001), and upper limb regions (χ^2 (7) = 208.0 , p≤ 0.001).

Diagnostic Group Differences in Prodromal Symptoms

ANCOVA with age and medication as covariates were used to test for diagnostic group differences in the four symptom domains. Table 3 presents means and standard deviations by symptom domain for each diagnostic group; Figure 1 illustrates group mean differences. Results indicated an overall significant difference among the diagnostic groups for global symptom severity [F(3,127) = 39.3, p≤ 0.001], with a large effect size for the difference between groups (partial η^2= 0.48). Table 4 shows the univariate results, which revealed that the four diagnostic groups differed significantly on positive symptoms [F(3,129)=45.8, p≤ 0.001], negative symptoms [F(3,128)=21.1, p≤ 0.001], disorganized symptoms [F(3,129)= 23.5, p≤ 0.001], and general symptoms [F(3,129)=16.2, p≤ 0.001]. Post hoc tests were conducted to compare

diagnostic groups. The Prodromal group had significantly more severe positive symptoms compared to the 22q11 DS, NC, and OPD groups. Conversely, the 22q11 DS group had more severe negative symptoms relative to the SPD, NC, and OPD groups. The 22q11 DS and Prodromal groups also had more severe disorganized and general symptoms compared to the NC and OPD groups. There were no significant differences between the NC and OPD group in any symptom domain.

Associations between Movement Abnormalities and Prodromal Symptomology

Pearson's product moment correlations were used to examine the association between movement abnormalities and symptom domains using one-tailed tests. The entire sample of participants were included in the initial analysis and then separated by diagnostic subgroups. The results are summarized in Table 5. As shown, there are significant positive correlations between DISCUS movement scores for all body regions and symptom ratings for positive, negative, disorganized, and general symptom composites. When the diagnostic groups were examined overall movement in the NC group was positively correlated with negative, general, and disorganized control. Overall movement in the Prodromal group was positively correlated with negative and general symptoms. Conversely, overall movement in the 22q11 DS group was positively correlated with positive symptoms, but only a trend in this direction was observed for the Prodromal group. In the NC groups, movement abnormalities in the oral-facial and ocular region were positively correlated with both negative and disorganized symptoms. Movement abnormalities in the upper limbs were positively correlated with disorganized and general symptoms. In the Prodromal group movement abnormalities in the oral-facial and upper limbs region were positively correlated with negative symptoms. Movement abnormalities in the head-

neck-trunk regions were positively correlated with all four symptom domains. In the 22q11 DS group, movement abnormalities in the oral-facial and ocular region were positively correlated with positive symptoms. Movement abnormalities in the head-neck-trunk region were negatively correlated with general symptoms. Finally, in the OPD group movement abnormalities in the upper limbs were positively correlated with negative and general symptoms.

Correlations among movement scores in specific body regions were conducted for the entire sample. Spearman correlations revealed a positive association between oral-facial regions and upper limb movements (r= .334 , $p \leq 0.001$). The oral-facial region also showed positive associations with ocular (r=.398, $p \leq 0.001$), lingual (r=.341, $p \leq 0.001$), and head-neck-trunk (r=.312, $p \leq 0.001$) movements. Additionally, the upper limb region was positively associated with both lingual (r=.296, $p \leq 0.001$) and head-neck-trunk (r= .274, $p \leq 0.001$) movements. The lingual region and head-neck-trunk were also positively associated (r= .319, $p \leq 0.001$). Taken together, this pattern of findings supports the notion that movement abnormalities in different body regions share some neural mechanisms.

Discussion

The present study examined movement abnormalities in individuals with 22q11 DS and youth at clinical risk for psychosis. Both of these diagnostic groups have been shown to be risk syndromes for psychotic disorders (Basset et al., 2003; Siever et al., 1990). Examining the nature and severity of movement abnormalities in these populations has the potential to shed light on underlying neuropathophysiology that may be linked to the etiology of one or more subtypes of schizophrenia-spectrum disorders. The results indicate that both the 22q11 DS and Prodromal groups manifest elevated rates of movement abnormalities across various body regions, with

22q11 DS exhibiting the most severe abnormalities. Interestingly, the pattern of associations between prodromal symptomatology and movement abnormalities differs between the two groups.

Presence of Movement Abnormalities in 22q11 DS

The first aim of the present study was to determine whether patients with 22q11 DS manifest elevated rates of movement abnormalities when compared to healthy controls and other personality disorders. The literature on 22q11 DS motor dysfunction is sparse, and available studies have focused primarily on indexes of dexterity, coordination, reaction speed, and balance (Sobin et al., 2006; Swillen et al. 1999; van Aken et al., 2007). To date, no studies have examined dyskinetic movements. However, given that 22q11 DS increases risk for what may be a homogenous genetic subtype of schizophrenia, it is expected that these patients will exhibit movement abnormalities similar to those observed in the prodromal phases of psychosis. Therefore, it was hypothesized that 22q11 DS patients would manifest elevated rates in the oral-facial and upper limbs regions. As mentioned previously, these body regions have consistently exhibited the most significant rates of movement abnormalities in both adolescents with prodromal syndromes and unmedicated schizophrenia populations (Gervin et al., 1998; Mittal et al., 2007). The present results fully supported the hypothesis, as individuals with 22q11 DS had significantly elevated rates of movement abnormalities. For each body region the 22q11 DS group had the highest mean scores. Additionally, the 22q11 DS group showed significantly higher scores than the NC and OPD group across all body regions. These findings indicate that dsykinetic movements are a part of the 22q11 DS motor profile. This clinical characteristic is an

