Schizophrenia Bulletin vol. 35 no. 2 pp. 415–424, 2009
doi:10.1093/schbul/sbn126
Advance Access publication on September 12, 2008

Neurological Signs and Involuntary Movements in Schizophrenia: Intrinsic To and Informative on Systems Pathobiology

Peter F. Whitty[2], Olabisi Owoeye[3], and John L. Waddington[1,3,4]

[2]Department of Psychiatry, The Adelaide and Meath Hospital, Tallaght, Dublin, Ireland; [3]Cavan-Monaghan Mental Health Service, St Davnet's Hospital, Monaghan, Ireland; [4]Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, St Stephen's Green, Dublin 2, Ireland

While it has long been considered whether the pathobiology of schizophrenia extends beyond its defining symptoms to involve diverse domains of abnormality, in the manner of a systemic disease, studies of neuromotor dysfunction have been confounded by treatment with antipsychotic drugs. This challenge has been illuminated by a new generation of studies on first-episode schizophrenia before initiation of antipsychotic treatment and by opportunities in developing countries to study chronically ill patients who have remained antipsychotic naive due to limitations in provision of psychiatric care. Building from studies in antipsychotic-naive patients, this article reviews 2 domains of neuromotor dysfunction in schizophrenia: neurological signs and involuntary movements. The presence and characteristics of neurological signs in untreated vis-à-vis treated psychosis indicate a vulnerability marker for schizophrenia and implicate disruption to neuronal circuits linking the basal ganglia, cerebral cortex, and cerebellum. The presence and characteristics of involuntary movements in untreated vis-à-vis treated psychosis indicate an intrinsic feature of the disease process and implicate dysfunction in cortical-basal ganglia-cortical circuitry. These neuromotor disorders of schizophrenia join other markers of subtle but pervasive cerebral and extracerebral, systemic dysfunction, and complement current concepts of schizophrenia as a disorder of developmentally determined cortical-basal ganglia-thalamo-cortical/cerebellar network disconnectivity.

Key words: neuromotor disorder/dyskinesia/network dysfunction/disease process/antipsychotic naive

Introduction

That the pathobiology of schizophrenia may extend beyond its diagnostic features to involve broader domains of abnormality, in the manner of a systemic disease, has been considered for as long as the concept of schizophrenia itself. In relation to neurological abnormality, however, the rich clinical descriptions of the preneuroleptic era and their fundamental implications have experienced substantial neglect; following the introduction of neuroleptics (first-generation antipsychotic drugs) and recognition of their numerous neurological adverse effects, there followed the presumption that most neurological abnormalities in treated patients are a consequence of such treatment.

Over the modern era, the extent to which neurological abnormalities in medicated patients constitute adverse effects of their medication can only be resolved via comparison with otherwise matched groups of unmedicated patients, so as to define any disease-related component of such abnormality. Though this requirement is a scientific imperative, it presents ethical challenges.[1] Thus, from the 1950s through to the 1980s, these issues could be addressed only through (1) the historical record, (2) rare opportunities to assess antipsychotic-naive patient groups of uncertain representativeness, or (3) indirect indices such as relationships between extent of current neurological dysfunction and extent of prior/current exposure to antipsychotics.

Since the 1980s and the introduction of second-generation antipsychotic drugs, interest in these issues has been stimulated by 3 developments: the emergence of a new generation of studies on first-episode schizophrenia,[2,3] which provide an ethically propitious opportunity to study neurological function in antipsychotic-naive patients at the onset of diagnostic psychotic symptoms; opportunities in developing countries to study neurological function in patients with chronic psychotic illness who have remained antipsychotic naive due to limitations in provision of psychiatric care[4]; and new insights into the pathobiology of schizophrenia, indicating dysfunction not in any individual brain region(s) but, rather, in one or more interconnected network(s), the components of which subserve a diversity of functions and hence provide a substrate for a diversity of dysfunctions.[5,6]

[1]To whom correspondence should be addressed; tel: +353-1-402-2129, fax: +353-1-402-2453, e-mail: jwadding@rcsi.ie.

This article concerns the 2 domains of neurological dysfunction in schizophrenia that have generated the greatest empirical enquiry, the second of which has generated also considerable controversy: neurological signs (both "hard" and "soft")[7] and involuntary movements.[8] Hard neurological signs are held to localize and be diagnostic of specific brain abnormalities; while there are reports that they are overrepresented in patients with schizophrenia, as usually assessed under treatment with antipsychotics, the literature is limited and not wholly consistent regarding either extent or brain region localized.[7] In contrast, neurological soft signs (NSS) are held not to localize specific brain abnormalities but, rather, to constitute nondiagnostic, minor abnormalities in areas such as coordination, motor, sensory, and integrative functions; while there is an extensive literature on their elevated rate and clinical correlates in schizophrenia, there endures also a debate as to the extent to which such signs reflect the disease process of schizophrenia or its treatment.[7] Involuntary, choreoathetoid movements classically indicate dysfunction in the extrapyramidal motor system and implicate basal ganglia (striatum [caudate, putamen] and globus pallidus) disease but present a different challenge[8]; such involuntary movements have long been recognized to occur to excess in schizophrenia but have been interpreted primarily as an adverse effect of long-term treatment with antipsychotic drugs, ie, tardive dyskinesia, rather than an intrinsic feature of, and hence informative on, the disease process.[9]

Here, we consider each of these domains of neurological dysfunction in turn and then offer an integrative perspective on how they illuminate the debate on schizophrenia as a systemic disease.

Neurological Signs in Schizophrenia

Hard Neurological Signs

The presence of hard signs on clinical examination is considered a more robust finding than the presence of NSS because they are less likely to be influenced by artifacts such as medication. In schizophrenia, hard signs appear to be more static than soft signs over the first 6 months of illness, and higher levels are seen among patients compared with their siblings or healthy controls.[7,10–12] The notion that hard signs are a phenotype of schizophrenia needs further confirmation, ideally through longitudinal studies of high-risk cases over time. The frequency of hard signs among patients with schizophrenia vs other diagnostic groups is less clear, although one study reported that cerebellar signs were more common in schizophrenia than in patients with bipolar or substance misuse disorders.[10]

One limitation of the existing literature is the lack of a standardized clinical rating scale for hard signs. In general, hard signs tend to be rated as a subscale in the overall assessment of NSS, and there remains a high degree of variability over what constitutes a hard sign. The construction of a standardized assessment scale and applying it to never-medicated patients would help establish the rate and implications of hard signs in schizophrenia. Such studies should have a longitudinal design because the stability of hard signs needs verification beyond the first 6 months of illness.

