Development and Psychopathology, **11** (1999), 509–523
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Printed in the United States of America

Motor dysfunction and risk for schizophrenia

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Abstract

Motor dysfunction is associated with schizophrenia, and recent longitudinal studies indicate that it precedes the onset of clinical symptoms. Of particular interest is the heightened occurrence of involuntary movements, which are apparent as early as infancy and suggest the presence of subcortical brain abnormalities. In this article, we present the results of a study of spontaneous movements in adolescents with schizotypal personality disorder (SPD). SPD is a syndrome that has been shown to be genetically linked with schizophrenia and is often observed prior to the early adult onset of schizophrenia. Systematic coding of videotapes of diagnostic interviews revealed that the SPD group showed significantly more involuntary movements of the head, trunk, and upper limbs than did normals and adolescents with other personality disorders. There were no diagnostic group differences in the rate of voluntary movements. Salivary cortisol, measured before the interview, was positively correlated with involuntary movements. Taken together, the findings provide further support for the hypothesized etiologic relation between SPD and schizophrenia. Based on a neural diathesis-stress model, potential underlying mechanisms are discussed.

A relation between motor deficits and psychological maladjustment has been documented in numerous studies (for a review, see Neumann & Walker, 1996). This association holds for both children and adults, and it has been interpreted as supporting the biological basis of certain psychiatric disorders. More recently, researchers have speculated that the qualitative aspects of motor abnormalities might provide clues about the nature and locus of brain dysfunction in major mental illnesses, such as schizophrenia (Walker, 1994).

Schizophrenia is viewed by many as the most devastating of all mental illnesses because it has such pervasive functional implications and because the clinical onset is usually in late adolescence or early adulthood, a period when expectations for interpersonal competence increase. Although the defining features of the illness involve deficits in cognitive and socioemotional functioning, abnormalities in motor behavior have been observed in schizophrenia patients since the inception of the diagnosis. Yet, when compared to other lines of investigation, there have been relatively few empirical studies of the motor deficits associated with schizophrenia. As described below, there are several reasons why motor functions have been deemphasized by researchers, but the unfortunate consequence of this neglect may have been a deceleration of research progress.

This article is concerned with spontaneous movement abnormalities as a potential marker of vulnerability in adolescents at risk for schizophrenia. We begin by reviewing trends in the findings from empirical research. These suggest that motor dysfunction precedes the onset of clinical schizophrenia and that neuromaturational processes influence the manifestation of motor signs. We then present recent findings from our research on individuals who are presumed to be at risk for schizophrenia—namely, adolescents with schizotypal personality disorder (SPD). The findings indicate

This work was supported in part by a Research Scientist Development Award (MH00876) from the National Institute of Mental Health.

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https://doi.org/10.1017/S0954579499002187 Published online by Cambridge University Press

that abnormalities of spontaneous movement are present in SPD adolescents. In addition, the results suggest that the neural systems that influence the expression of clinical symptoms may also determine the manifestation of movement abnormalities.

Research on Motor Dysfunction in Psychiatric Disorders: Historical Background

It is now widely accepted that the integrity of the central nervous system (CNS) can have implications for all domains of human behavior. Yet, research on the motoric, cognitive, and socioemotional manifestations of CNS dysfunction has been divided along fairly rigid disciplinary and conceptual boundaries. The disciplinary divisions, which began to emerge at the turn of the century, persist to this day. Specifically, motor deficit has been the primary concern of neurology, whereas abnormalities in socioemotional behavior have been the main focus of psychiatry and clinical psychology. Interest in cognitive disorders, such as mental retardation and dementia, has cut across disciplines.

These disciplinary boundaries are largely a function of historically rooted assumptions about etiology (Rogers, 1988). The notion that nervous system dysfunction is responsible for motor disorders has a long history in medicine. In contrast, acceptance of the link between CNS function and disturbances in mood and thought processes lagged behind. Thus, from the 1950s through the 1970s, the term "functional disorders" was often used to refer to psychiatric disorders, with the assumption that they were not tied to CNS dysfunction, but rather were a consequence of social experience. In hindsight, it is obvious that this terminology reflected naive thinking about the nature of mind and behavior.

The introduction of antipsychotic medications in the 1950s contributed further to the confusion surrounding the meaning of motor signs in psychiatric patients. Antipsychotic drugs ("neuroleptics") produced characteristic movement abnormalities in some patients; these abnormalities are now referred to as tardive dyskinesia (Lang & Weiner, 1992). Drug-induced motor disturbances became a primary focus of clinical and research attention, further diminishing interest in the motor disturbances that occurred spontaneously in psychiatric patients. This relative neglect of involuntary movement abnormalities has been noted by several writers, and is pointedly acknowledged in the title of one recent article, "Not all that moves is tardive dyskinesia" (Khot & Wyatt, 1991).

Motor Dysfunction in Schizophrenia

Because antipsychotic and other psychotropic medications can affect motor functions, the most informative studies of motor deficit in schizophrenia are those conducted on nonmedicated patients. This research was reviewed in a recent paper (Walker, 1994). In brief, studies of nonmedicated schizophrenia patients have revealed abnormalities in voluntary movement (Manschreck, 1986), most notably a reduction in manual reaction time, as well as an increase in the rate of involuntary movement (Khot & Wyatt, 1991; Yarden & Discipio, 1971) These involuntary movements are of particular interest because they are typically not tremors, but rather "dyskinesias," such as writhing or jerky movements of the limbs and face, and abnormal ("dystonic") posturing of the upper limbs.