important addition to the 22q11 DS literature given that movement abnormalities may reflect neuropathology intrinsic to the pathogenesis of some schizophrenia-spectrum disorders.

Nature and Severity of Movement Abnormalities in Diagnostic Groups

Another aim of the study was to determine whether individuals with 22q11 DS and youth at clinical risk for psychosis differ in the nature or severity of movement abnormalities. While movement abnormalities have been documented in adolescents with SPD (Mittal et al., 2007; Neuman & Walker, 2003; Walker 1999), it is unclear how movement abnormalities compare in the two risk syndromes. The results showed that the 22q11 DS and Prodromal groups manifested significantly elevated rates of overall movement abnormalities in comparison to the NC and OPD groups. However, as noted above the 22q11 DS group consistently had higher movement abnormality scores across all body regions. The nature and severity of movement abnormalities for each body region differed between the risk groups. In the 22q11 DS group, the oral-facial, followed by the upper limbs region had the highest rates of movement abnormalities. In the Prodromal group the upper limbs had the highest rate of movement abnormalities. The oral-facial, head-neck-trunk, and ocular followed, and were all in a close range. Taken together, the overall findings are in line with our expectations, given the nature of the neural circuitry associated with the facial and upper body regions.

The motor circuits underlying the facial (oral-facial, ocular, lingual) and upper body regions involve a great degree of complex coordination with structures that have been implicated in psychosis. For example, these circuits tie into the cerebral cortex, thalamus, and basal ganglia (Mittal et al., 2010; Nesvag et al., 2008). These regions have all been implicated in schizophrenia pathology and show morphological abnormalities in patient populations (Graybiel, 1997; Kuperberg et al., 2003; Nesvag et al. 2008;). More specifically, the basal ganglia and thalamic

connections also have a key role in a wide range of cortical and subcortical interactions (Pappa & Dazzan 2009). Consequently, disturbances in these regions and associated pathways (cortico-striato-pallido-thalmic) could cause dysfunction in perception, attention, affective regulation, and information processing, as well as motor disturbances (Licher & Cummings, 2001; Pappa & Dazzan, 2009). Some researchers have suggested that malfunctions associated with the corti-striato-pallido-thalamic pathway are responsible for positive and negative symptoms (Gray, Humari, Lawrence, & Young, 1999; Graybiel 1997). More specifically, the ventromedial and adjacent areas of the putamen have been shown to mediate the facial and upper limbs regions. Interestingly, in a recent study Mittal and colleagues (2010) found that decreased putamen volume was associated with hyperkinetic movements in participants with a prodromal syndrome. Participants who converted over a 2-year follow-up period showed significantly smaller volumes and a trend towards elevated dsykinetic movements compared to those who did not convert. In the present study, the elevated movement scores in the facial and upper body regions in both the 22q11 DS and Prodromal groups suggest a shared underlying neuropathology. As noted above, this pathology likely involves complex interactions between motor and nonmotor circuits that have the potential to manifest in both dsykinetic movements and prodromal symptoms.

Association Between Movement Abnormalities and Symptomology

The third aim of the study was to examine how movement abnormalities are linked with prodromal symptoms in 22q11 DS and youth at clinical risk for psychosis. Research on the relationship between movement abnormalities and symptoms have been relatively mixed. Specifically, some studies reveal that only negative symptom severity is associated with movement abnormalities while others have found that only positive symptom severity is

associated with movement abnormalities (Caligiuri, 1994; Cassady et al., 1998; Fenton 1994; Neuman & Walker, 2003). In one study both positive and negative symptoms are associated with movement abnormalities (Neumann & Walker, 1999). However, these mixed findings may be a result of patient population differences and/or treatment effects in the course of illness at time of data collection.

Based on previous findings in at-risk populations, it was hypothesized that in both the 22q11 DS and Prodromal groups the rate/severity of movement abnormalities would be positively correlated with negative symptom severity. Interestingly, this hypothesis was only partially supported. In the Prodromal group, overall movement severity was positively correlated with negative symptoms. Movement abnormalities within each body region yielded slightly varied symptom associations. The oral-facial and upper limbs were significantly correlated with negative symptoms while the head-neck-trunk was correlated with all four symptom dimensions. The general findings in the Prodromal group were, therefore, in line with our expectation and consistent with previous reports (Mittal et al., 2007).

