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Motor Symptoms and Schizophrenia

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Abstract
Classical schizophrenia literature reports motor symptoms as characteristic of the disorder. After the introduction of neuroleptic drugs, the existence of genuine motor disorders was challenged. Renewed interest arose as symptoms were found in never-medicated patients. Reports focused on abnormal involuntary movements, parkinsonism, neurological soft signs, catatonia, negative symptoms, or psychomotor slowing. Since these syndromes refer to different concepts, however, the definitions are not congruent and the symptoms overlap. The prevalence rates of motor symptoms in schizophrenia are surprisingly high, and recent studies indicate a possible pathobiology. In particular, the development and maturation of the human motor system appears to be closely linked to the emergence of motor symptoms observed in schizophrenia. Post-mortem and neuroimaging results demonstrated aberrant structure and function of premotor and motor cortices, basal ganglia, thalamus, and the connecting white matter tracts. Animal models have focused on aberrant neurotransmission and genetic contributions. Findings of localized abnormal oligodendrocyte function and myelination point to the special role of the white matter in schizophrenia, and recent studies specifically found an association between motor abnormalities and white matter structure in schizophrenia. This review of the literature supports the idea that motor symptoms are closely related to the neurodevelopmental disturbances of schizophrenia and a distinct syndromal dimension with its own pathophysiology.

Introduction

Altered motor behavior has consistently been reported in the classic schizophrenia literature [1–5]. Early schizophrenia investigators acknowledged a wide range of motor symptoms to be associated with the disorder. These comprehensive clinical descriptions were later widely neglected when scientific attention shifted to treatment-related motor symptoms.

Recent reviews have addressed the nosological problems concerning catatonia [6–8], the meaning of abnormal involuntary movements and neurological soft signs (NSS) in schizophrenia [9–11], psychomotor slowing [12], and motor deficits or neurological abnormalities in antipsychotic naïve schizophrenia patients [10, 13, 14]. Since these reviews focused on specific aspects of motor deficits or on special populations, a comprehensive view of motor

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phenomena is difficult to develop, since the descriptions, definitions, and interpretations vary largely with the conceptual frameworks [15]. The current literature shows that there are several distinct, but largely overlapping concepts of motor disorders that are based on substantially diverse assumptions about their pathophysiology.

This selective review focuses on the signs and neurobiology of motor disorders in schizophrenia without a priori assumptions about their putative nature or nosological meaning. After an outline of the historical descriptions of motor symptoms, we will provide an overview of current concepts, as well as of the epidemiological and neurobiological evidence. Finally, we will review the possibility that disorders of the motor loop are the underlying cause of motor symptoms in schizophrenia.

History

Case notes from a 19th century asylum in England included descriptions of a variety of motor symptoms that today resemble catatonia, abnormal involuntary movements, or parkinsonism [16]. Lacking our modern concepts of motor syndromes in schizophrenia, the notes were descriptive, reporting, 'grimaces, fidgets, jerkiness, and twitching', gesticulating, rigidity, staring, and mutism.

In 1874, Kahlbaum [2] described a series of cases with predominant motor symptoms which he termed catatonia. Later, Kraepelin [17] integrated a syndrome of specific, persistent motor symptoms as the catatonic subtype in dementia praecox [8]. He noted, however, that catatonic symptoms such as negativism, mannerisms, grimacing, stereotypies, and echophenomena also occurred in other subtypes [5, 18]. Bleuler [1] noted several motor symptoms, including irregular muscular contractions, muscle fibrillations of the face, tremor, diminished arm swing during gait, and apraxia-like symptoms, as well as the catatonic symptoms described by Kahlbaum [2]. Bleuler [1] estimated that more than 50% of schizophrenia patients present with either persistent or recurrent catatonic symptoms. In his conceptualization, however, he did not consider catatonia a basic phenomenon, but rather an accessory, nonspecific symptom of schizophrenia [1]. Later, with the increasing influence of phenomenological psychopathology, diagnostic and pathogenetic concepts of schizophrenia focused on cognitive symptoms, including delusions, hallucinations, and disorders of self-perception. These symptoms were considered to be primary phenomena, while motor and emotional symptoms were interpreted as secondary phenomena for diagnosis [19–21]. During this period, detailed descriptions of a diversity of motor symptoms with a neuropathological understanding of the phenomena, including specific symptom patterns, outcomes, and inheritance, can be found only in the work of less influential authors [3, 4].