Both prospective and archival longitudinal studies have demonstrated that motor abnormalities are apparent long before the emergence of clinical schizophrenia (Walker, 1991). In fact, abnormalities in movement may be most pronounced during infancy in individuals who later develop schizophrenia. Fish, Marcus, Hans, Auerbach, and Perdue (1992), in a landmark investigation of "high-risk" infants born to schizophrenic mothers, found that those with greater delays in motor development during the first 2 years of life were more likely to be diagnosed with schizophrenia or spectrum disorders (e.g., SPD) in adulthood. Similarly, our analyses of childhood home movies of adult-onset schizophrenia patients revealed that they manifested significant motor skills delays and movement abnormalities during the first 2 years when compared to their healthy siblings and a com-

https://doi.org/10.1017/S0954579499002187 Published online by Cambridge University Press

parison group with mood disorders (Walker, Savoie, & Davis, 1994). Like adult patients, the preschizophrenia infants showed a dyskinetic syndrome that included choreoathetoid movements and dystonic posturing. The observation that spontaneous movement abnormalities were more pronounced in the first 2 years of life is undoubtedly due to the fact that motor skills are in ascendance at this time, and individual differences are, therefore, more readily apparent. But as noted above, findings from studies of adult schizophrenia patients suggest that motor signs persist across the life span in schizophrenia patients, although they may be more readily apparent during certain developmental periods.

At this point our knowledge of movement abnormalities in schizophrenia is essentially restricted to the early premorbid period (infancy to middle childhood) and the postonset period. We are not aware of any published studies on the nature of spontaneous movement abnormalities during the developmental stages immediately preceding the onset of clinical symptoms (viz., adolescence and early adulthood). Some investigators have reported motor proficiency deficits in adolescent offspring of mothers with schizophrenia (Dworkin, Cornblatt, Friedman, Kaplansky, Lewis, Rinaldi, Shilliday, & Erlenmeyer–Kimling, 1993; Marcus, Hans, Auerbach, & Auerbach, 1993); however, systematic studies of movement abnormalities in at-risk adolescents have not been reported.

Adolescence is a period of significant interest to psychopathology researchers because the prodromal signs of schizophrenia typically emerge at this time. Both prospective and retrospective studies have shown that adjustment problems, such as social withdrawal and subtle thought abnormalities, increase markedly during adolescence in preschizophrenic individuals (Neumann, Grimes, Walker, & Baum, 1995; Walker, Baum, & Diforio, in press). It has thus been suggested that attempts at preventive intervention may ultimately prove to be most effective during the peripubertal period. Yet, numerous important questions about this critical developmental stage remain unanswered. Chief among these is the question of whether spontaneous movement abnormalities are apparent during the adolescent period when prodromal signs become noticeable. More specifically, does the nature or severity of movement abnormality predict the emergence of clinical symptoms of psychiatric disorder?

One strategy for answering these questions involves the prospective study of individuals at heightened behavioral risk for schizophrenia. Adolescents with schizotypal personality disorder constitute such a group. The study of these subjects provides the opportunity to explore the nature of motor functions in individuals who are presumed to be at heightened risk for schizophrenia but who have not been exposed to drug treatment. Further, because the postpubertal period is a critical one for the emergence of clinical symptoms and syndromes, adolescent samples are ideally suited for identifying markers of risk.

Schizotypal Personality Disorder

Schizotypal personality disorder (SPD) is one of several "Axis II" personality disorders described in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The diagnostic criteria include unusual perceptual experiences, suspiciousness, and social deficits. These signs are milder versions of the clinical symptoms that define schizophrenia, and they are similar to the prodromal signs that precede the onset of the initial episode of schizophrenia (Neumann et al., 1995). It has been shown that this syndrome occurs in preadolescent and adolescent children (Wolff, Townsend, McGuire, & Weeks, 1991; Asarnow & Ben-Meir, 1988; Nagy & Szatmari, 1986; Wolff, 1991) as well as adults (Siever, Silverman, Horvarth, Klar, Coccaro, Keefe, Pinkham, Rinaldi, Mohs, & Davis, 1990).

There is now an extensive body of research documenting the links between schizophrenia and SPD (Siever et al., 1990; Siever, Kalus, & Keefe, 1993). Initial evidence was provided by behavior genetic studies which showed that schizotypal symptoms occurred at a higher rate in the biological relatives of schizophrenia probands than in the relatives of controls (Kendler, Gruenberg, & Strauss, 1981). Subsequent studies have documented

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that individuals who meet diagnostic criteria for SPD manifest cognitive deficits (Raine & Mednick, 1995) and brain abnormalities (Cazzulo, Vita, Giobbio, Dieci, & Sacchetti, 1991) similar to those observed in schizophrenia patients. As noted, Fish demonstrated that motor dysfunction in infant offspring of schizophrenic mothers was associated with an increased risk for SPD, as well as schizophrenia, in early adulthood. Two recent investigations have shown that SPD is associated with premorbid childhood behavioral deficits which parallel those reported in studies of schizophrenia patients (Walker et al., in press; Olin, Raine, Cannon, Parnas, Schulsinger, & Mednick, 1997). For example, both SPD and schizophrenia are associated with a marked increase in social problems and thought abnormalities during adolescence (Walker et al., in press).