Conversely, in the 22q11 DS group overall movement was correlated with positive symptoms. The oral-facial and ocular regions were positively correlated with positive symptoms, while the head-neck-trunk was negatively correlated with general symptoms. The nature of the items in the general symptoms scale, especially the mood symptoms, may be implicated here, as movement abnormalities have not been found to be associated with mood symptoms (Woods et al., 1986). The findings for the 22q11 DS group did not support our hypothesis and raise a number of questions in regards to shared neural substrates. It should also be noted that in the normal control group overall movement was positively correlated with the disorganized, general and negative symptoms. Thus, even at the lower end of the range of symptom severity and

movement abnormalities, the associations tend to be positive. There were no significant correlations in the OPD group.

Potential mechanisms linking movement abnormalities and prodromal symptoms.

Taken together the results suggest that the two diagnostic groups have both shared and unique abnormalities in brain function that give rise to phenotypes that are only partially overlapping. It is possible that individuals with 22q11 DS have more pronounced movement abnormalities because the deletion results in additional dysfunction in brain regions linked to motor behavior. Previous research has documented widespread brain anomalies in the frontal cortices, cingulated gyrus, pons, and cerebellum of 22q11 DS patients (Bishet al., 2006; Eliez, Schmitt, White, Wellis, & Reiss, 2001; Shashi et al. 2010;). While these anamolies may contribute to some unique motor behavior in 22q11 DS, there is also evidence of related pathophyisological processes underlying the movement abnormalities in the two groups. Individuals with 22q11 DS and youth at clinical risk may have similar striatal brain abnormalities and/or hyperdopaminergic transmission that contribute to elevated levels of dyskinesias and prodromal symptomatology.

Basal ganglia dysfunction has been implicated in psychosis and has also been reported in both 22q11 DS and clinically-at risk populations (Campbell et al., 2006; Delong & Wichman 2007; Keshaven et al., 1998; Lawrie et al., 2001). It is crucial to consider the basal ganglia structures as part of a larger, more complicated system. The basal ganglia constitutes an important forebrain system that collects signals from the entire cerebral cortex (sensory, association, motor, and limbic areas), redistributes respective signals, and send outputs back to the frontal lobes through the thalamus (Draganski et al., 2008; Mehler-Wex et al., 2006; Pappa & Dazzan, 2009). Therefore, the basal ganglia is involved in a number of cortical and subcortical

interactions. Additionally, the basal ganglia is comprised of subcortical nuclei that include the caudate and putamen (which together make up the striatum). The caudate is thought to play a role in cognitive function, the ventral striatum is involved in reward and reinforcement, and the putaman is known to be important for motor control. The connectivity between these structures and the cortex, could underlie psychotic symptoms and could also be the substrate for movement abnormalities.

This type of basal ganglia dysfunction has the potential to underlie both of the risk syndromes in the present study. Campbell and colleagues (2006) found that severity of schizotypy scores positively correlated with gray matter density in the basal ganglia of children and adolescents with 22q11 DS. Meanwhile, neuroimaging studies on drug-naïve schizophrenia patients and high-risk individuals have shown a reduced size of basal ganglia structures compared to healthy controls (Keshaven et al., 1998; Lawrie et al., 2001). Basal ganglia dysfunction has also been reported in adolescents with SPD (Delong & Wichman 2007). It is important to consider the role of neurotransmitters in subcoritcal pathways. For example, it has been found that discrete connections between the basal ganglia and cerebral cortex reciprocally interconnect with a diverse set of cortical areas that are regulated by dopamine (Delong & Wichman, 2007). Specific alterations in dopamine neural activity, particularly in frontal-striatal regions, may also play a role in the presentation of prodromal symptoms and movement abnormalities (Caligiuri et al., 1993).

Dopamingeric pathology is assumed to play a role in the pathophysiology of schizophrenia-spectrum disorders (Klawans 1988, Wang & Goldman-Rakic 2003; Howes & Kapur, 2009). It has been implicated in the presentation of both psychotic symptoms and movement abnormalitie. Disrupted dopamingeric neurotransimssion has been documented in

both clinically at-risk populations and 22q11 DS. For example, Howes et al. (2009) found that elevated striatal dopamine uptake predates the clinical onset of psychotic symptoms in prodromal patients. The dopamine levels of the prodromal patients approached those seen in schizophrenia populations. Research on 22q11 DS patients has also revealed dopamine elevations. In 22q11 DS, COMT (catecho-o-methyltransferase) is among the genes in the deleted region. The haplosufficency of COMT is hypothesized to result in low enzyme activity and high dopamine levels (Duham et al., 1992; Graf et al., 2001; Gothelf et al., 2005). Boots et al. (2008) examined neuro-endocrine and peripheral dopamingeric markers at baseline and following an acute dopamingeric depletion challenge in adults with 22q11 DS and healthy controls. The results showed that 22q11 DS individuals had disrupted dopamingeric activity resulting in elevated levels. There is limited data available on dopamine transmission in the striatum, as indexing this requires PET with administration of ligands. However, using PET, Boots and colleagues (2010) found that striatal dopamine transmission is not dysfunctional in individuals with 22q11 DS. But these results should be evaluated with caution, given a small sample size (n= 12). In summary, there are complex and diverse mechanisms of dopamine transmission in cortical and subcortial regions of the brain. Additional research and replication of dopamine transmission in the striatal region and D2 receptor binding is needed for both risk populations. However, the available literature suggests that dopamine dysfunction, particularly in striatal regions, has the potential to underlie both vulnerability to psychosis and manifestation of movement abnormalities.