Nature of NSS

The term neurological soft signs (NSS) was first used in the 1940s to describe nondiagnostic abnormalities in the neurological examinations of children with schizophrenia. NSS are defined as minor abnormalities on neurological examination in the absence of other fixed or transient features of neurological disorder.[13] They reflect difficulties in the areas of coordination, motor, sensory, and integrative functions and are considered a normal occurrence in childhood. However, increased rates of NSS are found in children with behavioral and learning difficulties and in children following premature delivery, low birthweight, meningitis, and malnutrition.[13–19] NSS improve during adolescence, and as a result they are considered to represent a developmental phenomenon; this is supported by the association between NSS and age, with scores repeatedly lower in older children.[20]

NSS have been reported in medical conditions such as head injury, cerebral tumors, dementia, and neurodegenerative diseases. However, the nonspecific nature of NSS has resulted in criticism of their use in clinical practice within the field of neurology.[21] From a neurologist's perspective, the primary objective of the neurological examination is localization, and localization comes from hard, not soft, signs. Nevertheless, the persistence of NSS beyond adolescence is likely to represent abnormal neurodevelopment, and as a result they have been more widely studied in conditions thought to have a neurodevelopmental basis, such as schizophrenia. The overrepresentation of these signs among patients with schizophrenia is well documented, but their relationship to treatment, response to treatment, course, and prognosis is less clear. The increase in first-episode studies, especially those involving antipsychotic-naive patients, now helps to improve our understanding of the significance of these neurological abnormalities in schizophrenia.

NSS as Markers of Disease

Patients with schizophrenia have higher rates of NSS compared with controls, and as many as 90% of patients have at least one sign at first presentation.[22] Among all patients with schizophrenia, this figure rises to 98%,[23] suggesting that it is unusual not to find some neurological dysfunction in this patient group. The significance of this finding is not clear because NSS are not specific to schizophrenia and have been reported in other psychotic and

Table 1. Studies of Neurological Soft Signs in Antipsychotic-Naive, Primarily First-Episode Patients With Schizophrenia

Study	NSS Scale	*N*	Comparison Group
John[32]	NES	40	30 Healthy controls
Mittal[36]	NSSS	19	None
Varambally[37]	CARS and NES	32	32 Healthy controls
Emsley[38]	NES	66	None
Sanders[39]	NES	59	51 Healthy controls; 27 other psychotic disorders
Keshavan[40]	NES	90	93 Healthy controls; 39 other psychotic disorders
Venkatasubramanian[41]	NES	21	21 Healthy controls
Shibre[42]	NES	200	78 Healthy controls
Browne[22]	NES and CNE	35	None
Gupta[43]	Clinical examination	26	117 Healthy controls; 126 medicated schizophrenia
Sanders[44]	NES	17	15 Healthy controls

Note: NSS, neurological soft signs; NES, Neurological Evaluation Scale; NSSS, Neurological Soft Sign Scale; CARS, Co-operative Ataxia Rating Scale; CNE, Condensed Neurological Examination.

nonpsychotic disorders. Patients with bipolar disorder,[24,25] substance misuse,[26,27] antisocial personality disorder,[28] and obsessive compulsive disorder (OCD)[29] have all been shown to have higher than expected rates of NSS. In the case of OCD, there is increasing evidence that neurological dysfunction is present in the frontal-subcortical circuitry.[30] In order for NSS to act as disease markers, different patterns of neurodysfunction are needed to discriminate schizophrenia from other disorders. One study examined NSS among first-episode schizophrenia patients with and without OCD and concluded that the 2 groups of patients did not differ in the level or type of neurodysfunction displayed. Similarly, among patients with bipolar disorder[24] and other nonschizophrenia psychoses,[24,31] there are no clear individual or groups of signs that discriminate these conditions. Consequently, NSS can be considered as general markers of brain dysfunction that do not discriminate between schizophrenia and other psychotic or non-psychotic disorders.

Even though NSS do not appear to discriminate between schizophrenia and other psychiatric disorders, NSS might still serve as markers of a disease process. A number of studies have examined the presence of NSS in individuals with a family history of schizophrenia, most commonly unaffected siblings of probands, and concluded that such persons have increased rates of NSS compared with healthy controls.[12,33–35] This indicates that NSS have a genetic component and that increased risk for schizophrenia is associated with higher levels of NSS. The emergence of longitudinal early intervention studies provides an opportunity to determine if the presence of NSS in high-risk cases can predict later development of schizophrenia. Combining NSS with other phenotypes of schizophrenia also has the potential to increase the predictive role of these signs in terms of diagnosis.

Factors Related to NSS

Antipsychotic Medication. The core relationship of NSS to schizophrenia is best addressed by examining rates of NSS among patients prior to the commencement of antipsychotic treatment. Comparing the rate of NSS in antipsychotic-naive patients with that in treated patients and healthy controls can establish whether NSS are intrinsic to the disease process or a side effect of treatment.

Table 1 lists the studies that have measured NSS in antipsychotic-naive patients. The common finding throughout these studies is that NSS are present before the commencement of treatment, with approximately one-fifth of antipsychotic-naive patients experiencing increased rates of NSS at first presentation.[22,43,45] Further, NSS appear to be independent of the type of antipsychotic medication because similar rates are observed among patients treated with atypical and conventional antipsychotics.[46–48] One possibility is that medication can contribute to the overall level of NSS because one study found that NSS were present in 23% of antipsychotic-naive and 46% of medicated patients.[43] Nevertheless, NSS appear to be an intrinsic component of the disease process of schizophrenia that are present before the onset of diagnostic symptoms and not solely a consequence or side effect of treatment.

Psychopathology. Psychopathology has an important influence on the severity of NSS and should be assessed when measuring the level of neurodysfunction. Schröder et al[49] initially reported that NSS were closely related to psychopathology and varied with clinical course. In acute settings, NSS are increased in accordance with psychopathology and improve with treatment of symptoms. This finding has been replicated in a number of first-episode studies where high levels of NSS at first presentation are

related to the high levels of psychopathology at this stage[50]; high levels of positive symptoms and impairment in attention appear to increase NSS, which ameliorate on commencement of antipsychotic medication. However, persistence of NSS beyond the acute stage is associated with negative symptoms, indicating that NSS may be a function of these symptoms or possibly an independent factor relating similarly to negative symptoms, cognitive impairment, and neurological function.[7]