It is generally assumed that SPD will progress to schizophrenia in a subgroup of patients. Drawing on diathesis-stress models, investigators have speculated on the factors that might serve to potentiate the progression from a schizotypal syndrome to clinical schizophrenia (Cantor–Graae, McNeil, Torrey, Quinn, Bowler, Sjostrom, & Rawlings, 1995; Walker & Gale, 1995). It has been suggested that exposure to perinatal complications may trigger the expression of Axis I disorder in schizotypal subjects (Walker & Gale, 1995; Cannon, Mednick, & Parnas, 1989) and there has been a long-standing interest in the role of psychosocial stress as a potentiating factor (Norman & Malla, 1993a, 1993b). In a recent paper (Walker & Diforio, 1997), we propose a neural model of the mechanisms mediating the effects of stress on the expression of psychotic symptoms. Although a detailed description of the model is beyond the scope of this paper, a brief overview will be presented, and the reader is referred to Walker and Diforio (1997) for a more comprehensive discussion.

The hypothalamic–pituitary–adrenal (HPA) axis, which governs the release of cortisol, is one of the major brain systems mediating the biological response to stress (Cullinan, Herman, Helmreich, & Watson, 1995; Biron, Dauphin, & Di Paolo, 1992; Breier, 1989; Breier, Davis, Buchanan, Moricle, & Munson, 1993; Cador, Cole, Koob, & Stinus, 1993). The HPA system is of relevance to schizophrenia because cortisol release alters the activity of several neurotransmitter systems (e.g., glutamate, serotonin, and dopamine). Most notably, it augments dopamine (DA) activity. Abnormalities in DA neurotransmission, primarily overactivity, have been implicated in the neuropathophysiology of both psychotic symptoms and movement abnormalities (Alexander, Viken, & Bates, 1997; Csernansky, Murphy, & Faustman, 1991; Davis, Khan, Ko, & Davidson, 1991). Thus, the HPA system is a plausible candidate as a neural moderating system which influences the expression of abnormalities in DA neurotransmission.

We review clinical research findings which demonstrate that schizophrenia is associated with heightened baseline cortisol and an increased cortisol response to pharmacological challenge (Walker & Diforio, 1997). Consistent with this pattern of findings, neuroimaging of schizophrenia patients has revealed significant volumetric reductions in the hippocampus, a region that plays a critical role in the regulation of HPA activity. Specifically, the hippocampus contains a relatively high density of receptors that are activated by cortisol. It appears that the activation of these receptors triggers negative feedback to the HPA axis, thus dampening its activity. Research with animals has shown that a variety of prenatal factors can produce elevated cortisol *and* hippocampal damage in offspring. Included among these prenatal events are some that have been shown to be linked with schizophrenia in offspring—namely, maternal viral infection, nutritional deficiency, hypoxia, and maternal exposure to stress. Thus, prenatal complications can compromise the HPA system and potentiate the expression of abnormalities in DA neurotransmission, as well as other neurotransmitter systems. Further, because prenatally induced HPA dysregulaton persists into adulthood, it may be exacerbated over time due to the damaging effects of chronically elevated cortisol on the hippocampus and cortical regions.

The identification of factors that predict

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the course of schizotypal syndromes would represent significant progress in our understanding of the development of schizophrenia and spectrum disorders. This article presents the results of a study of spontaneous movements in adolescents who are participating in our recently initiated, prospective research project on the developmental course of SPD. The ultimate objective is to identify factors that predict the onset of psychotic symptoms. The project focuses on adolescents because it is assumed that pubertal and postpubertal neuromaturational processes play a role in triggering the expression of latent vulnerabilities for psychotic disorders.

Our initial evaluation of these subjects included measures of physical and neurohormonal characteristics, as well as an extensive diagnostic interview. We conducted assessments of dysmorphic physical features because it has been repeatedly demonstrated that schizophrenia patients manifest significantly more minor physical anomalies (MPAs; Green, Bracha, Satz, & Christenson, 1994; Green, Satz, & Christenson, 1994; Lohr & Flynn, 1993) and dermatoglyphic asymmetries (DAs; Bracha, Torrey, Bigelow, Lohr, & Linington, 1991; Markow & Gottesman, 1989; Mellor, 1992; Markow & Wendler, 1986) when compared with normals and other psychiatric patients. MPAs are structural irregularities in craniofacial features (e.g., low-set ears, increased intercanthal distance) and the extremities (e.g., single palmar crease, curved fingers). DAs are differences in fingerprint ridge counts between corresponding fingers on the right and left hands. These dysmorphic features are presumed to originate in the prenatal period and to reflect abnormalities in neurodevelopment (Brixey, Gallagher, McFalls, & Parmalee, 1993; Cantor–Graae, McNeil, Sjostrom, Nordstrom, & Rosenlund, 1995; Waldrop & Halverson, 1971). We found that SPD adolescents showed a significantly higher rate of MPAs and DAs than normal and psychiatric comparison groups (Davis–Weinstein, Diforio, Schiffman, Walker, & Bonsall, 1999). With the aim of testing the prediction that SPD is linked with a heightened biological response to stress, we also measured saliva cortisol and found that it was elevated in the SPD adolescents when compared to normal adolescents and those with other Axis II disorders. It is noteworthy that the first cortisol measure, obtained immediately after the participants arrived for the assessment, was the most discriminative. This suggests that the novelty of the setting (Schneider, 1992) elicited a greater biological stress response in the SPD group. These findings are consistent with the reports of elevated baseline cortisol in adult schizophrenic patients, and provide support for the "neural" diathesis-stress model described in Walker and Diforio (1997).

In this paper we present data on spontaneous movements in adolescents with SPD. As outlined above, movement abnormalities are of particular interest because knowledge of their neuropathophysiology is relatively advanced and, as has been hypothesized to be the case for schizophrenia, hyperkinesias have been shown to be subserved by DA activity (Lang & Weiner, 1992) and exacerbated by stress (Hollister, Muller–Oerlinghausen, Rickels, & Shader, 1993). Thus, the presence and nature of movement abnormalities may shed light on the neural mechanisms involved in mental disorders. The study described here tests the hypotheses that SPD adolescents will show an elevated rate of "involuntary" motor activity and that the rate of involuntary movement will be linked with cortisol release. Further, given past findings that abnormalities of movement in preschizophrenia children predominate in the upper limbs (Walker et al., 1994), it is predicted that the same regional distribution will characterize SPD adolescents.