It is also important to consider the findings in light of the developmental trajectory. The age differences between the two risk groups may have important implications for movement abnormality severity and symptomology. The two diagnostic groups are at different points of the developmental trajectory, with the 22q11 DS group much closer to the age of clinical onset. If

psychotic symptoms and movement abnormalities are presumed to reflect a shared neural mechanism, we would except more severe movement abnormalities to accompany more severe symptoms. Consistent with this, in the present study the 22q11 DS group had higher overall prodromal symptom severity, as well as higher movement abnormality scores. It may be that closer proximity to age-of onset is associated with greater neural dysfunction that is reflected in both motor and symptom severity.

Another consideration is the composition of the two diagnostic groups. The 22q11 DS is a relatively homogenous group. While there is a wide range of phenotypes associated with the disorder, the genetic deletions that characterize the group are consistent in certain chromosomal regions. In comparison, the Prodromal group represents individuals with similar phenotypes, but likely varied etiological determinants and some false positives. It is possible that the relative rates of movement abnormalities in other Prodromal samples will differ. Given previous findings (Mittal et al., 2007; Neumann & Walker 2003), it is expected that samples of youth at clinical-risk will still show elevated rates of movement abnormalities. However, the severity may vary depending on the make-up of the sample. This is important to consider when making direct comparisons between the Prodromal and 22q11 DS groups.

Limitations and Future Directions

The present study was limited by modest sample size and a cross-sectional design. Future studies should focus on longitudinal studies of these two risk groups, particularly 22q11 DS. Examining longitudinal changes in the nature and associations of movement abnormalities and symptoms will add to conceptualizations of etiology. A longitudinal design may also clarify if age and proximity to clinical-onset influence movement and symptom associations. Additionally,

a follow-up study that addresses conversion to psychosis in the two groups would help determine the predictive power of movement abnormalities and their relation to psychosis vulnerability.

Age differences may also pose a limitation, as the 22q11 DS group was significantly older. Because of the inherent challenges in ascertaining patients with 22q11 DS, a relatively rare disorder, limiting the age range would further compromise recruitment, so age could not be readily controlled. While the statistical analyses controlled for age, future studies of large samples may allow for an examination of age effects and developmental processes with greater statistical power. Medication status was also a potential limitation. Although there were no differences in results when medication was covaried, the motor side effects associated with antipsychotic and stimulant use nonetheless pose potential confounds.

Conclusions

The present study examined the association between movement abnormalities and prodromal symptoms in two diagnostic groups, both of which show increased risk for psychosis. The results add to a growing body of literature that suggests a relationship between movement and symptoms, particularly in the pre-onset period. Further, the study provides evidence that dyskinetic movements may be an important characteristic of the 22q11 DS profile and may be linked with an elevated vulnerability to psychosis.

Given our understanding of the neural circuitry that underlies motor dysfunction, future studies that utilize neuroimagining to identify brain structural/functional abnormalities associated with movement abnormalities in 22q11 DS and prodromal patients will be important. Such studies hold promise for elucidating the neural substrates involved in both movement abnormalities and subclinical signs of risk for psychosis.

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Table 1.
Common Dyskinetic Movement Abnormalities

Appearance
Hyperkinesias
Chorea - irregular, rapid, uncontrolled, involuntary, excessive movement that flows randomly from one part of body to another
Athetosis- slow, writhing, continuous, uncontrollable movement usually in the head, neck, tongue, or hands
Ballism- large, explosive flinging movements of the arms and legs
Dystonia- sustained muscle contractions that cause twisting and repetitive movements or abnormal postures in face and/or limbs
Myoclonus- a sudden, brief, shock-like involuntary muscle contraction that can occur singularly or repetitively
Stereotypy- movements of frequent repetitions that serve no obvious purpose
Hypokinesias
Akinesia- poverty of movement and movement initiations
Bradyskinesia- marked slowness of movement
Rigidity- uniform increase in resistance to passive movements in individual joints
Tremor- rhythmic, involuntary muscular contraction characterized by oscillations of a part of the body

