Curr Psychiatry Rep (2017) 19: 97
https://doi.org/10.1007/s11920-017-0856-9

Motor System Pathology in Psychosis

Sebastian Walther[1] · **Vijay A. Mittal**[2,3,4,5,6]

Published online: 30 October 2017

Abstract
Purpose of Review Motor abnormalities are an intrinsic feature of psychosis. Neurological soft signs, Parkinsonism, dyskinesia, and other motor phenomena are frequently observed in subjects at clinical or genetic risk for psychosis as well as first-episode patients, chronic patients. Here, we review the most recent literature on motor assessments and pathophysiology in psychosis.
Recent Findings Instrumental measures of fine motor performance, balance, spontaneous motor activity, and gesture indicated motor abnormalities in subjects at risk and across stages of schizophrenia. Motor phenomena are associated with distinct symptom dimensions and may indicate poor outcomes. Neuroimaging studies demonstrated altered neural maturation within critical motor networks in subjects at risk. Furthermore, specific categories of motor dysfunction were associated with distinct structural and functional alterations in the motor system in schizophrenia.
Summary Motor abnormalities provide a unique window into the pathobiology of psychosis and have the potential to guide screening, staging, and outcome prediction.

Keywords Movement abnormality · Motor · Schizophrenia · Psychosis

This article is part of the Topical Collection on *Schizophrenia and Other Psychotic Disorders*

✉ Sebastian Walther
sebastian.walther@upd.unibe.ch

[1] Translational Research Center, University Hospital of Psychiatry, University of Bern, Murtenstrasse 21, 3008 Bern, Switzerland

[2] Department of Psychology, Northwestern University, Evanston, IL, USA

[3] Department of Psychiatry, Northwestern University, Evanston, IL, USA

[4] Department of Medical Social Sciences, Northwestern University, Evanston, IL, USA

[5] Institute for Policy Research, Northwestern University, Evanston, IL, USA

[6] Institute for Developmental Science, Northwestern University, Evanston, IL, USA

Introduction

Reports of peculiar movements have been observed since the earliest conceptions of psychosis (for review: [1]). Indeed, motor signs were described as critical diagnostic hints to psychosis in classical psychiatric textbooks [2–4]. Later, motor abnormalities fell out of focus for several reasons, foremost among them was an increasing weight placed on subjective symptoms over behavioral signs in operationalized diagnostic criteria [5]. Further, although the co-occurrence of Parkinsonian features in schizophrenia was noted decades before, antipsychotic pharmacotherapy was introduced [6], and early reports indicating motor abnormalities precede the outbreak of psychosis by several years [7] serious dedicated study of motor signs fell out of focus the erroneous perception that these phenomena were solely due to side-effects took hold [8].

Within the past decade, motor symptoms of psychosis have regained attraction, in part owing to a renewed emphasis on behavioral diagnostic markers [9], and new empirical data demonstrating motor abnormalities are present across the schizophrenia spectrum, including drug-naïve first-episode patients [10], subjects at clinical high risk [11], subjects at genetic risk [12], individuals with schizotypal personality disorder [13], or in individuals exhibiting schizotypy [14] and non-clinical psychosis [15]. Further, highly sensitive

instrumental devices have been put forward for screening and staging motor function in schizophrenia, as they may complement traditional ratings of motor signs with measures of subtle subclinical behaviors that still have significant relevance [16, 17]. Finally, advancements in neuroimaging allowed for investigating the associations between motor abnormalities and brain structure and function [18]. In this selective review, we will discuss the advances in motor assessment that aid exploring the clinical correlates and neurobiology of motor abnormalities in psychosis. These efforts provide the basis for the development of targeted treatment approaches and refined screening instruments in the future.

Types of Motor Abnormalities

Distinct motor abnormalities have been reported in psychosis, some of which relate to clinical syndromes, single tasks, or a preference of extreme values in a continuum of motor function. Some of the motor phenomena are hyperkinetic, i.e., lead to excessive movement. For example, abnormal involuntary movements—also termed dyskinesia—refer to repetitive, fast, irregular movements affecting predominantly the upper limb, neck, and facial muscles. Likewise, stereotypies refer to purposeless repetitive movement sequences. Other movement disorders are hypokinetic. For example, Parkinsonism may include rigor, tremor, bradykinesia, hypomimia, or increased salivation. Relatedly, psychomotor slowing is observed in fine motor tasks such as line drawing or writing and in reduced total body movement, which is captured in gait or spontaneous motor activity as measured with wrist actigraphy [1].