After the introduction of antipsychotic pharmacology, the intricate differential diagnosis between extrapyramidal side effects and intrinsic motor symptoms further challenged the understanding of the syndrome [15, 22]. At one point, motor symptoms occurring in schizophrenia were attributed exclusively to antipsychotic treatment effects [23, 24], even though extrapyramidal symptoms had been reported in the preneuroleptic era [25, 26].

Neurological signs in schizophrenia have been investigated since the 1970s [22, 27–29]. In the 1980s, neurological signs were interpreted as an expression of the neurobiology of schizophrenia and have received consistent attention since [9, 30]. During this time, however, researchers regained interest in spontaneous movement disorders in schizophrenia, and rare populations of never-medicated patients were investigated [15, 31–33].

Clinical Perspectives

At least one motor sign has been reported to be prevalent in 66% of first-episode, never-medicated patients [34], in 59% of patients on admission [35], and in 80% of chronically medicated patients [36]. After a brief description of the conceptual overlaps, the following sections will introduce the main motor signs and the available prevalence rates (table 1). A short list of available assessment tools for motor symptoms in schizophrenia is appended in the online supplementary table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000339456).

Conceptual Overlap

A considerable proportion of patients presents with more than one motor phenomenon [34, 35, 37–39]. Today, it is impossible to determine whether the co-occurrence of various motor symptoms is due to lack of conceptual clarity, a strong intercorrelation, or a common neuronal basis. Furthermore, different investigators may pose different names for the same symptom. Rogers [15] preferred avoiding theory-laden terms and, in 1985, proposed the problem as a 'conflict of paradigms'. Symptom definitions in the current rating scales are still confusing and overlapping. Depending on the underlying concepts, re-

Table 1. Prevalence rates of motor symptoms in schizophrenia patients

	First episode medication naïve	First episode medicated	Chronic medication naïve	Chronically medicated
NSS (>1 symptom)	78–97% [51, 94]	48–100% [95, 96]	23% [97]	39–98% [52, 98]
Dyskinesia	12–13% [34, 99]	3% [57]	35–51% [33, 76]	29–100% [38, 56, 100]
Parkinsonism	18–27% [34, 75, 99]	34–43% [57, 73, 101]	15% [76]	23–55% [37, 38]
Catatonic symptoms (≥2 signs)	17% [67]	5% [57]	no data available	10–32% [49, 70]

duced movement can be referred to as stupor, bradykinesia, or avolition [40]. Involuntary movements can be described as parakinesia or dyskinesia; involuntary face movements, grimacing, tics, or mannerisms [11, 15]. Likewise, rigidity is considered a sign of both parkinsonism and catatonia [41–43]. Rating scales for NSS include items that are also present in scales for parkinsonism or dyskinesia: rigor, tremor, adventitious overflow, or poor balance [9]. Likewise, most catatonia scales include rigor [8, 44].

In both chronic and first-episode schizophrenia patients, dyskinesia and parkinsonism can co-occur [34, 35, 37–39, 44–46]. In order to disentangle motor symptoms, factor-analytic studies have been performed [34, 35]. Parkinsonism and retarded catatonia are highly intercorrelated [40, 47, 48], and the factor 'positive catatonia' is correlated with dyskinesia [34, 48]. Furthermore, negative symptoms are highly correlated with catatonia ratings, NSS, dyskinesia, and parkinsonism [11, 35, 39, 40, 49, 50]. In addition, NSS are associated with dyskinesia and parkinsonism [51, 52], as well as with cognitive function [50]. Finally, psychomotor slowing seems to be related to catatonic symptoms [50, 53].