Table 2.
Clinical and Demographic Characteristics by Diagnostic Group

		NC (n = 27)	Prodromal (n = 49)	22q11 DS (n = 31)	OPD (n = 30)
Age (Mean ± SD)*		14.26 ± 1.91	14.22 ± 1.68	18.90 ± 4.64	14.87 ± 1.74
Sex (*n*, %)	Male	13 (48.1%)	32 (65.3%)	14 (45.2%)	11 (36.6%)
	Female	14 (51.8%)	17 (34.6%)	17 (54.8%)	19 (63.3%)
Race (*n*, %)	Caucasian	15 (55.5%)	33 (67.3%)	25 (80.6%)	16 (53.3%)
	African American	12 (44.4%)	14 (28.6%)	4 (12.9%)	11 (36.6%)
	Asian American	0 (0%)	2 (4.1%)	0 (0%)	1 (3.3%)
	Hispanic	0 (0%)	0 (0%)	2 (6.4%)	0 (0%)
	Other	0 (0%)	0 (0%)	0 (0%)	2 (6.6%)
Medication (*n*, %)**	Stimulants	2 (0.07%)	14 (28.6%)	5 (16.1%)	4 (13.3%)
	Antidepressants	1 (0.04%)	14 (28.6%)	6 (19.3%)	3 (0.1%)
	Antipsychotics	2 (0.07%)	6 (12.2%)	3 (10.0%)	1 (0.03%)

*p < .05. **p < .01.

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Table 3.
Means and Standard Deviations of Movement Abnormalities and SIPS Symptom Ratings by Diagnostic Group

Variable	NC 1	Prodromal 2	22q11 DS 3	OPD 4	Total	Group Differences
Oral-Facial (Mean ± SD)	0.08 ± 0.4	0.2 ± 0.8	2.8 ± 2.6	0.3 ± 0.9	0.8 ± 1.8	3 > 4, 2 > 1
Ocular (Mean ± SD)	0.1 ± 0.6	0.2 ± 0.7	0.3 ± 0.7	0.2 ± 0.8	0.2 ± 0.9	3 > 4, 2 > 1
Lingual (Mean ± SD)	0.0 ± 0.0	0.0 ± 0.2	0.3 ± 0.8	0.0 ± 0.0	0.1 ± 0.4	3 > 2 > 1,4
Head/Neck/Trunk (Mean ± SD)	0.7 ± 0.3	0.2 ± 1.0	0.7 ± 1.4	0.0 ± 0.0	0.2 ± 0.9	3 > 1, 2, 4
Upper Limbs (Mean ± SD)	1.0 ± 1.1	1.2 ± 1.7	2.2 ± 1.7	0.7 ± 1.2	1.2 ± 1.6	3 > 2 > 1, 4
SIPS Positive Symptoms (Mean ± SD)	0.5 ± 0.4	2.2 ± 0.9	1.7 ± 0.8	0.6 ± 0.4	1.4 ± 1.0	2 > 3 > 1,4**
SIPS Negative Symptoms (Mean ± SD)	0.3 ± 0.5	1.7 ± 1.1	2.2 ± 0.9	0.7 ± 0.7	1.3 ± 1.1	3 > 2 > 1, 4**
SIPS Disorganized Symptoms (Mean ± SD)	0.2 ± 0.3	1.5 ± 1.0	1.7 ± 1.0	0.4 ± 0.4	1.0 ± 1.0	3 > 2 > 1,4**
SIPS General Symptoms (Mean ± SD)	0.3 ± 0.4	1.5 ± 1.1	1.8 ± 1.0	0.6 ± 1.0	1.1 ± 1.0	3 > 2 > 1,4*

*p < .05. **p < .01.

Table 4.
Analysis of Covariance with Age and Medication Status: Prodromal Symptoms

Source	*df*	*F*	*p*	η^2
Positive Symptoms	3, 129	45.83	.00**	.516
Negative Symptoms	3, 128	21.13	.00**	.331
Disorganized Symptoms	3, 129	23.50	.00**	.353
General Symptoms	3, 129	16.24	.00**	.274

*p < .05. **p < .01.

Table 5.
Association Between Movement Abnormality and Prodromal Symptomology

		Symptomatology			
	Body Region	Positive	Negative	Disorganized	General
NC	Overall	.099	.572**	.485**	.528**
	Oral-Facial	.057	.567**	.448*	.091
	Ocular	.078	.648**	.450**	.159
	Lingual				
	HNT	-.332*	-.146	-.071	.097
	Upper Limbs	.069	.286	.329*	.613**
22q11 DS	Overall	.386*	-.046	.033	-.025
	Oral-Facial	.361*	.098	.049	.021
	Ocular	.462**	.192	.255	.086
	Lingual	-.046	-.311	-.137	-.122
	HNT	-.062	-.194	-.128	-.369*
	Upper Limbs	.013	-.281	-.092	-.102
Prodromal	Overall	.193	.338*	.239	.305*
	Oral-Facial	.069	.286*	.121	.152
	Ocular	-.001	-.043	-.210	.122
	Lingual	.100	-.120	-.123	-.057
	HNT	.267*	.306*	.371**	.264*
	Upper Limbs	.128	.290*	.239	.246*
OPD	Overall	.098	.308	-.049	.285
	Oral-Facial	.232	.111	.108	.113
	Ocular	.069	.162	.087	.101
	Lingual				
	HNT				
	Upper Limbs	-.012	.405*	-.215	.383*

*p < .05. **p < .01.