Neurological soft signs (NSS) refer to problems in motor sequencing and coordination, suggested to reflect neurodevelopmental delay, as these signs usually decrease with age during late childhood [19]. Catatonia is a psychomotor syndrome that occurs in psychosis, but also in other psychiatric disorders and medical conditions. Catatonia symptoms cover a range of motor abnormalities, both hyperkinetic and hypokinetic, as well as autonomic instability [20]. Finally, individuals in the psychosis spectrum exhibit deficits in gesture behavior [21, 22•]. Together, motor abnormalities are quite heterogeneous, with historic and partly overlapping constructs. Yet, the field is still struggling to revise the current taxonomy of motor abnormalities in order to disentangle underlying pathobiology or the association with symptom dimensions.

Recent Advances in Motor Assessments

For each type of motor abnormality, at least one observer-based clinical rating scale is currently available, providing reliable prevalence rates of motor abnormalities [1]. However, the application is challenged by intensive training requirements, conceptual overlap between motor abnormalities, and the limited availability of expert users [16]. Reliability between research sites or between clinics can also be challenging. Instruments to measure motor behavior are being evaluated with great enthusiasm, due to increased objectivity (not subject to rater bias) and sensitivity, as well as the easy application in longitudinal studies and in studies outside of expert/laboratory settings. Further, as the field continues to develop these approaches with standardized applications/software and apparatus (tablet computers, smartphones) accessibility as well as reliability will benefit substantially [23, 24]. Examples of instrumental measures are given in Table 1. Most existing studies have investigated balance and fine motor performance (tapping into NSS), or spontaneous motor activity (reflecting both hyper and hypokinetic movements). However, instrumentation is also being applied to understanding other motor domains, as well as to traditional behavioral tasks that tap into motor dysfunction in psychosis. Of particular interest is the task performance and spontaneous use of hand gestures, given the link between motor abnormalities and nonverbal communication [21]. Likewise, drawing and writing tasks or coin rotation inform on psychomotor slowing and dexterity [26, 27, 33, 34]. Finally, there is no specific instrumentation for catatonia, although reduced spontaneous motor activity and increased duration of immobility can be monitored with wrist actigraphy [35]. For the clinical routine, a combination of rating scales with instrumental measures is advised in order to capture the presence and trajectory of motor abnormalities in individuals with psychosis.

Clinical Utility of Motor Assessments

Motor assessments have provided insight on the prevalence of these behaviors throughout the psychosis spectrum. If initial studies can be replicated, motor assessments will guide screening for psychosis risk and disorder staging. In this chapter, we review the evidence for motor abnormalities in specific situations.

Screening the Psychosis Risk

Cohort studies have focused on delayed motor development in subjects who later developed schizophrenia or on abnormal motor behavior in subjects at genetic risk for schizophrenia. For instance, delayed achievement of motor milestones in infancy was found to be associated with both later schizophrenia and parental psychosis in a national cohort study from Finland [36]. Likewise, a Danish cohort study of 7-year-old children detected inferior performance on tasks including dexterity and balance in offspring of schizophrenia patients compared to the

Table 1 Examples of instrumental measures of motor abnormalities (adapted from [16])

Instrument/task	Motor abnormality	Example references
Force variability/average normalized jerk	Hyperkinesia/dyskinesia	[25]
Hand writing kinematics—velocity scaling/movement sensors/line copying task	Hypokinesia/psychomotor slowing	[26–28]
Actigraphy	Reduced spontaneous motor activity/psychomotor slowing/hypokinesia	[29, 30]
Balance	Neurological soft signs	[31••]
Data glove	Gesture dysfunction	[32]

Instruments may capture features of multiple motor abnormalities. For example, most instruments will also measure characteristics of catatonia, while none of them is specific to catatonia

controls [37••]. Another Finnish cohort study reported that lower physical activity at age 9–16 years predicted later development of non-affective psychosis [38]. These studies corroborate motor development as an interesting marker of psychosis risk in the general population. Indeed, in a population-based sample of children and adolescents, we found a prevalence of 13% for abnormal involuntary movements, and subjects with abnormal involuntary movements were more likely to qualify for clinical high-risk criteria [39•]. Likewise, instrumental measures of dyskinesia, i.e., force variability, indicated a link between dyskinesia and auditory verbal hallucinations a group of non-psychotic otherwise healthy subjects [40•]. Finally, subjects with high familial risk for psychosis have fine motor impairments with altered laterality compared to controls [41].