Method

Participants

The participants in this study were 15 adolescents (9 males) who met DSM-IV criteria for schizotypal personality disorder (SPD group), 16 adolescents (11 males) who met DSM-IV criteria for another Axis II disorder or conduct disorder (other personality disorder [OD]), and 18 adolescents (13 males) who did not meet criteria for any Axis II disorder (normal control [NC] group). At the time of the initial

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evaluation, none of the subjects met diagnostic criteria for an Axis I disorder. (These subjects are a subgroup of a larger sample of 67 who are participating in a prospective investigation of at-risk adolescents. For technical reasons, videotapes of the SCID interview were not available for 18 of the participants.)

Participants were recruited from the community using announcements directed at parents. The announcements described the diagnostic criteria for SPD in general, lay terms, and informed parents that assessments of children who manifested such problems were being conducted for research purposes at the Emory Psychological Center. A screening interview was conducted with respondents over the telephone to determine whether their child met study criteria (i.e., no major physical illnesses or mental retardation). In addition to identifying children who were likely to meet diagnostic criteria for SPD, the telephone screen was also intended to identify children with "other" Axis II disorders for inclusion in the psychiatric comparison group. Those who met study criteria and agreed to participate were scheduled for an assessment.

The control group was comprised of individuals who did not meet DSM-IV criteria for any Axis I or II disorder. Some were drawn from respondents to the research announcement and others were adolescents whose parents had registered them for participation in psychological research at the University.

For the sample of 49 included in these analyses, the mean age was 15.1 ($SD = 1.51$) for the SPD group, 15.7 ($SD = 2.35$) for the OD group, and 14.7 ($SD = 2.54$) for the NC group. Analysis of variance revealed no significant difference among the groups in mean age, nor were there differences among the groups in race or sex composition.

The diagnostic evaluation included the Structured Clinical Interview for DSM Personality Disorders (SCID-II) questionnaire (Spitzer, Williams, Gibbon, & First, 1990a), the SCID-II interview questionnaire (Spitzer, Williams, Gibbon, & First, 1990b), and the SCID-I/P Psychotic Screen (Spitzer, Williams, Gibbon, & First, 1990c). All subjects provided informed consent. Following standard procedures, the SCID-II questionnaire was completed first, and the responses were used as a guide in the administration of the interview. Diagnostic interviews were conducted by advanced doctoral students in clinical psychology who had undergone systematic training in the administration of the SCID. All interviews were videotaped, and interrater reliability for diagnoses was .80. Diagnostic discrepancies were resolved by consensus.

As expected, there was a high rate of comorbidity, such that many of the subjects met criteria for more than one disorder. Thus some subjects in the SPD group also met criteria for another Axis II disorder (Avoidant, $n = 4$; Obsessive–Compulsive, $n = 1$; Paranoid, $n = 4$; Dependent, $n = 1$; Borderline, $n = 3$; Conduct Disorder, $n = 1$). The OD group diagnoses were Dependent, $n = 1$; Obsessive–Compulsive, $n = 4$; Paranoid, $n = 3$; Schizoid, $n = 3$; Borderline, $n = 1$; Conduct Disorder, $n = 6$; Passive–Aggressive, $n = 5$; and Not Otherwise Specified, $n = 2$. (The total diagnoses exceeds the number of subjects due to comorbidity.)

Assessment of motor behavior

Each participant was videotaped during the administration of the SCID interview. Interviews were conducted in private rooms, and the participant was videotaped while seated in a chair which faced a wall-mounted camera behind the interviewer. A total of 24 min of each videotape was coded for the occurrence of movements. Four 6-min segments of each interview were selected for coding (first 6 min, Minutes 15–20, Minutes 30–36, and the last 6 min of the interview). The intention was to obtain behavioral samples that spanned the entire interview.

The coding scheme was devised to obtain measures of voluntary and involuntary movements. Seven body regions were coded: the head (including face), trunk, arms, hands, fingers, legs, and feet. Voluntary movements were defined as any movement that was intended to convey meaning (e.g., nodding, gestures, illustrators) or achieve a purpose (e.g., reaching for an object, scratching, rearranging clothing, repositioning). Movements were

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coded as involuntary if they occurred with no apparent intent or goal. Typical examples of movements falling in this category were writhing and alternating extensions and flexions of the fingers or wrist, facial grimacing, twitching and exaggerated tongue or lip movements, shaking of the legs or arms, foot tapping, ankle rotation, and writhing trunk movements. (Although it is obvious that the intentionality of a movement cannot be unequivocally established, our findings on the interrater reliability for the coding categories, as well as the differential discriminative power of the categories, lend support to the validity of the distinction.)

For each 6-min videotape segment, three main body regions were coded separately: (a) head and trunk; (b) arms, hands, and fingers; and (c) feet and legs). Thus, coders viewed each segment at least three times to complete the coding.

Three research assistants were trained in the application of the coding procedures over a 2-month period using tapes of nonparticipants. Coding of the subject tapes was begun after all pairs of raters had achieved a minimum interrater reliability of .70 (Pearson correlation) for coding, independently, each body region and movement type in a 6-min segment. The mean reliability at the end of the training period was .86, ranging from .72 to .95 across body regions. Raters were blind to the diagnostic status of all subjects.