Figure 1. *Prodromal Symptom Severity by Diagnostic Group*

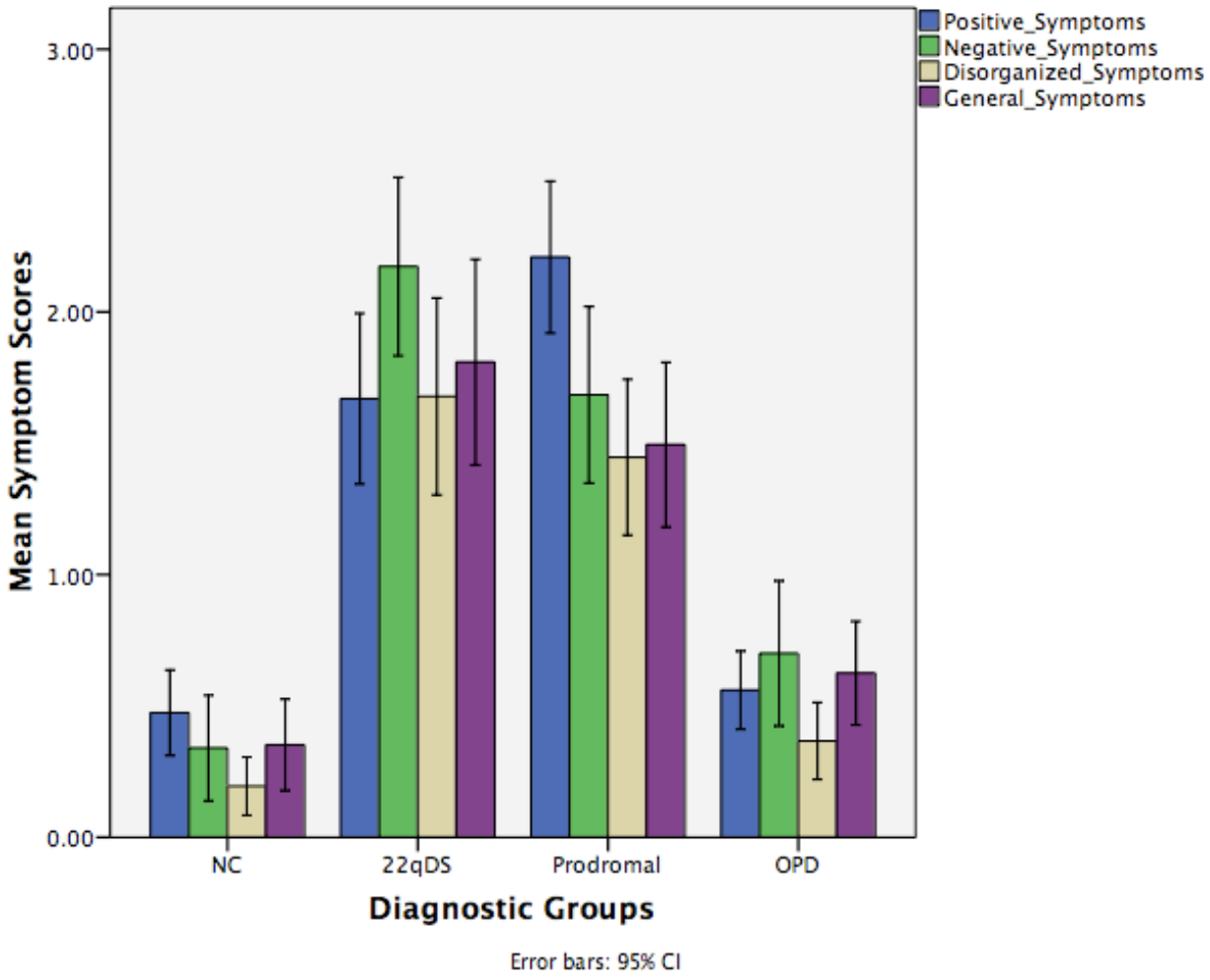


Figure 2. *Movement Abnormality