Other Factors. Regarding other indicators of neurodysfunction, NSS are increased among patients who are mixed-handed.[22,24] Obstetric complications and minor physical anomalies are also associated with increased rates of NSS in schizophrenia, and combination studies of phenotypes can increase the predictive validity of NSS.[32,51] However, there is a relative shortage of information on the potential relationship between NSS and dyskinesia, especially among first-episode and antipsychotic-naive patients. NSS and dyskinesia have both been described independently in antipsychotic-naive patients at the time of the first episode[52]; see "Involuntary Movements in Schizophrenia" below. As part of our ongoing studies,[10,24] we analyzed this relationship among first-episode schizophrenia patients at presentation and at 4-year follow-up, with NSS measured using the Condensed Neurological Examination (CNE) and dyskinesia assessed using the Abnormal Involuntary Movement Scale (AIMS): among 64 patients assessed at both time points, preliminary results indicated no significant correlation between CNE score and AIMS score at first presentation; however, at follow-up there was a significant relationship between NSS and AIMS scores. The significance of this finding needs further exploration because other factors such as medication might have influenced levels of dyskinesia. Longitudinal examination of first-episode cohorts can help determine if dyskinesia and NSS both reflect a primary neurodysfunction in schizophrenia or whether they are secondary to other disease factors.

Outcome

Earlier studies involving non–first-episode cohorts indicated that NSS were progressive and deteriorated over time.[53–55] More recently, some first-episode studies have concluded that NSS are static and remain unchanged at follow-up.[38,56] However, not all first-episode studies support this finding, and improvement in NSS has been reported in the first 6 months and over the first 4 years of illness.[10,24,57] As discussed above, NSS are related to symptoms, and improvement in NSS might be a direct result of improvement in psychopathology following treatment of the acute first episode. However, it is also possible that the plasticity of the brain enables it to recover or compensate for earlier injury, with subsequent improvement in NSS over time. This is supported by findings that NSS reduce with age in healthy children and adolescents and that a younger age at onset of schizophrenia is associated with increased NSS.[58]

In terms of prognosis, earlier studies reported an association between NSS and more chronic and severe forms of illness; however, some first-episode studies found no association with outcome.[38,55,56,59–61] More recently, Prikryl and colleagues reported an association between persistence of NSS at 1 year following a first episode of schizophrenia and poor treatment response and outcome.[62] Further, NSS have been shown to improve over the early stages of illness, but this reduction is less pronounced for those with a more chronic course of illness.[57] Similarly, one study reported an association between change in NSS and outcome over the first 4 years of schizophrenia, with improvement in NSS score predictive of a more favorable outcome.[24] In summary, there is growing evidence that NSS are related to functional outcome among first-episode patients, and in addition to negative symptoms they characterize more severe forms of illness.

Future Research on Neurological Signs

At present, most of the scales used to measure NSS were devised using non–first-episode cases, and no scales have been validated in antipsychotic-naive first-episode samples. Similarly, in the case of one of the most widely used scales (Neurological Evaluation Scale), the various subscales have not been validated in first-episode samples. Two studies[63,64] validated subscales in non–first-episode samples, and similar studies of first-episode patients would further validate the conceptual categories of NSS that are widely used today. Some of the inconsistency in findings across studies could be accounted for by the different scales used to measure NSS, with some scales more likely to be influenced by changes in mental state while others focus more on harder signs that tend not to show the same degree of variation over time. Future research should further validate the assessment scales used in first-episode samples, and harder signs should be included as standard in each assessment of NSS.

There are inconsistencies in the findings on the stability of NSS over the course of illness. One limitation of studies to date is the reliance on total NSS total scores at follow-up, and it may be that different NSS items contribute to total scores at various time points. Emsley et al[38] examined the temporal stability of neurological abnormalities in first-epiosode schizophrenia. Using a factor analytic approach, the authors concluded that problems in the areas of motor sequencing and attention are replicable across samples. With the increase in high-risk and first-episode studies measuring NSS in prepsychotic and antipsychotic-naive subjects, there are now greater opportunities to follow up representative samples beyond the early course of illness. This would allow assessment of the stability of individual signs and categories of signs on a longitudinal rather than cross sectional basis. Such

studies would more accurately characterize the true stability or progression of NSS over the course of illness.

Involuntary Movements in Schizophrenia

The Historical Record

To understand fully the status of involuntary movements in schizophrenia as an integral component of the disease process, and an index of systems pathobiology, it is necessary to consider the challenges along an extended time line having 3 phases: firstly, how involuntary movements were initially recognized and accepted readily as a feature of the disease process; secondly, how this perspective was not only lost but also became heresy on reinterpretation of such movements as primarily an adverse effect of long-term treatment with antipsychotic drugs (ie, tardive dyskinesia); and thirdly, how subsequent application of the scientific method has led to the pardoning of heretics, vindication of the historical record, and new insights into the systems pathobiology of schizophrenia. Here we elaborate our previous reviews on these challenges[8,65,66]; see also Fenton[67]

While involuntary, choreoathetoid movements in schizophrenia have been described for as long as we have had a concept of this disorder, indeed for more than a 100 years, the extent and meaning of this clinical reality did not endure beyond the 1950s. We have previously reviewed the historical record in extensio: from initial descriptions of the motor disorders of severe psychiatric illness by Kahlbaum in the 1870s and the many clinical observations by Kraepelin in the 1890s/early 1900s of involuntary ''choreic movements'' and ''athetoid ataxia'' among patients with dementia praecox; through the reconceptualization of such movements by Bleuler as psychogenic mannerisms accessory to psychotic illness; to the exhaustive psychopathological classifications of the German school over the first half of the 20th century, including Leonhard's identification of involuntary movements as an organic feature of sufficient prominence to warrant recognition as parakinetic catatonia.[8,68]

The Intervening Schema. From the 1950s through to the 1980s, these historical, disease-related concepts were lost and replaced by a new schema predicated on the causal role of long-term treatment with antipsychotic drugs in the pathobiology of involuntary movements; this concept of tardive dyskinesia, which rapidly attained an enduring clinical, pathophysiological, and medicolegal identity, has previously received exhaustive review.[65,69]

The Contemporary Record in Developed Countries

Chinks in the hold of tardive dyskinesia over conceptualization of involuntary movements in schizophrenia emerged with the publication in the early-mid 1980s of 2 seminal studies, followed by a series of elaborating reports (table 2).