Involuntary Movements

Abnormal, involuntary movements in schizophrenia have been extensively reviewed [10, 11, 13, 54]. Spontaneous and tardive dyskinesias (TD) comprise abnormal, involuntary, repetitive movements of the orofacial, limb, trunk, and respiratory musculature [54]. Prevalence rates indicate that abnormal, involuntary movements occur throughout the course of the disease (table 1), and are more prevalent with increasing age, approaching 100% in the elderly [55, 56]. Antipsychotic medication improved dyskinesia in previously medication-naïve patients [57]. However, the clinical distinction between spontaneous and drug-induced dyskinesia is difficult to discern, and in chronic patients, the rate of drug-induced dyskinesia is supposed to prevail [55].

A recent meta-analysis calculated an odds ratio of 3.59 for spontaneous dyskinesia in schizophrenia [58]. However, a large negative study (n = 908) of Southeast Asian drug-naïve, first-episode schizophrenia subjects was not included in the meta-analysis [59]. The negative finding in Southeast Asians suggests an ethnicity effect [59]. In addition, spontaneous abnormal movements were reported in schizophrenia spectrum disorders and prodromal states [60–63], suggesting that the vulnerability for schizophrenia was associated with these movement disorders [11, 62].

Neurological Signs

NSS refer to neurological abnormalities in the domains of coordination, sensory integration, and sequential motor acts [9, 30]. Specific motor signs assessed, e.g. gait, balance, finger-thumb opposition, dysdiadochokinesia, finger-to-nose test, fist-edge-palm test, fist-ring test and Ozeretski test NSS, tend to be stable over time [9, 30]. Indeed, NSS are prevalent in early stages (table 1), sometimes associated with psychopathology, and independent of medication; they may be ameliorated by antipsychotic treatment [9, 11, 30]. NSS are also found in schizophrenia spectrum disorders [64].

Catatonic Symptoms

Catatonia is a syndrome of abnormal motor behavior, but also includes impaired volition and affect. Clinical definitions are inconsistent and up to 40 symptoms have been described as catatonic [8, 41, 65]. A variety of rating scales have been published, but there are unresolved questions concerning inconsistent item and syndrome definitions and syndrome thresholds [8]. Pure motor signs include posturing, mannerisms, immobility, rigor, stereotypies, catalepsy, grimacing, and waxy flexibility. Signs associated with volition include automatic obedience, negativism, refusal to eat, withdrawal, and ambitendency. Furthermore, signs suggest an inability to suppress complex motor activities that are either self-initiat-

ed (rituals or stereotypies) or induced (echophenomena) [66]. Finally, stupor, excitation, nudism, verbigeration, perseveration, staring, and vegetative instability have been interpreted as catatonic [3, 5, 15, 18, 42, 43]. In schizophrenia, the most frequent catatonic symptoms are mutism, posturing, stereotypies, and mannerisms [35, 67]. Due to these definition problems, the reported prevalence rates of catatonia in schizophrenia vary extensively (table 1). In a birth cohort study from Israel, 7.6% of the subjects who developed schizophrenia by the age of 35 years displayed the catatonic subtype [68]. The prevalence of catatonia appeared to decrease over the past century [69, 70]. However, this effect is attributed to a decreased recognition of the syndrome rather than to a real decline in prevalence rates [8, 71]. Indeed, moving away from categorical data, surprisingly high rates of schizophrenia patients endorse at least 1 sign in catatonia rating scales: 80% in chronically medicated patients [36] and 31% in first-episode, medication-naïve patients [67]. In first-episode patients, catatonic symptoms were responsive to antipsychotic treatment [57].