The coding scheme yielded ratings of the frequency of occurrence of voluntary and involuntary movements for each of the seven body regions during the four interview segments. The ratings were summed across the four segments to obtain an aggregate measure for each of the 14 variables. These frequencies were divided by the number of minutes scored, to yield the number of movements per minute.

Salivary cortisol

Saliva samples were obtained for cortisol assay four times during the course of the assessment. For all subjects, the initial sample was obtained at approximately 12:30 and subsequent samples were obtained at 60-min intervals. In this way consistency was maintained in the portion of the diurnal rhythm measured across subjects. The laboratory procedures for the cortisol assay are described in Davis–Weinstein et al. (1999). As noted, the first cortisol measure proved to be the most discriminating among the diagnostic groups. This measure was used in the present analyses.

Results

Preliminary analyses were conducted to examine the pattern of intercorrelations (Pearson) among the movement ratings, averaged across the four segments. These are listed in Table 1. In general, the ratings of voluntary and involuntary movement were relatively independent. Only a few of the coefficients are statistically significant, and these relations are modest. Thus, it appears that there is no systematic association between rates of voluntary and involuntary movement.

There are some significant moderate relations among rates of involuntary movements in various body regions, particularly among the upper body regions: trunk, head, and arms. Involuntary movements of the arm show the most consistent relations with movement in other body regions. Correlations among voluntary movements in various body regions are generally stronger than those among involuntary movements.

Diagnostic-group differences

The mean movement scores, by diagnostic group, are presented in Table 2. As predicted, there were significant effects of diagnostic-group on rates of involuntary movement. Univariate tests showed significant diagnostic-group differences for involuntary movements of the head, $F(2, 47) = 7.26$, $p = .002$, arms, $F(2, 47) = 5.88$, $p = .005$, hands, $F(2, 47) = 3.41$, $p = .04$, and fingers, $F(2, 47) = 4.62$, $p = .02$. The diagnostic-group effect for ratings of involuntary trunk movements showed a trend toward significance, $F(2, 47) = 2.61$, $p = .08$. Independent sample t tests were conducted to compare pairs of diagnostic groups, and the results are illustrated in Table 2. Consistent

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Table 1. *Pearson correlations among movement ratings*

	Voluntary							Involuntary						
	Trunk	Head	Arms	Hands	Fingers	Legs	Feet	Trunk	Head	Arms	Hands	Fingers	Legs	Feet
Voluntary														
Trunk	—	.38*	.32*	.20	–.00	.36*	.35*	.35*	.22	.32*	–.10	.16	.11	.02
Head		—	.31*	.27*	.27*	.19	.06	.10	.17	.08	–.10	.09	.30*	.03
Arms			—	.92*	.68*	.23	–.05	–.04	–.04	–.14	–.28*	.07	.13	–.07
Hands				—	.71*	.23	.00	.17	.09	.23	–.27	.15	.09	.01
Fingers					—	.05	–.00	–.02	–.07	–.02	–.25*	–.01	.17	.01
Legs						—	.82*	.01	.17	.05	–.09	.23	.14	.27*
Feet							—	.01	.38*	.05	–.04	.25*	.04	.45*
Involuntary														
Trunk								—	.50*	.61*	.00	.18	.11	.04
Head									—	.45*	–.03	.30*	.12	.18
Arms										—	.00	.35*	.28*	.20
Hands											—	–.23	.12	.14
Fingers												—	.36*	.18
Legs													—	.39*
Feet														—

*$p < .05$.

with our hypotheses, when compared to the NC group, the SPD group showed significantly more involuntary movements of the arms, hands, fingers, head, and trunk. When compared to the OD group, SPD adolescents showed greater involuntary movements of the head, arms, hands, and fingers. Comparison of the NC and OD groups yielded no differences in the rate of any involuntary movements.

There were no differences among the groups in voluntary movements, and the only voluntary movement that marginally differentiated the groups was finger movement, $F(2, 47) = 2.35$, $p = .11$, with the OD group showing a lower rate than normals.

For illustrative purposes, the mean rates of selected voluntary and involuntary movements by time segment and diagnostic group are presented in Figure 1.

Figures 1a and 1b show the rates of involuntary arm and head movements, respectively. The SPD group shows an elevation in involuntary movements for both body regions and this persists across the four time periods sampled from the interview. In contrast, Figures 1c and 1d illustrate that the diagnostic groups are indistinguishable in the rate of voluntary movements of the arms and head.

In order to derive a global index of involuntary movement, principal component analysis was conducted on the five ratings that dis-

Table 2. *Means and standard deviations of involuntary-movement frequencies per minute by diagnostic group*

Group	Trunk	Head	Arms	Hands	Fingers	Legs	Feet
Normal controls	.15[b]	.32[b]	.62[b]	2.4[b]	5.15[b]	3.65	3.61
	(.31)	(.38)	(.77)	(1.57)	(2.37)	(3.04)	(3.59)
Other disorders	.21	.45[b]	.66[b]	2.49[b]	6.20[b]	3.61	3.85
	(.46)	(.54)	(.91)	(1.92)	(2.72)	(2.71)	(2.54)
Schizotypal personality disorders	.53[a]	1.36[a]	1.74[a]	3.96[a]	7.94[a]	4.18	4.21
	(.67)	(1.34)	(1.35)	(2.06)	(2.70)	(3.30)	(2.72)

Note: Values with different superscripts are significantly different. Standard deviations are in parentheses.