Table 2. Studies of Involuntary Movements in Antipsychotic-Naive, First-Episode Through Chronically Ill Patients With Schizophrenia or Schizotypal Personality Disorder

Study	Patients	Mean Age (y)	*N*	Criteria	Prevalence (%)
Honer[70]	First episode	22	167	ESRS	4
Chorfi[71]	First episode	24	50	AIMS	0
Cortese[72]	First episode	24	39	ESRS	13
Chatterjee[73]	First episode	26	89	SDS	1
Puri[75]	First episode	27	27	AIMS	7
Gervin[52]	First episode	28	49	AIMS, S&K	10
Fenn[76]	Acutely ill	28	22	AIMS, S&K	14
Fenton[77]	Acutely ill	28	94	Descriptive	15
Cassady[78]	Schizotypal	32	34	MPRC-IMS	12
McCreadie[79]	Chronically ill	45	12	AIMS	0
McCreadie[80]	Chronically ill	47	143	AIMS	35
Owens[81]	Chronically ill	67	47	AIMS, S&K	51

Note: ESRS, Extrapyramidal Signs Rating Scale; AIMS, Abnormal Involuntary Movement Scale; SDS, Simpson Dyskinesia Scale; S&K, Schooler and Kane criteria; MPRC-IMS, Maryland Psychiatric Research Center Involuntary Movement Scale.

The first study[81] examined a rare group of 47 patients with chronic schizophrenia who has remained antipsychotic naive because of a psychodynamic, therapeutic community approach to their care. The primary and in this context somewhat shocking result, attained using conventional rating scales for tardive dyskinesia, was the presence of involuntary movements in 51% of antipsychotic-naive patients, this prevalence being only slightly, though significantly, exceeded by that among antipsychotic-treated patients of the same cohort after adjustment for age[82]; the phenomenology, distribution, and severity of involuntary movements in antipsychotic-naive patients were indistinguishable from classical tardive dyskinesia. This study provided empirically robust and iconoclastic evidence to validate, with contemporary rigor, the historical record of involuntary movements in patients with chronic schizophrenia who had never received treatment with antipsychotic drugs.

In the second study, Rogers[83] described the motor status of 100 patients with schizophrenia who had experienced long-term hospitalization from the preneuroleptic era. Movement disorder was defined descriptively, to avoid the ''conflict of paradigms'', ie, should a given involuntary movement in chronic psychotic illness be described in neurological terms as orofacial dyskinesia or in psychodynamic terms as pseudoexpressive mannerisms? Retrospective review revealed 71% as having motor abnormality at admission in the preneuroleptic era; there

were no differences in movements between patients currently receiving antipsychotics and those with no or minimal exposure. This study provides strong support for a disorder of motor control that is integral to schizophrenia and includes involuntary movements.

Subsequent studies have elaborated these findings. An extensive study on tardive dyskinesia[74] encountered a small number of elderly inpatients with schizophrenia who had never received antipsychotics because their psychosis had evolved into the "defect state" before the introduction thereof; an additional patient had received only transient treatment. Involuntary orofacial movements indistinguishable from "tardive" dyskinesia were identified in 4 of these 5 patients, each of whom had traversed essentially a lifetime of untreated illness; the topography and severity of these movements was indistinguishable from those of age-matched counterparts who had received several decades of exposure to antipsychotics. A subsequent study[77] reviewed the medical records of 94 chronically-ill patients with schizophrenia who at the time of first admission in the 1950s did not receive antipsychotics; the particularly extensive medical records for this cohort of patients allowed the extraction of verbatim descriptions of abnormal movements, several of which were clearly compatible with contemporary definitions of tardive dyskinesia. Movement disorder was present in 28% of patients; involuntary orofacial movements, indistinguishable from tardive dyskinesia, present in 15%. These studies provide further substantive evidence for involuntary movements in patients with chronic schizophrenia who have never received treatment with antipsychotics.

The Contemporary Record in Developing Countries

Three developing countries (India, Morocco, and Nigeria) have provided opportunities to examine involuntary movements in patients with chronic schizophrenia who have remained antipsychotic naive due to limitations in provision of psychiatric care.

Though an initial note from Morocco appeared negative,[71] a subsequent, more systematic study[76] examined 22 antipsychotic-naive patients and found choreoathetoid movements in 14%; these movements were qualitatively identical to tardive dyskinesia but differed in distribution, being more prominent in the limbs with milder severity in the orofacial region.

Though an initial study in a small number of patients in Nigeria appeared negative,[79] a subsequent, more extensive study in India[80] indicated involuntary movements in 38% of antipsychotic-naive patients with chronic schizophrenia; this prevalence was indistinguishable from that found in patients exposed to antipsychotics, though the prevalence of similar movements among the normal elderly in the same area (15%) was unusually high. A composite report on an enlarged sample of 143 antipsychotic-naive patients with chronic schizophrenia[4] indicated involuntary movements in 35%, with some evidence for basal ganglia pathology on MRI.[80] Whether involuntary movements are evident in the first-degree relatives of probands with such movement disorder remains unclear.[85,86]

The New Era of First-Episode Studies

While the studies reviewed above have clearly demonstrated involuntary movements in diverse populations of patients with schizophrenia who have never been exposed to antipsychotic drugs, the emergence over the past 2 decades of a new generation of studies on first-episode schizophrenia[3,87] provides an unparalleled opportunity for the prospective study of neurological function in antipsychotic-naive patients from the onset of diagnostic psychotic symptoms (table 2).

In the first such study, Chatterjee et al[73] found one of 89 patients to evidence involuntary movements. However, our own study[52] found involuntary orofacial movements in 10% of 49 antipsychotic-naive patients; as this rate was lower (3%) among a group of otherwise similar patients who had been minimally medicated with antipsychotics before assessment, this raises the possibility that antipsychotics may mask mild involuntary movements in young patients. Subsequent studies have reported generally similar findings in antipsychotic-naive, first-episode schizophrenia, ie, 7% of 27 patients,[75] 13% of 39 patients,[72] and 4% of 167 patients.[70] Additionally, similar findings have been reported in individuals with untreated schizophrenia spectrum personality, ie, 12% of 34 subjects, essentially those with schizotypal rather than schizoid personality.[78]

In summary, spontaneous involuntary movements in young, unmedicated patients with schizophrenia are present to a previously unappreciated extent. When considered together with the findings in older antipsychotic-naive patients reviewed above, the rate and severity of involuntary movements appears to rise with increasing chronicity of untreated psychosis.[67]

Clinical Correlates of Spontaneous Dyskinesia in Schizophrenia

Inevitably, relatively modest numbers of antipsychotic-naive patients with schizophrenia means that systematic studies on clinical correlates of involuntary movements are limited in comparison with those concerning tardive dyskinesia. However, while few, the available studies are heuristic in relation to systems pathobiology.