Parkinsonism

Parkinsonism has 6 main clinical features: resting tremor, rigidity, bradykinesia, loss of postural reflexes, flexed posture, and motor blocking (freezing) [72]. In schizophrenia, muscle rigidity and bradykinesia were the most frequently reported parkinsonian signs [10]. The Caligiuri group [73, 74] used a variety of instrumental measures to reappraise spontaneous parkinsonism in schizophrenia, a finding that has later been replicated using clinical rating scales [13, 34, 35, 75, 76]. Meta-analytic results demonstrated an odds ratio of 5.32 for spontaneous parkinsonism in never-treated schizophrenia subjects [58]. Parkinsonism of unmedicated first-episode patients was shown to deteriorate with antipsychotic treatment in some patients (28%), while in others, parkinsonism was unchanged (15%) or ameliorated (6%) with treatment [57]. Spontaneous parkinsonism was suggested to predict neuroleptic-induced parkinsonism [73]. Drug-induced parkinsonism has been shown in first- and second-generation antipsychotics at high incidence and prevalence rates [23, 37, 77].

Negative Syndrome

Negative symptoms constitute one dimension of schizophrenia. They refer to the loss of affective experience and expression, as well as to a number of symptoms associated with disturbances of volition, such as apathy, avolition, and anhedonia. Negative symptoms may be associated primarily with schizophrenia or may develop secondary to social deprivation, antipsychotic medication, or depression [78, 79]. As a result, the patients are less active. The psychomotor poverty syndrome has been linked to negative symptoms, comprising decreased spontaneous movements and flattened affect [80]. Indeed, the objectively assessed amount of movement has been associated with negative symptoms [81–83].

Psychomotor Slowing

Morrens et al. [12] have reviewed the data on reduced processing speed (psychomotor slowing) that can be assessed with reaction time, fine motor, drawing and writing, or the symbol digit substitution task. They found a high prevalence of slowing, which was associated with negative symptoms, but independent from antipsychotic medication [12, 84, 85]. Furthermore, reduced physical activity in schizophrenia patients was reported in epidemiologic studies using self-reports [86, 87], as well as in instrumental assessments using gait analyses [88, 89] or wrist actigraphy [83, 90–93].

Consistently, considerable prevalence rates have been reported for motor symptoms in schizophrenia (table 1). For illustration purposes, we have chosen the low cutoff scores of most studies, i.e. 1 NSS symptom or 2 catatonia symptoms. However, prevalence rates vary between studies because of different instruments and cutoff scores.

Some motor symptoms in schizophrenia are persistent over time. This applies particularly to drug-induced movement disorders in chronic patients [102–104] but also to parkinsonism in medication-naïve patients [57, 99]. NSS deteriorate in chronic patients over time [104]. In contrast, NSS in first-episode patients were observed to improve during an episode, even more so in patients with an overall favorable outcome [105–107]. The course of catatonia is heterogeneous. Catatonic symptoms may resolve with treatment in some cases, however persistence or deterioration are also frequently observed [8, 34, 42, 67, 108–112]. Finally, intraindividual variations in symptom presentation and severity have been reported for all motor signs in schizophrenia.

Neurobiology of the Motor System in Schizophrenia

Motor System Anatomy

The human motor system in the brain includes the motor and premotor cortices, the basal ganglia, brainstem, the cerebellum, and the white matter tracts connecting these components [for review, see 72, 113]. We

will briefly focus on the anatomy and function of motor cortices, basal ganglia, and corresponding fiber tracts associated with schizophrenia or motor dysfunction. The system is organized in different parallel loops. Cortical motor fields include the primary motor cortex (M1), the supplemental motor area (SMA), the dorsal and ventral premotor areas (PMd and PMv, respectively), and the rostral and caudal cingulate motor areas (CMAr and CMAc, respectively). All of them are somatotopically organized and interconnected to M1. Each of the cortical areas projects to the basal ganglia and receives input from the motor thalamus [113]. The lateral premotor fields (PMd and PMv) are involved in goal-directed movements, while the medial premotor fields (SMA, pre-SMA, CMAr, and CMAc) engage in motor planning and execution. Furthermore, the latter group has been implicated in volitional aspects of behavior and drive [114]. The basal ganglia involved in motor behavior comprise the striatum (including caudate and putamen), the globus pallidus (internal and external division), the subthalamic nucleus (STN), and the substantia nigra [72, 113]. Two main loops are involved in motor control. The first is the excitatory-acting *direct pathway*, including 2 inhibitory γ-aminobutyric acid (GABA)ergic synapses from the striatum to the internal pallidum and thalamus; the putaminal neurons of the direct pathway contain dopamine D_2 receptors. The second is the inhibitory *indirect pathway*, including 3 inhibitory GABAergic synapses from the striatum to the external pallidum, to the STN, to the internal pallidum, and the thalamus. The putaminal neurons of the indirect pathway have dopamine D_1 receptors, and the synapses between STN and internal pallidum are glutamatergic. Both pathways start with glutamatergic inputs from (pre)motor cortices to the striatum and end with glutamatergic afferents from the thalamus to the motor cortices [115]. Under normal conditions, the output of both pathways is balanced, leading to an inhibitory tone on the thalamic nuclei, which is disinhibited whenever an action is performed [72, 116].