Severity by Body Region and Diagnostic Group*

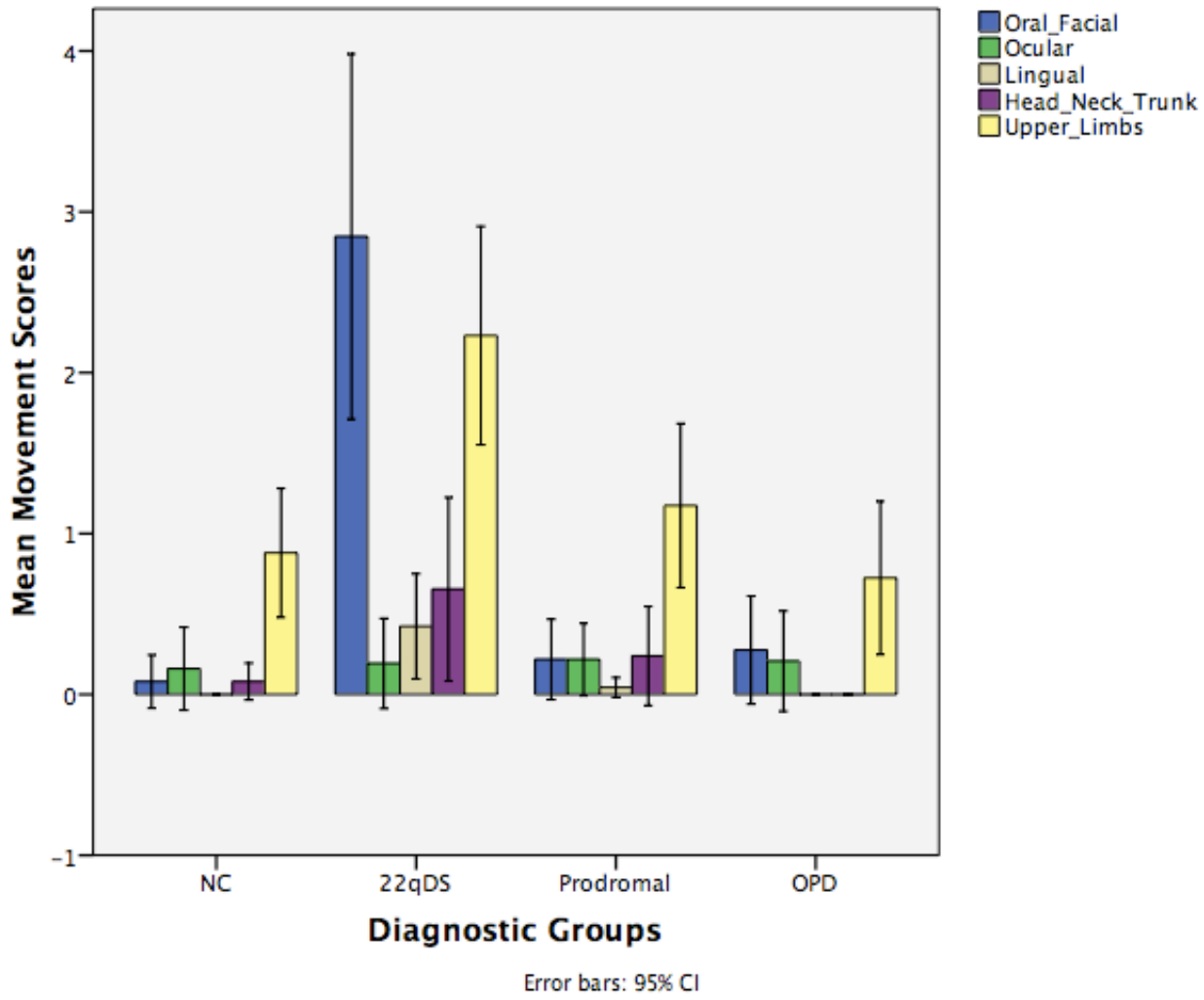
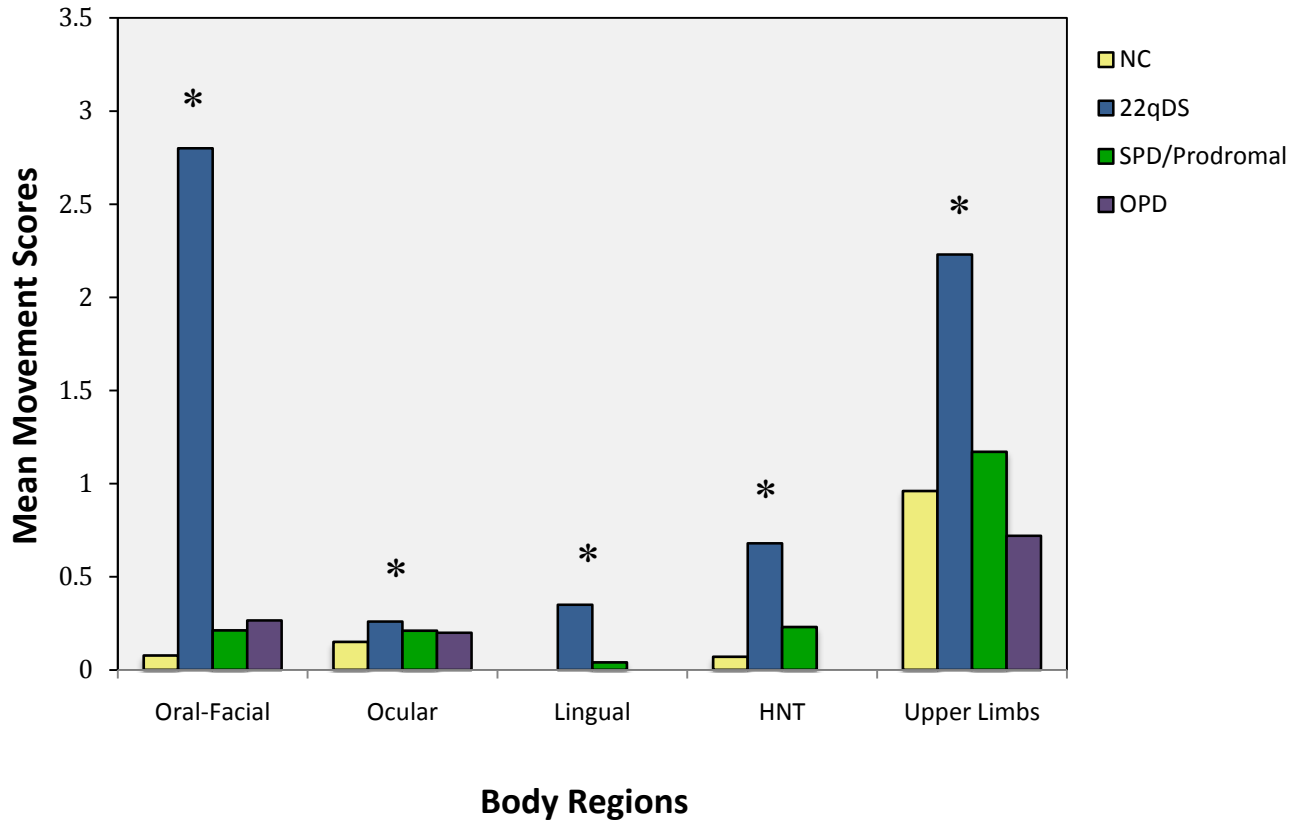