In terms of demographics, prevalence of involuntary movements in antipsychotic-naive patients appears associated with increasing age; this echoes a long-standing literature on tardive dyskinesia in schizophrenia.[8,65,69] During the course of untreated schizophrenia, increasing age may be a proxy for increasing duration of illness; thus, this relationship may account for a low prevalence

of involuntary movements in studies of antipsychotic-naive patients experiencing their first psychotic episode and a higher prevalence in those who have remained untreated over chronic illness.

Regarding cognitive and psychopathological factors, prevalence of involuntary movements in antipsychotic-naive patients may be associated with extent of cognitive dysfunction and negative symptoms; this again echoes a long-standing literature on tardive dyskinesia, particularly in relation to executive (frontal) dysfunction.[8,66] It appears that the prevalence of involuntary movements increases over the lifetime trajectory of schizophrenia in both untreated and treated patients and may converge with increasing cognitive impairment in both groups with advancing age/chronicity of illness.

On this basis, involuntary movements in untreated schizophrenia may be just one manifestation of greater cerebral dysfunction, involving particularly the basal ganglia, frontal cortex, and/or brain regions interacting with the basal ganglia and frontal cortex; thus, antipsychotic treatment appears to enhance the appearance of involuntary movements in schizophrenia patients having vulnerability to such movement disorder as an intrinsic component of the disease process. We have shown[88] that in elderly patients approaching the limits of human longevity in the course of several decades of antipsychotic treatment, the prevalence of involuntary movements approaches 100%, in particular association with executive (frontal) dysfunction; this suggests that vulnerability to tardive dyskinesia is essentially 100% over a lifetime of illness as an intrinsic component of the disease process and that on approaching this "end stage" the distinction between "tardive dyskinesia and spontaneous involuntary movements may be more semantic than real.

Specificity of Spontaneous Dyskinesia to Schizophrenia

Spontaneous involuntary movements in the healthy and thus unmedicated elderly are relatively infrequent, with a prevalence of 1%–8%; however, both prevalence and severity rise considerably with a diversity of organic brain disorders that are not common indications for antipsychotic treatment.[8,65] In the only systematic, comparative study,[89] a higher prevalence of spontaneous involuntary movements was reported in untreated schizophrenia (23%) vis-à-vis nonpsychotic patients (7%) having primarily affective and personality disorders.

Spontaneous Dyskinesia Before Onset of Psychosis

Notably, spontaneous involuntary movements have been reported in 2 groups of individuals prior to the onset of schizophrenia and subsequent treatment with antipsychotics. In a unique study, Walker et al[90] reviewed childhood home movies of adult patients who were subsequently diagnosed with schizophrenia; over the first 2 years of life, more neuromotor abnormalities were found in preschizophrenia subjects compared with various control groups, including choreoathetoid movements and posturing of the upper limbs; similar findings were reported by Rosso and et al.[91] Similarly, Jones et al[92] in a birth cohort study found that those subjects who went on to develop schizophrenia in early adulthood were reported to show an excess of grimacing/twitching movements over childhood.

These findings add to the proposition that involuntary movements appear integral to the disease process of schizophrenia and suggest that such movements may be evident even before the emergence of diagnostic psychotic symptoms in young adulthood.

Parkinsonian and Other Extrapyramidal Features in Antipsychotic-Naive Patients With Schizophrenia

If involuntary movements are indicative of dysfunction in the extrapyramidal motor system and implicate basal ganglia disease, the question arises as to whether other signs of extrapyramidal dysfunction, such as Parkinsonism, may also be intrinsic to the disease process of schizophrenia.

Although the historical literature noted similarities between some clinical characteristics of schizophrenia and Parkinsonism,[93] Caligiuri et al[94] published the first contemporary report of Parkinsonism in antipsychotic-naive patients: clinical evaluation of 24 newly diagnosed patients with schizophrenia revealed 21% to evidence rigidity and 12% bradykinesia, while quantitative methods revealed 29% to evidence rigidity and 37% tremor; the same quantitative methods indicated 4% of controls to evidence rigidity in the absence of other extrapyramidal features.

Subsequent investigations have confirmed these initial findings. In further studies of first-episode psychosis, one[73] reported extrapyramidal features, primarily mild rigidity and akinesia, in 17% of 89 antipsychotic-naive patients in association with higher risk for antipsychotic-induced Parkinsonism; subsequent studies reported rigidity in 4% of 27 patients,[75] in 2% of 174 patients,[95] and in 18% of 39 such patients.[72] In the most comprehensive first-episode study,[70] Parkinsonism was present in 27% of 167 antipsychotic-naive patients (hypokinesia, 20%; tremor, 3%; akathisia, 6%); dystonia was evident in 2% thereof. Among chronically ill, antipsychotic-naive patients in India, Parkinsonism has been reported in 15% of 142 patients[4,80] but not in their first-degree relatives.[85]

These findings extend the concept of movement disorder in untreated schizophrenia, through involvement not just of involuntary movements but also of Parkinsonian features, as an intrinsic component of a disease process involving dysfunction in basal ganglia-cortical mechanisms.

Pathobiology of NSS and Involuntary Movements Integral to Schizophrenia: Cortical-Subcortical Network Dysfunction

In untreated vis-à-vis treated schizophrenia, NSS and their clinical correlates implicate disruption to neuronal circuits linking the basal ganglia, cerebral cortex, and cerebellum, while involuntary movements and their clinical correlates implicate dysfunction in cortical-basal ganglia-cortical circuitry. Thus, these 2 domains of neurological disorder appear to share, in considerable part, some common pathobiology in cortical-subcortical/cerebellar dysfunction in a manner that is complementary to and elaborative of contemporary notions on the pathobiology of schizophrenia.

More specifically, current concepts of schizophrenia as a disorder of developmentally determined cortical-basal ganglia-thalamo-cortical/cerebellar network disconnectivity[5,6,97–100] would predict the psychopathology and cognitive impairment of schizophrenia to be accompanied by NSS and movement disorder as intrinsic aspects of the disease process. As reviewed above, both the historical record and contemporary studies are consistent with this proposition.

Parenthetically, these data also suggest that any perspective of antipsychotic drugs as the essential cause of neurological dysfunction in schizophrenia, and of tardive dyskinesia and Parkinsonism in particular, is incomplete. An alternative perspective is one in which antipsychotic drugs interact with the underlying disease process to precipitate and accentuate intrinsic motor phenomena.[8,65,66]

The neuromotor disorders of schizophrenia thus join other markers of subtle but pervasive cerebral and extracerebral, systemic dysfunction that can be evident both before the emergence of psychosis and thereafter in terms of increased physical morbidity and mortality, as detailed in companion articles in this issue of the *Bulletin*.

Funding

Cavan-Monaghan Mental Health Service.