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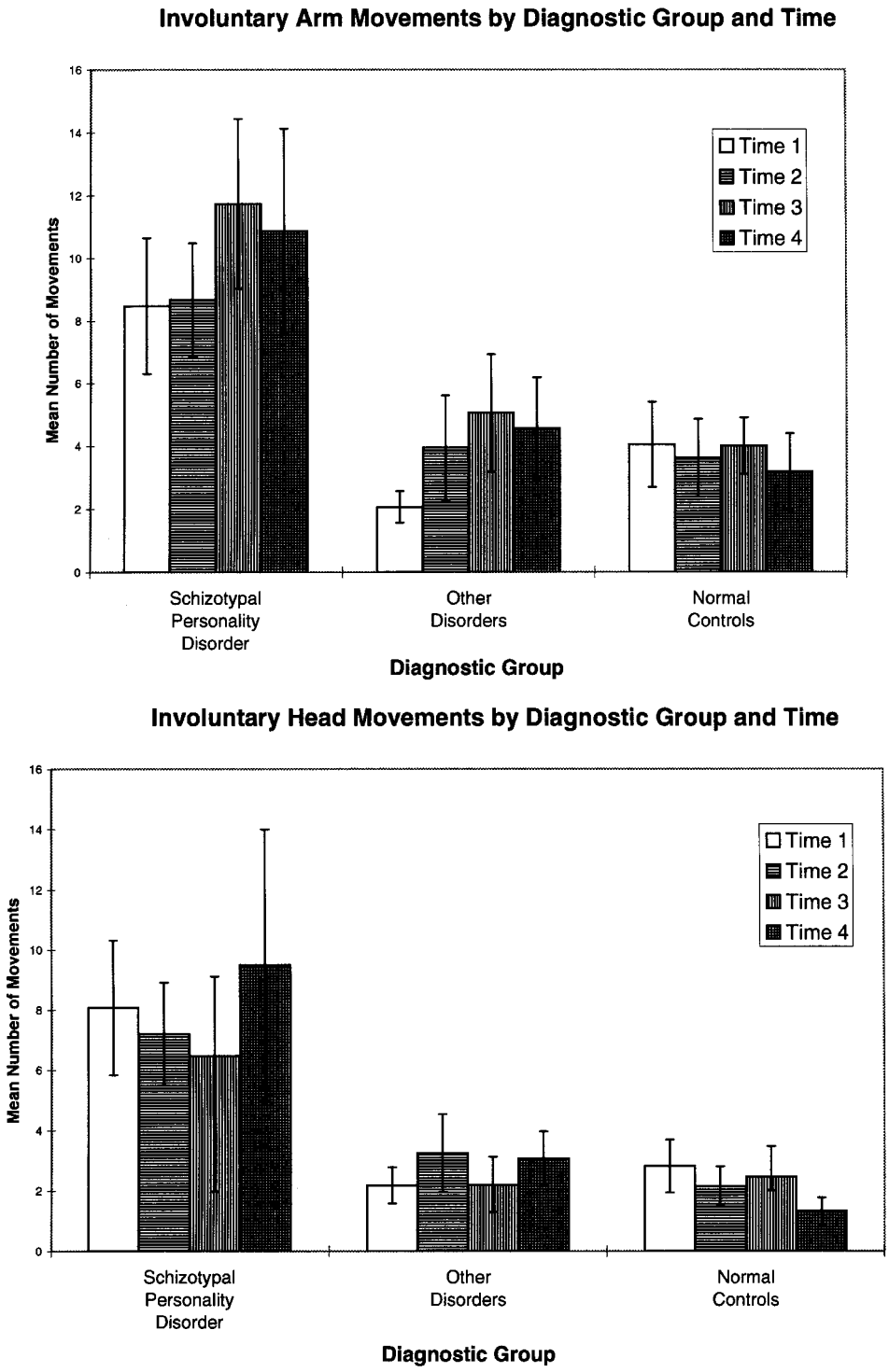


Figure 1. Rates of movement by time and diagnostic group.