Figure 3. *Group Differences in Movement Abnormalities by Body Region*



*Indicates significant group differences at p ≤ .001

Figure 4. *Correlation between Positive Symptoms and Total Movement for 22q11 DS (left) and Prodromal (right)*

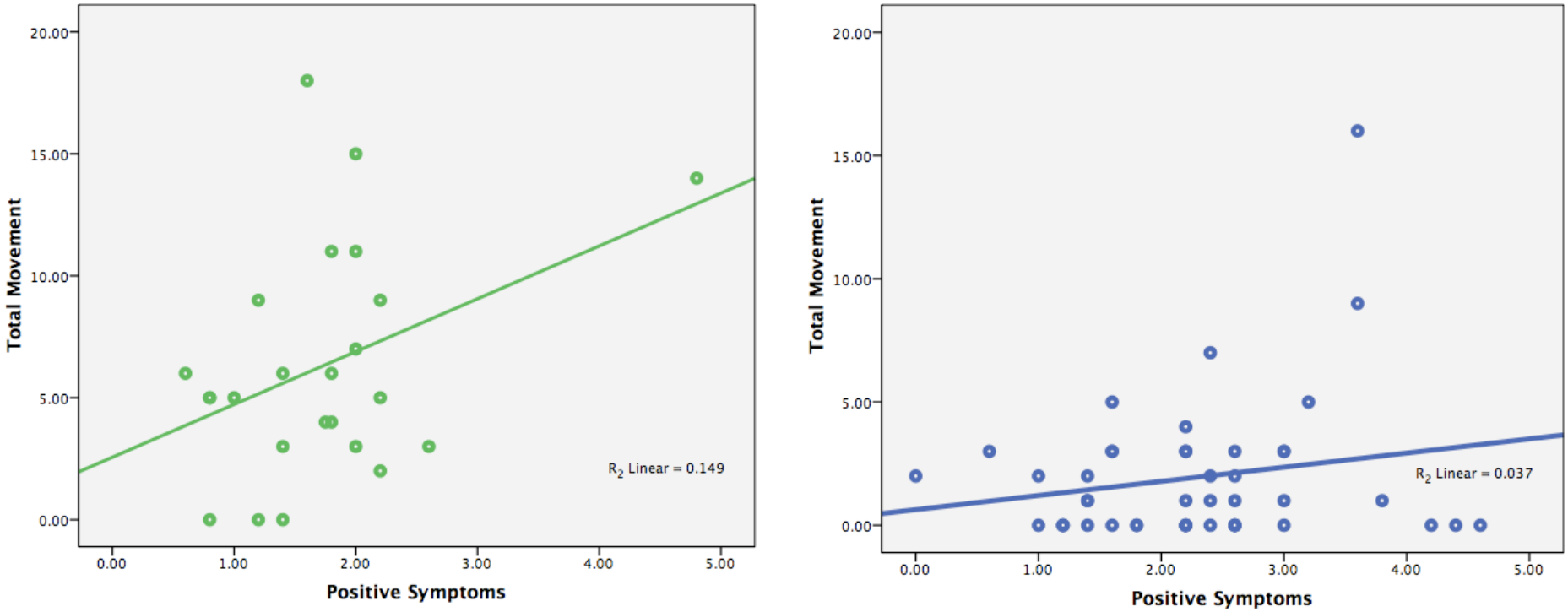


Figure 5. *Correlation between Negative Symptoms and Total Movement for 22q11 DS (left) and Prodromal (right)*