References

1 Waddington JL. Tardive dyskinesia. *BMJ*. 1998;296:1004.
2. Baldwin P, Browne D, Scully PJ, et al. Epidemiology of first-episode psychosis: illustrating the challenges across diagnostic boundaries through the Cavan-Monaghan study at 8 years. *Schizophr Bull*. 2005;31:624–638.
3. Weiden PJ, Buckley PF, Grody M. Understanding and treating "first-episode" schizophrenia. *Psychiatr Clin N Am*. 2007;30:481–510.
4. McCreadie RG, Srinivasan TN, Padmavati R, Thara R. Extrapyramidal symptoms in unmedicated schizophrenia. *J Psychiatr Res*. 2005;39:261–266.
5. Waddington JL, Morgan M. Pathobiology of schizophrenia: implications for clinical management and treatment. In: Murray RM, Lieberman JA, eds. *Comprehensive Care of Schizophrenia: A Handbook of Clinical Management and Treatment.* London, UK: Martin Dunitz; 2001:27–35.
6. Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and disconnection in schizophrenia. *Biol Psychiatry*. 2006;59:929–939.
7. Bombin I, Arango C, Buchanan RW. Significance and meaning of neurological signs in schizophrenia: two decades later. *Schizophr Bull*. 2005;31:962–977.
8. Bocti C, Black DN, Waddington JL. Dyskinesia in patients with schizophrenia never treated with antipsychotics: conceptual and pathophysiological implications. In: Bedard MA, ed. *Mental and Behavioural Dysfunction in Movement Disorders.* Totawa, NJ: Humana Press; 2004:489–498.
9. Kane JM. Tardive dyskinesia circa 2006. *Am J Psychiatry*. 2006;163:1316–1318.
10. Kinney DK, Yurgelun-Todd DA, Woods BT. Neurologic signs of cerebellar and cortical sensory dysfunction in schizophrenics and their relatives. *Schizophr Res*. 1999;35:99–104.
11. Ismail B, Cantor-Graae E, McNeil TF. Neurological abnormalities in schizophrenic patients and their siblings. *Am J Psychiatry*. 1998;155:84–89.
12. Woods BT, Kinney DK, Yurgelun-Todd DA. Neurological 'hard' signs and family history of psychosis in schizophrenia. *Biol Psychiatry*. 1991;30:806–816.
13. Shaffer D, OConnor PA, Shafer SQ. Neurological soft signs: their origins and significance for behaviour. In: Rutter M, ed. *Developmental Neuropsychiatry.* New York, NY: Guildford Press; 1983:145–163.
14. Pine DS, Wasserman GA, Fried JE, et al. Neurological soft signs: one-year stability and relationship to psychiatric symptoms in boys. *J Am Acad Child Adolesc Psychiatry*. 1997;36:1579–1586.
15. Adams RM, Kocis JJ, Estes RE. Soft neurological signs in learning-disabled children and controls. *Am J Disord Child.* 1974;128:614–618.
16. Jongmans M, Mercuri E, deVries L, et al. Minor neurological signs and perceptual-motor difficulties in prematurely born children. *Arch Disord Child Fetal Neonatal Educ*. 1997;76:9–14.
17. Hertzig ME. Neurological 'soft' signs in low-birthweight children. *Dev Med Child Neurol*. 1981;23:778–791.
18. Grimwood K, Anderson VA, Bond L, et al. Adverse outcomes of bacterial meningitis in school-age survivors. *Paediatrics*. 1995;95:646–656.
19. Galler JR, Ramset F, Solimano G. A follow-up study of the effects of early malnutrition on subsequent behavioural development. II. Fine motor skills in adolescence. *Paediatr Res*. 1985;19:524–527.
20. Zabala A, Robles O, Parellada M, et al. Neurological soft signs in adolescents with first episode psychosis. *Eur Psychiatry*. 2006;21:283–287.
21. Stephenson JBP. Commentary. Soft signs: soft neurologist. *Arch Disord Child.* 2001;85:371–374.
22. Browne S, Clarke M, Gervin M, et al. Determinants of neurological dysfunction in first episode schizophrenia. *Psychol Med*. 2000;30:1433–1441.
23. Lane A, Colgan K, Moynihan F, et al. Schizophrenia and neurological soft signs: gender differences in clinical correlates and antecedent factors. *Psychiat Res*. 1996;64:105–114.
24. Whitty P, Clarke M, McTigue O, et al. Diagnostic specificity and predictors of neurological soft signs in schizophrenia, bipolar disorder and other psychoses over the first 4 years of illness. *Schizophr Res*. 2006;86:110–117.