The motor loop receives cortical input via the neostriatum and the STN. The STN is a key input region, receiving direct glutamatergic afferents from the (pre)motor cortices and dopaminergic input from the substantia nigra [117]. Recent evidence also suggests that there are dopaminergic projections to the extrastriatal basal ganglia (globus pallidus, substantia nigra, and STN), where dopamine may facilitate motor activity [118].

This short description is simplified, as the human motor system is far more complex than the current models suggest. In addition, most models focus exclusively on dopamine, GABA, and glutamate, even though more neurotransmitters are involved.

Neuropathology

Neuropathological studies in schizophrenia have focused on the limbic system, the hippocampus, and the dorsolateral prefrontal cortex [for review, see 119, 120]. However, reports on the motor system are rare. The results on neuron density in the premotor, motor, and anterior cingulate cortices (ACC) are inconclusive [120]. However, reduced synaptic density and aberrant wiring were found in the ACC; interestingly, Fornito et al. [121] found brain volume reduction in Brodmann area 24, which contains the cingulate motor areas (CMAr and CMAc). The results for basal ganglia remain inconsistent [120]. However, a recent study indicated reduced neuron number and volume of the putamen and caudate in schizophrenia [122]. Furthermore, reduced thalamus volumes were found [for review, see ref. 120, 123]. It has been suggested that antipsychotic drugs have differential regional effects on basal ganglia structure [124]. An influential review on the involvement of the basal ganglia in schizophrenia pathology was written by Graybiel [125].

In general, disturbed GABAergic neurotransmission was found in several brain regions, including the anterior cingulate and primary motor cortex [126]. Furthermore, GABA synthesis is reduced in the caudate nucleus, anterior nucleus of the thalamus, and ACC [127]. The GABAergic tone within the basal ganglion system further suggests that some motor symptoms may be the result of GABAergic dysfunction in schizophrenia. Dysfunctional GABA transmission has been suggested as a putative cause of some catatonic symptoms such as stupor [128–130].

Glutamatergic dysfunction has been suggested in the pathogenesis of schizophrenia [131, 132]. Some studies have investigated this issue within the schizophrenia motor system and indicated altered glutamate neurotransmission in the caudate and putamen [133, 134]. Higher levels of glutamatergic neurotransmission were found in the cerebrospinal fluid of schizophrenia patients with TD [135]. Moreover, in akinetic catatonic schizophrenia, glutamate hyperfunction was suggested as *N*-methyl-D-aspartate (NMDA) antagonists were reported to alleviate acute hypokinetic catatonia [128, 136].

In summary, neuropathological alterations in the motor system in schizophrenia have been located in the ACC, putamen, caudate, and thalamus. In addition, GABAergic deficits also included M1.