While these reports substantiate earlier findings of motor abnormalities in psychosis from cohort studies [42], another line of evidence stems from subjects at ultra-high risk of psychosis (UHR), who have experienced some attenuated symptoms indicating elevated risk for imminent conversion to psychosis. A considerable proportion of these UHR subjects will suffer from schizophrenia spectrum disorders within the next years. Abnormal motor function has been repeatedly demonstrated in these UHR subjects. For example, UHR subjects demonstrate less dextrality in a fine-motor drawing task, and this is predictive of positive symptom progression within the next year [43•]. Likewise, increased postural sway a marker of cerebellar dysfunction indicates negative symptom progression in UHR subjects [31••]. Relatedly, UHR subjects exhibit more beat and retrieval gestures than healthy controls in a clinical interview situation, and mismatch gestures are linked to negative symptom severity [44]. Furthermore, beat gesture frequency is associated with increased postural sway in this population [45]. Finally, UHR subjects demonstrate lower spontaneous motor activity levels than controls [15]. While motor abnormalities assessed with rating scales predicted the conversion to psychosis in UHR subjects [46–48], instrumental measures still have to provide evidence for their use in predicting transition. Given the increased sensitivity of instrumental measures, data supporting this claim should arrive soon. Indeed, we are currently working on this question.

Motor Abnormalities in Early Psychosis

First-episode patients have considerable rates of motor abnormalities (up to 66%), even when they are antipsychotic-naïve [10]. Furthermore, motor abnormalities seem to predict unfavorable outcome. Motor abnormalities are more frequent in first-episode patients with a deficit syndrome who have poorer outcomes [49]. Most importantly, spontaneous Parkinsonism in drug-naïve first-episode patients predict poor cognitive function at 6 months follow-up [50••]. A recent naturalistic longitudinal study in first-episode patients indicated that NSS decreased over 1 year, while Parkinsonism and hyperkinesias increased [51]. However, the temporal dynamics of NSS appeared unrelated to changes in psychopathology. Likewise, another study recently reported that clinical parameters were weakly associated with several motor abnormalities in a first-episode psychosis sample [52]. A recent large prospective study on drug-induced movement disorders in early psychosis reported a high prevalence (39%) of movement disorders and considerable stability (55%) across 3 years follow-up [53•].

Our work indicates that first-episode psychosis patients have higher levels of spontaneous motor activity than chronic patients, even when controlling for age, medication exposure, and negative symptoms [29]. We have also observed that during their first episode, few patients with schizophrenia spectrum disorders already present with severe gesture errors, but the pattern of deficits is similar to that of chronic patients at lower prevalence rates [54]. Together, motor abnormalities are frequent in first-episode psychosis supporting the claim that motor symptoms are not exclusively associated with illness chronicity. Abnormal motor behavior in the first episode may indicate poor outcome.

Motor Abnormalities in Schizophrenia

Motor abnormalities are commonly found in chronic schizophrenia. However, the association with symptom domains and the longitudinal stability of these phenomena is less clear. In a sample of chronic schizophrenia patients with long treatment histories, one study identified 8% with axial rigor in at least two body parts [55]. These patients were not different from those without axial rigor

in terms of treatment history or antipsychotic exposure, suggesting a distinct association of Parkinsonian-like rigor with chronic schizophrenia. Other older studies indicated that with more advanced age, the rate of movement abnormalities approaches 100% [56]. Likewise, naturalistic longitudinal studies suggest that lowering antipsychotic dosage or switching to a second-generation antipsychotic will not necessarily ameliorate dyskinesia or Parkinsonism [57].

Levels of spontaneous motor activity (assessed with wrist actigraphy) in schizophrenia patients appear to be stable between psychotic episodes, with low activity indicating the course of negative symptoms: decrease within an episode and increase between subsequent psychotic episodes [58]. Movement patterns derived from activity data are also linked to symptoms, particularly instable patterns predicted severity of positive symptoms and disorganization [30]. In addition, objective assessment of physical activity indicates that low activity is associated with poor cognitive function in schizophrenia [59].

In terms of hand gestures, schizophrenia patients use gestures less frequently during conversation and have problems with imitation of finger gestures [32, 60]. Up to 50% of schizophrenia patients have severe gesture deficits, which are associated with motor abnormalities, negative symptoms, and poor frontal lobe function [22•, 34, 61]. Gesture deficits have even been found to predict poorer functional outcome after 6 months [62••].