25. Negash A, Kebede D, Alem A, et al. Neurological soft signs in bipolar I disorder patients. *J Affect Disord*. 2004;80:221–230.
26. Keenan E, O'Donnell C, Sinanan K, O'Callaghan E. Severity of alcohol dependence and it's relationship to neuropsychological impairment and family history. *Acta Psychiatr Scand*. 1997;95:272–276.
27. Mohr F, Hubmann W, Cohen R, et al. Neurological soft signs in schizophrenia: assessment and correlates. *Eur Arch Psychiatr Clin Neurosci*. 1996;246:240–248.
28. Lindberg N, Tani P, Stenberg JH, Appelberg P, Porkka-Heiskanen T, Virkkunen M. Neurological soft signs in homicidal men with antisocial personality disorder. *Eur Psychiatry*. 2004;19:433–437.
29. Bolton D, Gibb W, Lees A, et al. Neurological soft signs in obsessive compulsive disorder: standardised assessment and comparison with schizophrenia. *Behav Neurol*. 1998;11:197–204.
30. Poyurovsky M, Faragian S, Pashinian A, et al. Neurological soft signs in schizophrenia patients with obsessive-compulsive disorder. *J Neuropsychiatr Clin Neurosci*. 2007;19:145–150.
31. Keshavan MS, Sanders RD, Sweeney JA, et al. Diagnostic specificity and neuroanatomical validity of neurological abnormalities in first-episode psychoses. *Am J Psychiatry*. 2003;106:1298–1304.
32. John JP, Arunachalam V, Ratnam B, Isaac MK. Expanding the schizophrenia phenotype: a composite evaluation of neurodevelopmental markers. *Compr Psychiatry*. 2008;49:78–86.
33. Chen YL, Chen YH, Mak FL. Soft neurological signs in schizophrenic patients and their nonpsychotic siblings. *J Nerv Ment Dis*. 2000;188:84–89.
34. Yazici AH, Demir B, Yazici KM, Göğüş A. Neurological soft signs in schizophrenic patients and their nonpsychotic siblings. *Schizophr Res*. 2002;58:241–246.
35. Compton MT, Bollini AM, McKenzie Mack L, et al. Neurological soft signs and minor physical anomalies in patients with schizophrenia and related disorders, their first-degree biological relatives, and non-psychiatric controls. *Schizophr Res*. 2007;94:64–73.
36. Mittal VA, Hasenkamp W, Sanfilipo M, et al. Relation of neurological soft signs to psychiatric symptoms in schizophrenia. *Schizophr Res*. 2007;94:37–44.
37. Varambally S, Venkatasubramanian G, Thirthalli J, Janakiramaiah N, Gangadhar BN. Cerebellar and other neurological soft signs in antipsychotic-naïve schizophrenia. *Acta Psychiatr Scand*. 2006;114:352–356.
38. Emsley R, Turner HJ, Oosthuizen PP, Carr J. Neurological abnormalities in first-episode schizophrenia: temporal stability and clinical outcome correlates. *Schizophr Res*. 2005;75:35–44.
39. Sanders RD, Schuepbach D, Goldstein G, Haas GL, Sweenwy JA, Keshavan MS. Relationships between cognitive and neurological performance in neuroleptic-naïve psychosis. *J Neuropsychiatr Clin Neurosci*. 2004;16:480–487.
40. Keshavan MS, Sanders RD, Sweeney JA, et al. Diagnostic specificity and neuroanatomical validity of neurological abnormalities in first-episode psychoses. *Am J Psychiatry*. 2003;106:1298–1304.
41. Venkatasubramanian G, Latha V, Gnagadhar BN, et al. Neurological soft signs in never-treated schizophrenia. *Acta Psychiatr Scand*. 2003;108:144–146.
42. Shibre T, Kebede D, Alem A, et al. Neurological soft signs (NSS) in 200 treatment-naïve cases with schizophrenia: a community-based study in a rural setting. *Nord J Psychiatry*. 2002;56:425–431.
43. Gupta S, Andreasen N, Arndt S, et al. Neurological soft signs in neuroleptic-naïve and neuroleptic-treated schizophrenic patients and normal comparison subjects. *Am J Psychiatry*. 1995;152:191–196.
44. Sanders RD, Keshavan MS, Schooler NR. Neurological examination abnormalities in neuroleptic-naïve patients with first-break schizophrenia: preliminary results. *Am J Psychiatry*. 1994;151:1231–1233.
45. Wolff AL, O'Driscoll GA. Motor deficits and schizophrenia: the evidence from neuroleptic-naïve and populations at risk. *J Psychiatr Neurosci*. 1999;24:304–314.
46. Boks MP, Liddle PF, Russo S, Knegtering R, van der Bosch RJ. Influence of antipsychotic agents on neurological soft signs and dyskinesia in first episode psychosis. *Psychiatr Res*. 2003;109:167–170.
47. Jahn T, Hubmann W, Karr M, et al. Motoric neurological soft signs and psychopathological symptoms in schizophrenic psychoses. *Psychiatr Res*. 2006;142:191–199.
48. Bersani G, Gherardelli S, Clemente R, et al. Neurologic soft signs in schizophrenic patients treated with conventional and atypical antipsychotics. *J Clin Psychopharmacol*. 2005;25:372–375.
49. Schröder J, Niethammer R, Geider FJ, Binkert M, Jauss M, Sauer H. Neurological soft signs in schizophrenia. *Schizophr Res*. 1991;6:25–30.
50. Mittal VA, Hasenkamp W, Sanfilipo M, et al. Relation of neurological soft signs to psychiatric symptoms in schizophrenia. *Schizophr Res*. 2007;94:37–44.
51. Peralta V, Cuesta MJ, Serrano JF. Obstetric complications and neurological abnormalities in neuroleptic-naive psychotic patients. *Eur Arch Psychiatr Clin Neurosci*. 2006;256:407–413.
52. Gervin M, Browne S, Lane A, et al. Spontaneous abnormal involuntary movements in first-episode schizophrenia and schizophreniform disorder: baseline rate in a group of patients from an Irish catchment area. *Am J Psychiatry*. 1998;155:1202–1206.
53. Chen EY, Kwok CL, Au JW, Chen RY, Lau BS. Progressive deterioration of soft neurological signs in chronic schizophrenic patients. *Acta Psychiatr Scand*. 2000;102:342–349.
54. Madsen AL, Vorstrup S, Rubin P, Larsen JK, Hemmingsen R. Neurological abnormalities in schizophrenic patients: a prospective follow-up study 5 years after first admission. *Acta Psychiatr Scand*. 1999;100:119–125.
55. Torrey EF. Neurological abnormalities in schizophrenic patients. *Biol Psychiatry*. 1980;15:381–389.
56. Chen EY, Hui CL, Chan RC, et al. A 3-year prospective study of neurological soft signs in first-episode schizophrenia. *Schizophr Res*. 2005;75:45–54.
57. Bachmann S, Bottmer C, Schröder J. Neurological soft signs in first-episode schizophrenia: a follow-up study. *Am J Psychiatry*. 2005;162:2337–2343.
58. Biswas P, Malhotra S, Malhotra A, Gupta N. Comparative study of neurological soft signs in schizophrenia with onset in childhood, adolescence and adulthood. *Acta Psychiatr Scand*. 2007;115:295–303.
59. Johnstone EC, Macmillan JF, Frith CD, Benn DK, Crow TJ. Further investigation of the predictors of outcome following first schizophrenic episodes. *Br J Psychiatry*. 1990;157:182–189.
60. Sanders RD, Keshavan MS, Schooler NR. Neurological examination abnormalities in neuroleptic-naïve patients with first-break schizophrenia: preliminary results. *Am J Psychiatry*. 1994;151:1231–1233.