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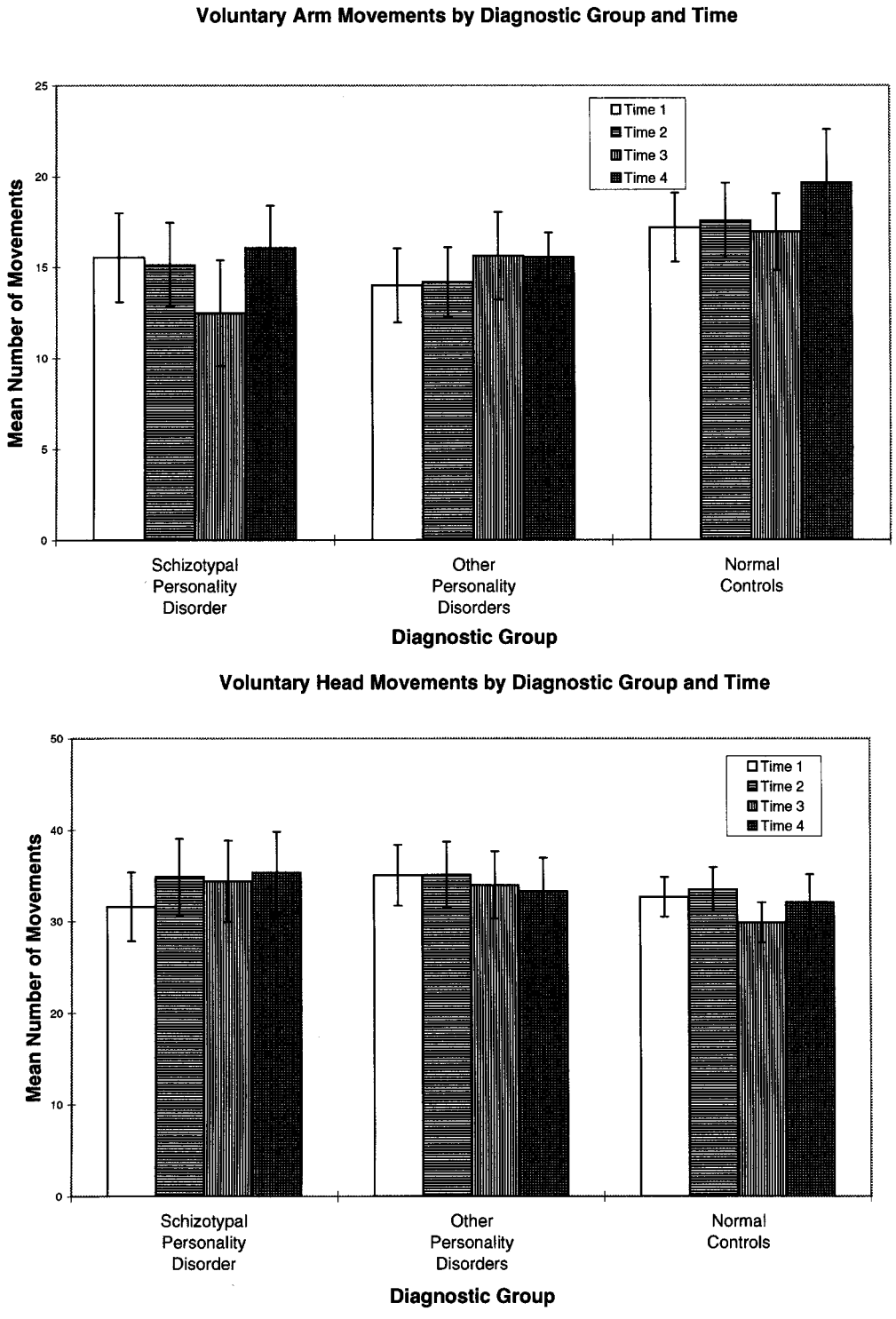


Figure 1. Continued.

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Table 3. *Loadings of involuntary motor ratings on Factors 1 and 2*

	Factor 1 (45% of Variance)	Factor 2 (23% of Variance)
Arms	.83	.15
Fingers	.56	–.52
Hands	–.11	.87
Head	.77	.08
Trunk	.80	.27

tinguished the diagnostic groups—namely, involuntary movements of the head, trunk, arms, hands, and fingers. The unrotated solution revealed two factors with eigenvalues greater than 1, and the variable loadings for each are listed in Table 3. As can be seen, Factor 1 accounts for 45% of the total variance and suggests a general factor, in that all but one of the motor variables has a significant loading. The second factor accounts for 23% of the total variance and is primarily determined by ratings of hand movements. For each subject, regression factor scores were derived for further analysis.

ANOVA revealed a highly significant diagnostic group difference in Factor 1, $F(2, 47) = 10.27$, $p < .0005$, but not Factor 2, $F(2, 47) = .35$, $p = .69$. Scores on Factor 1 were .91 ($SD = 1.19$), –.17 ($SD = .69$), and –.37 ($SD = .60$) for the SPD, OD, and NC groups, respectively. *T* tests indicated that the SPD group scored significantly higher on Factor 1 than both the OD and NC groups.

Correlational analyses were conducted to determine the relation of involuntary movements with cortisol release and dysmorphic features. Using all subjects, the Pearson correlation between the first cortisol measure (μg/dl) and Factor 1 scores was significant, $r = .32$, $p = .01$. The correlations of Factor 1 scores with MPAs and FAs were $r = .29$, $p = .02$, and $r = .26$, $p = .03$, respectively. Factor 2 scores showed no relation with the other measures.

Discussion

The results of the present study provide further evidence that SPD represents the mild end of the spectrum of schizophrenic disorders. Like schizophrenia patients, the SPD adolescents manifested more involuntary movements of the upper limbs and trunk than age-matched normals or adolescents with other disorders. The findings also provide some clues about the neural mechanisms that might be involved in the co-occurrence of involuntary movements and schizophrenia-spectrum symptoms.

Diagnostic group differences in movement abnormalities

Three aspects of the diagnostic group differences reported here are especially noteworthy. First, the differences are restricted to involuntary movements, rather than being generalized across ratings of both voluntary and involuntary movements. Given that the two categories of movement were rated with comparable reliability and yielded similar distributions, the results indicate that the excess motor behavior of SPD adolescents is specific to involuntary movement and not a consequence of global increases in activity level.

Second, the excess involuntary movements in the SPD group are specific to the upper limbs and body, and are not apparent in the lower limbs. This is consistent with previous observations of schizophrenia patients, whose involuntary movements occur primarily in the upper limbs, face, and trunk. Finally, the diagnostic specificity of the findings is noteworthy. The group differences in involuntary movement are robust, and the SPD group differs as much from the OD group as it does from the NC group.

As described earlier, the occurrence of movement abnormalities in schizophrenia patients has been taken as support for the presence of CNS dysfunction. Similarly, it is reasonable to infer that the elevated rate of involuntary movement in individuals with SPD indicates impairment of the CNS in this syndrome. Because research has elucidated the neural circuits that play a role in movement disorders, we can draw on this knowledge to speculate on the neural mechanisms that might be involved in schizophrenia.

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The potential neural substrates

Our finding of a positive correlation between mean cortisol and involuntary movements is consistent with the demonstrated relation between stress and exacerbation of involuntary movements in neurological patients (Hollister et al., 1993; Yanagisawa, 1992). A neural mechanism to account for this association is provided by the evidence that cortisol release augments DA activity.