Neuroimaging Findings

Since the 1970s, an increasing number of papers on neuroimaging in schizophrenia have been published. Most studies have focused on prefrontal cortical abnormalities by investigating structure, perfusion, and function. Again, the proportion of studies specifically addressing motor symptoms has remained low. Structural neuroimaging studies reported increased volumes of the caudate, putamen, and globus pallidus in medicated schizophrenia patients [137]. However, in the putamen of unmedicated patients, volumes were reduced [138]. In contrast, thalamic volumes are reduced in schizophrenia [139–142]. In both chronic and first-episode schizophrenia meta-analyses, researchers reported widespread gray matter reductions in the thalamo-cortico-striatal circuit, including the medial dorsal nucleus of the thalamus, the ACC, and the caudate nucleus [121, 142, 143]. The findings on resting state cerebral blood flow (CBF) and metabolism of the basal ganglia were inhomogeneous [for review, see ref. 144]. A meta-analysis of magnetic resonance spectroscopy findings demonstrated reduced glutamate and increased glutamine levels in the frontal cortex of schizophrenia patients [132]. Patient treatment with antipsychotic medications is a major limitation of the literature on the motor system in schizophrenia patients; these medications affect brain structure and neurotransmission [for review, see ref. 124].

Neuroimaging results for dyskinesia remain inconclusive, with reduced ventricle-to-brain ratios [145], reduced caudate volumes [146], increased volumes of the left lentiform nucleus (putamen and globus pallidus) [147], or no changes reported [148]. Glucose metabolic rates in the globus pallidus and primary motor cortex were found to be higher in patients with dyskinesia [149]. Likewise, neurological signs were linked to structural alterations. Indeed, motor deficits as a component of NSSs were found to be associated with gray matter loss in the motor cortices, caudate nucleus, and thalamus (see also online suppl. table 2) [150–155].

In catatonia, no structural abnormalities have emerged so far. However, single case reports noted reduced bilateral frontal CBF [156] or hypometabolism [157], along with bilateral thalamic hypermetabolism [157]. Similarly, the case series of Northoff et al. [129, 158] of a mixed-diagnosis catatonia group (3/10 with schizophrenia) revealed hypoperfusion in the middle and right lower prefrontal cortex. The finding was corroborated by functional magnetic resonance imaging (fMRI) demonstrating hypoactivation of M1 during a sequential finger opposition task in akinetic patients [159, 160]. In addition, fMRI revealed reduced activation of the SMA in simple motor tasks in catatonic or akinetic patients [160, 161]. Furthermore, one study demonstrated reduced $GABA_A$ density in the left M1 of akinetic catatonia patients [129], emphasizing a GABAergic dysfunction in catatonia.

Parkinsonian symptoms assessed with scales or instrumental measures were found to correlate with striatal D_2 receptor occupancy [162, 163]. No study on parkinsonism in schizophrenia applied fMRI or elaborated structural imaging.

Persistent negative symptoms, as in deficit schizophrenia, were associated with reduced volumes of bilateral frontal and temporal lobes, left ACC, left SMA, and right putamen as compared to non-deficit patients [164, 165]. In a large factor analysis, negative symptoms were linked with widespread reductions in prefrontal gray matter and thalamic volume [166].

Motor slowing, as measured by actigraphy, has been associated with reduced left ACC volume [81], and reduced CBF in the CMAr and bilateral prefrontal cortex [91]; similarly, psychomotor retardation correlated with CBF in the left dorsolateral prefrontal cortex and inversely with CBF in bilateral caudate nuclei [167].

Alterations in the premotor areas were linked to motor skill learning in schizophrenia, e.g. reduced pre-SMA gray matter volume [168] or aberrant signal changes in ACC, and premotor and motor cortices in schizophrenia [169, 170]. In addition, a variety of studies applied simple hand motor tasks, demonstrating reduced activation of SMA and M1 in schizophrenia [161, 171]. For a complete list of related studies, please refer to the online supplementary table 3. As methodological issues limit a majority of these studies, replication of the findings with current neuroimaging standards would be informative.

In summary, neuroimaging results of different modalities support the view of altered structure and function of the motor system in schizophrenia. Some of the specific symptoms are related to dysfunctions of the basal ganglia, and premotor and motor cortices. Disturbances in the initiation of movements, as studied with finger tapping in akinetic patients, have been associated with M1 or SMA hypofunction [159, 160], whereas disturbed voluntary action was associated with alterations if the SMA and ACC, including the CMA [81, 91, 164, 165].