Spontaneous hypokinetic movements (e.g., bradykinesia) also appear to be associated with disease course irrespective of medication and are prevalent in chronic schizophrenia [63, 64]. Body-worn sensors have proven highly valid in assessing bradykinesia in chronic patients [28].

Even though the etiology of motor abnormalities is much more debated in chronic schizophrenia than in the first-episode or in subjects at risk, motor symptoms are valuable indicators of symptom domains or outcome. Repeated measurement of motor behavior either continuously or intermitted may provide a substitute marker of symptom progression [65].

Specificity to Schizophrenia

It is also important to consider evidence indicating that motor behaviors may be useful for differentiating psychotic disorders from affective psychosis. Early work in this area indicated that particular movement abnormalities, including dyskinesias, were specific to schizophrenia patients (including medication naïve participants) when compared to other psychiatric groups including depression and bipolar disorder [66] as well as affective psychosis [67]. Recent evidence supports this notion; for example, a well-powered birth-cohort study observed fine motor, coordination, and balance deficits in the children of parents with schizophrenia but not the children of parents with bipolar disorder [37••]. However, a study in first-episode psychoses indicated that schizophrenia differs from bipolar disorder in NSS severity, whereas psychotic depression was similar to schizophrenia in all motor phenomena [68]. Future research in this area will be very important for determining if motor signs can be used as an effective diagnostic tool in this regard. This would prove highly useful as the condition in both categories is difficult to initially diagnose, but require different treatments.

Pathophysiology of Motor Abnormalities

Motor System Alterations in Psychosis in General

A considerable proportion of the typical structural and functional brain alterations implicated in schizophrenia overlap with structures, networks, and neurostransmitters govern the motor system. Normatively, while the basal ganglia (cortico-striatal-pallido-thalamic) circuits help to select/inhibit a particular motor or sequence, the cerebellar (cerebellar-thalamic-cortical) circuits work to fine tune or add skill to these movement behaviors. These circuits work in close concert, and both are highly implicated in the pathophysiology of schizophrenia, playing a central role in the dopamine (DA) hypothesis and cognitive dysmetria concept, respectively [69, 70]. For example, structural changes in schizophrenia have been reported in the thalamus, striatum, motor cortex, or cerebellum [18, 71]. Furthermore, a meta-analysis of fMRI basal ganglia activation indicated reduced activation in schizophrenia across tasks and samples [72].

These links have been supported by studies across imaging modalities. For example, resting-state functional connectivity studies repeatedly report increased connectivity in schizophrenia compared to controls, particularly in bidirectional connections between thalamus and motor cortex [73–75]. Using measures of resting-state functional connectivity derived from BOLD fMRI, motor system dysfunction in schizophrenia can be described as hypo- or hyperconnectivity in comparison to controls. For example, in a large study in unmedicated first-episode patients, functional connectivity was found to be reduced between substantia nigra and striatum as well as between striatum and thalamus [76•]. But at the same time, increased resting-state connectivity between thalamus and motor cortex was noted, a finding, which was further corroborated by a number of recent investigations [76•, 77•, 78••]. Interestingly, alterations in thalamo-cortical functional connectivity were found to be associated with general symptom severity, indicating a window to the core pathology in schizophrenia [76•, 77•]. In line with this, investigators have observed increased resting-state functional connectivity between

the motor cortex and thalamus in UHR subjects, in addition to increased structural connectivity in the motor network [79, 80].

Motor System Alterations Linked to Aberrant Motor Behavior in Psychosis

Beyond the general association of motor system pathology with schizophrenia, studies are beginning to delve into the specific links between motor behavior abnormalities and alterations of the motor system in schizophrenia. For instance, motor abnormalities such as NSS or hypokinesia are related to structural and functional alterations within the motor system [18]. Our group also used actigraphy to monitor spontaneous motor behavior and found distinct associations of resting-state perfusion in motor cortices with real world motor activity [81]. Likewise, we and others have noted that reduced motor activity is related to structural connectivity between motor cortices and basal ganglia or thalamus in patients with schizophrenia investigating white matter properties with diffusion tensor imaging (DTI) [82–84]. Furthermore, severity ratings of abnormal motor behavior have been found to be correlated with white matter properties in schizophrenia [85]. We also found that patients with motor abnormalities had increased gray matter volume of the supplementary motor area (SMA) [86]. Moreover, the largest study to date in acute catatonia demonstrated increased resting-state perfusion within the SMA in schizophrenia patients with catatonia compared to both controls and schizophrenia patients without catatonia history [87•]. Particularly, patients with the retarded catatonia type, i.e., severe motor inhibition, had the highest perfusion values in the SMA. These findings are well in line with abovementioned studies supporting motor system dysfunction even in the resting state. Further evidence corroborating this finding comes from a recent study of resting-state functional connectivity within the motor system [78••]. We observed that schizophrenia patients exhibited abnormally increased functional connectivity between regions of interest within the motor system, some of which correlated with the severity of motor abnormalities. Particularly, thalamo-cortical connectivity to the primary motor cortex correlated with catatonia and connectivity between primary motor cortex and motor regions of the cerebellum correlated with activity levels.