Abnormal movements have been shown to be associated with impairment in the neural circuits that link the dorsal striatum with the motor cortex (Alexander, Crutcher, & DeLong, 1990). As mentioned above, it has been hypothesized that hyperkinesias are due to overactivation of ascending DA pathways in motor circuits. Because there are topographically organized subcircuits for the facial region, upper limbs, and lower limbs, movement abnormalities can be specific to one body region. The orofacial and upper limb regions are predominantly represented in the ventromedial and adjacent areas of the putamen, whereas the lower limbs are represented in the dorsolateral area.

Similarly, overactivation of DA pathways in the circuit that links the striatum with the limbic cortex has been hypothesized to be involved in the production of psychotic symptoms (for a review, see Walker, 1994). Thus, given the augmenting effect of cortisol release on DA activity, both hyperkinesias and schizophrenia-spectrum symptoms would be expected to be associated with elevations in cortisol release. Recently, several authors have pointed out evidence that there are functional interconnections among the motor, limbic, and prefrontal circuits, and that these interconnections are the biological basis for integration among sensory, motor, and motivational processes (Joel & Weiner, 1994). A localized abnormality in DA neurotransmission could, therefore, influence multiple behavioral domains and account for the relation between movement abnormalities and psychiatric status.

Origins of the neuropathophysiology. As described by Walker and Diforio (1997), overactivity of the HPA axis has been documented in mood disorders and panic disorder, as well as schizophrenia. Thus, heightened cortisol release is not unique to schizophrenia and is most plausibly viewed as a nonspecific factor that moderates the expression of vulnerabilities for psychopathology. Further, the evidence reviewed earlier indicates that prenatal events contribute to abnormalities in HPA function.

This suggests the possibility that prenatal factors interact with genetically determined liabilities in the epigenesis of schizophrenia. Studies of discordant monozygotic (MZ) twins provide evidence consistent with this assumption. Neuroimaging studies have revealed that among MZ twin pairs who are discordant for schizophrenia, the affected co-twins have significantly larger ventricles and smaller hippocampal volumes (Suddath et al., 1990). Thus, the affected twins have acquired brain abnormalities that are causing or triggering their vulnerability to schizophrenia. Although the origins of the morphological differences between co-twins cannot be unequivocally established, it is known that the hippocampus is particularly sensitive to perturbation during fetal development. Further, co-twins from MZ pairs can differ dramatically in physical indicators of fetal health. It is therefore plausible that prenatally acquired damage to the hippocampus is contributing to the expression of schizophrenia in the affected co-twin.

We have mentioned that the DA system is a candidate as the neural substrate for schizophrenia. Recent theorizing has focused on abnormalities in DA receptors as the critical factor. Presuming this to be the case, geneticists are exploring the connection between schizophrenia and genes that influence DA receptor function. Thus, the inherited liability for schizophrenia may involve a defect in the DA system.

Recent research has revealed that some of the effects of adrenal steroids on CNS function are "nongenomic" in nature, whereas others involve "genomic" actions that are delayed in onset and prolonged in duration (McEwen, 1994). Further, as described by McEwen (1994) in his review of these effects, the actions of steroid hormones on the brain are partially determined by interaction with

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neurotransmitter systems. Thus it is plausible that adrenal steroids play a role in determining the neuronal expression of the genotype(s) associated with schizophrenia. In other words, the environmental "stressors" that are presumed to trigger the behavioral expression of schizophrenia may do so via the influence of steroids on gene expression.

Developmental outcomes. Ultimately, the chief goal of our longitudinal study is to determine whether the developmental course of SPD can be predicted from measures obtained in the initial assessment. Adolescence and early adulthood are associated with maturational changes in the limbic circuit that is presumed to be involved in the neuropathophysiology of schizophrenia (Benes, 1994). There is also evidence that these periods are associated with increasing activity of the HPA axis, and a consequent increase in cortisol release (Davis–Weinstein et al., unpublished paper; Kiess, Meidert, Dessendorfer, Scheiver, Kessler, & Konig, 1995). It is, therefore, not surprising that these developmental periods are characterized by significant changes in psychiatric status. We anticipate our follow-up assessments will reveal that some SPD adolescents retain their diagnosis, some improve, and some develop Axis I disorders, particularly schizophrenia.

It has been suggested that motor dysfunction is among the earliest indicators of abnormality in subcortical DA pathways. Thus, involuntary movements may prove to be a marker of risk for the later development of schizophrenia symptoms. When combined with other indicators, such as MPAs, FAs, and cortisol release, predictive power may be further enhanced. The derivation of a multifactor risk index with adequate sensitivity and specificity would provide a basis for exploring preventive interventions.

The developmental course of movement abnormalities in schizophrenia and spectrum disorders is of significant theoretical interest, yet has received relatively little attention from investigators. From a neurophysiological perspective, there are bases for predicting both *increases* and *decreases* in movement abnormalities with age. Cortisol release appears to increase with age, particularly in adolescence and late adulthood (Walker & Diforio, 1997), so this would be expected to result in an increase in movement abnormalities with age. On the other hand, DA release and receptor densities decrease with age, and this would lead to a reduction in the kinds of involuntary movements that have been observed in schizophrenia (Walker, 1994). Research on the natural course of movement abnormalities in schizophrenia is difficult because of the motoric side effects of antipsychotic medications. Thus, longitudinal studies of subjects with SPD may offer a greater opportunity for elucidating developmental changes in motor dysfunction.

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