61. Dazzan P, Murray RM. Neurological soft signs in first-episode psychosis: a systematic review. *Br J Psychiatry*. 2002;(suppl 43):s50–s57.
62. Prikryl R, Ceskova E, Kasparek T, Kucerova H. Neurological soft signs and their relationship to 1-year outcome in first-episode schizophrenia. *Eur Psychiatry*. 2007;22:499–504.
63. Jahn T, Cohen R, Hubmann W, et al. The Brief Motor Scale (BMS) for the assessment of motor soft signs in schizophrenic psychoses and other psychiatric disorders. *Psychiatry Res*. 2006;142:177–189.
64. Krebs MO, Gut-Fayand A, Bourdel M, Dischamp J, Olié J. Validation and factorial structure of a standardized neurological examination assessing neurological soft signs in schizophrenia. *Schizophr Res*. 2000;45:245–260.
65. Waddington JL. Schizophrenia, affective psychoses and other disorders treated with neuroleptic drugs: the enigma of tardive dyskinesia, its neurobiological determinants and the "conflict of paradigms". *Int Rev Neurobiol*. 1989;31: 297–353.
66. Waddington JL. Psychopathological and cognitive correlates of tardive dyskinesia in schizophrenia and other disorders treated with neuroleptic drugs. In: Weiner WJ, Lang AE, eds. *Advances In Neurology.*Vol 65: New York, NY: Raven Press; 1995: 211–229.
67. Fenton WS. Prevalence of spontaneous dyskinesia in schizophrenia. *J Clin Psychiatry*. 2000;61:10–14.
68. Waddington JL, Crow TJ. Abnormal involuntary movements and psychosis in the preneuroleptic era and in unmedicated patients: implications for the concept of tardive dyskinesia. In: Wolf M, Mosnaim AD, eds. *Tardive Dyskinesia: Biological Mechanisms and Clinical Aspects.* Washington, DC: American Psychiatric Press; 1988:51–66.
69. Kane JM, Smith JM. Tardive dyskinesia: prevalence and risk factors. *Arch Gen Psychiatry*. 1982;39:473–481.
70. Honer WG, Kopala LC, Rabinowitz J. Extrapyramidal symptoms and signs in first-episode, antipsychotic exposed and non-exposed patients with schizophrenia or related psychotic illness. *J Psychopharmacol*. 2005;19:277–85.
71. Chorfi M, Moussaoui D. Lack of dyskinesia in unmedicated schizophrenics. *Psychopharmacology*. 1989;97:423.
72. Cortese L, Caligiuri MP, Malla AK, Manchanda R, Takhar J, Haricharan R. Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naïve schizophrenia patients. *Schizophr Res*. 2005;75:65–75.
73. Chatterjee A, Chakos M, Koreen A, et al. Prevalence and clinical correlates of extrapyramidal signs and spontaneous dyskinesia in never-medicated schizophrenic patients. *Am J Psychiatry*. 1995;152:1724–1729.
74. Waddington JL, Youssef HA. The lifetime outcome and involuntary movements of schizophrenia never treated with neuroleptic drugs. *Br J Psychiatry*. 1990;156:106–108.
75. Puri BK, Barnes TR, Chapman MJ, Hutton SB, Joyce EM. Spontaneous dyskinesia in first episode schizophrenia. *J Neurol Neurosurg Psychiatry*. 1999;66:76–78.
76. Fenn DS, Moussaoui D, Hoffman WF, et al. Movements in never-medicated schizophrenics: a preliminary study. *Psychopharmacology*. 1996;123:206–210.
77. Fenton WS, Wyatt RJ, McGlashan TH. Risk factors for spontaneous dyskinesia in schizophrenia. *Arch Gen Psychiatry*. 1994;51:643–650.
78. Cassady SL, Adami H, Moran M, Kunkel R, Thaker GK. Spontaneous dyskinesia in subjects with schizophrenia spectrum personality. *Am J Psychiatry*. 1998;155:70–75.
79. McCreadie RG, Ohaeri JU. Movement disorder in never and minimally treated Nigerian schizophrenic patients. *Br J Psychiatry*. 1994;164:184–189.
80. McCreadie RG, Thara R, Kamath S, et al. Abnormal movements in never-medicated Indian patients with schizophrenia. *Br J Psychiatry*. 1996;168:221–226.
81. Owens DG, Johnstone EC, Frith CD. Spontaneous involuntary disorders of movement: their prevalence, severity, and distribution in chronic schizophrenics with and without treatment with neuroleptics. *Arch Gen Psychiatry*. 1982;39:452–461.
82. Crow TJ, Cross AI, Johnstone EC, Owen F, Owens DG, Waddington JL. Abnormal involuntary movements in schizophrenia: are they related to the disease process or its treatment? Are they associated with changes in dopamine receptors? *J Clin Psychopharmacol*. 1982;2:336–340.
83. Rogers D. The motor disorders of severe psychiatric illness: a conflict of paradigms. *Br J Psychiatry*. 1985;147:221–232.
84. Waddington JL, Youssef HA. The lifetime outcome and involuntary movements of schizophrenia never treated with neuroleptic drugs. *Br J Psychiatry*. 1990;156:106–108.
85. McCreadie RG, Thara R, Srinivasan TN, Padmavati R. Spontaneous dyskinesia in first-degree relatives of chronically ill, never-treated people with schizophrenia. *Br J Psychiatry*. 2003;183:45–49.
86. Tarbox SI, Pogue-Geile MF. Spontaneous dyskinesia and familial liability to schizophrenia. *Schizophr Res*. 2006;81:125–137.
87. Waddington JL. What have we learned from the new generation of prospective studies on first episode psychosis? *Schizophr Bull*. 2005;31:623.
88. Quinn J, Meagher D, Murphy P, Kinsella A, Mullaney J, Waddington JL. Vulnerability to involuntary movements over a lifetime trajectory of schizophrenia approaches 100%, in association with executive (frontal) dysfunction. *Schizophr Res*. 2001;49:79–87.
89. Fenton WS, Blyler CR, Wyatt RJ, McGlashan TH. Prevalence of spontaneous dyskinesia in schizophrenic and non-schizophrenic psychiatric patients. *Br J Psychiatry*. 1997;171:265–268.
90. Walker EF, Savoie T, Davis D. Neuromotor precursors of schizophrenia. *Schizophr Bull*. 1994;20:441–451.
91. Rosso IM, Bearden CE, Hollister JM, et al. Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr Bull*. 2000;26:367–378.
92. Jones P, Rodgers B, Murray R, Marmot M. Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet*. 1994;344:1398–1402.
93. Kennard MA. Value of equivocal signs in neurological diagnosis. *Neurology*. 1960;10:753–764.
94. Caligiuri MP, Lohr JB, Jeste DV. Parkinsonism in neuroleptic-naive schizophrenic patients. *Am J Psychiatry*. 1993;150: 1343–1348.
95. Chong SA, Subramaniam M, Verma S. Spontaneous parkinsonism in antipsychotic-naive patients with first-episode psychosis. *Can J Psychiatry*. 2005;50:429–431.
98. Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M. Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. *Biol Psychiatry*. 1999;46:908–920.
99. Picard H, Amado I, Mouchet-Mages S, Olie J, Krebs M. The role of the cerebellum in schizophrenia: an update of clinical cognitive, and functional evidences. *Schizophr Bull*. 2008;34:155–172.
100. Andreasen NC, Pierson R. The role of the cerebellum in schizophrenia. *Biol Psychiatry*. 2008;64:81–88.