In line with these findings, aberrant development of the motor system has been demonstrated in UHR subjects, as indicated by structural connectivity trajectories between cerebellum and thalamus as well as cerebello-thalamo-cortical functional connectivity. Research indicates that the alterations are not only linked to NSS but also to positive and negative symptom progression [88, 89••]. In addition, decreased functional connectivity in the cerebellar networks is found to be associated with poor postural control and negative symptoms in UHR subjects [90]. Further, dyskinetic movements have been linked with smaller striatal volumes in UHR youth [91]. Thus, motor abnormalities in psychosis seem to be associated with neural alterations in frontal-subcortical and cerebellar-thalamo-cortico projections. Future work will be important for continuing to map out connectivity between these systems as well as the influence of cortico-cortical networks [92]. Further, it will be important to incorporate other methodologies including electrophysiology, as recent studies indicate significant promise in utilizing event-related potentials (ERP) to understand deficits in motor slowing [93••].

Motor System Alterations Linked to Online Motor Tasks in Psychosis

Finally, aberrant neural activity in the motor system in schizophrenia has been found in studies employing specific motor tasks. Indeed, a task-based functional MRI study indicated aberrant force control in schizophrenia was associated with abnormal sensory feedback, particularly during externally triggered movement [94••]. Furthermore, a combined TMS and fMRI study reported that schizophrenia patients activate midline structures more during active motor inhibition than controls, probably compensating for reduced local intracortical inhibition [95]. Finally, during motor planning of hand gestures, schizophrenia patients have been observed to show less activation of the responsible brain regions, i.e., within the praxis network. These neural alterations during action planning are associated with poor gesture performance during the fMRI task [96•]. In sum, these studies provide evidence for very specific associations of task performance and neural alterations within the motor system in schizophrenia.

Outlook

Innovative research, incorporating instrumental approaches, has established the clinical relevance and importance of exploring the pathobiology of aberrant motor behavior across the schizophrenia spectrum as well as in schizophrenia risk syndromes. Future neuroimaging studies in patients need to tackle the longitudinal progression of symptoms and the trajectories of motor system alterations. For some of the motor symptoms such as Parkinsonism, applicable imaging markers are still missing. Therefore, more imaging studies testing clear hypotheses on the pathobiology of motor abnormalities are needed to disentangle which motor system alterations contribute to particular symptoms.

The next steps on the clinical agenda are novel instrumentation development, screening, staging, and targeted therapy. Indeed, we need to further integrate assessment of subtle and overt motor behaviors using widely available and novel technologies seen in smartphone and tablet computers (e.g.,

accelerometer, gyroscope, pressure sensitivity, global positioning system). Additionally, we need to conduct studies demonstrating the utility and effectiveness of motor assessment in screening for psychosis among subjects at risk and in staging those already affected. Furthermore, treatment approaches directly targeting the motor system should be evaluated. The most promising efforts are probably physical training (e.g., exercise) and non-invasive brain stimulation techniques. Particularly, non-invasive brain stimulation techniques such as tDCS and rTMS could target critical parts of the motor system directly, for example, the primary motor cortex, premotor cortices, and the cerebellum. Moreover, these techniques may be particularly beneficial to some patients in whom we may find indicators of motor system dysfunction. Thus, these efforts could be delivered in a truly individualized approach.

Conclusions

The nature of motor symptoms provides an excellent background for individualized targeted treatment approaches. Easily accessible motor abnormalities will potentially guide treatment decisions in the future to optimize the outcome of psychosis.

Compliance with Ethical Standards

Conflict of Interest Sebastian Walther reports a grant from Swiss National Science Foundation and personal fees from Ely Lilly, Janssen, and Lundbeck/Otsuka.

Vijay A. Mittal reports a grant from NIMH and a consultancy with Takeda.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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