Animal Models

Animal models of schizophrenia have the potential to test hypotheses of aberrant neurodevelopment and behavior to facilitate the understanding of neurobiology. However, current translational research methods target-

ing schizophrenia suffer from several inherent problems such as poor validity of interspecies comparisons [172]. There are animal models of basal ganglia dysfunctions that resemble Parkinson and Huntington's disease. It remains unclear, however, how much can be learned about schizophrenia from these models. Since positive symptoms have been associated with spontaneous or amphetamine-induced hyperactivity in rodent models of schizophrenia, most of the studies involve motor tasks [173].

Animal models of dyskinesia investigated the effects of dopamine receptor occupancy [174, 175], GABAergic transmission [176], and prenatal lesions [177]. A correlate of NSS was seen in mice lacking the presynaptic protein complexin 2, which was attenuated by a second hit [178]. Fine motor impairments were reported in rats with partial lesions in the substantia nigra [179].

Catalepsy has been used to model akinesia in drug-induced parkinsonism. The phenomenon occurs in rats at striatal D_2 receptor occupancy above 85% [180], but dopamine may not account for all cataleptic effects [174]. In addition, the administration of a D_1 antagonist in the STN led to catalepsy in rats, an effect not seen with a D_2 antagonist [181]. Catalepsy was also elicited by glutamate antagonists [182, 183].

Negative symptoms have been elicited by treatment with chronic phencyclidine, an NMDA antagonist [184–186]. Mutant mouse models of negative symptoms suggest an involvement of D_2 overexpression in avolition, even though most studies focused on impaired social behavior [187].

Reduced locomotion was seen in rats treated with typical and atypical antipsychotic drugs [174]. Perinatal treatment with MK-801 (an NMDA antagonist) increased motor activity during adolescence, but decreased locomotion during adulthood [188]. Similarly, postnatal mild hypoxia led to reduced locomotion in rats [189]. Furthermore, reduced locomotion was found in mutant mouse models of impaired glutamate or dopamine neurotransmission: vesicular monoamine transporter 2 gene-deficient mice [190], D-amino acid oxidase-knockout mice [191], cannabinoid-2-receptor-knockout mice [192], and sandy mutant mice that lack dysbindin [193].

Strikingly, two models of disturbed myelination with altered oligodendrocyte function resulted in reduced locomotor activity. First, in mutant ErbB4-deficient mice, oligodendrocytes were structurally altered, myelin thickness was reduced, and dopamine receptors were increased [194]. Hemopexin knockout mice had a similar pattern, with reduced myelin basic protein in motor cortex and basal ganglia, altered myelin structure, reduced myelin thickness, and impaired oligodendrocyte maturation [195]. Therefore, reduced locomotor activity can result from both neurotransmitter changes and white matter alterations.

White Matter

The disconnectivity hypothesis of schizophrenia pathophysiology has gained much attention in the last 2 decades [196, 197]. It suggests an important role for the white matter in schizophrenia symptoms. Postmortem studies indicated abnormal gene expression in the cingulate gyrus, profoundly affecting myelination and oligodendrocyte function of schizophrenia patients [198]. Schizophrenia patients further demonstrate increased interstitial white matter neurons, indicating deficient migration from the white matter to the cortex [199]. In fact, maldistribution of neurons in the prefrontal white matter has been replicated [for review, see 200], including the anterior cingulate white matter [201]. ErbB4 signalling is thought to be involved in alterations of neural development, neurotransmission, and synaptic plasticity in schizophrenia [202].

Altered ErbB4 signalling was associated with NMDA receptor hypofunction in the prefrontal cortex in schizophrenia [203]. Altered white matter structure may also affect the motor system. In Brodmann area 6, which comprises pre-SMA and SMA, schizophrenia patients had reduced NRG1 (neuregulin 1) C-terminal fragments indicating altered NRG1 signalling in this premotor area [204]. This is especially important since the tangential migration of thalamocortical axons critically depends on the NRG1 gene and their ErbB4 receptor [205]. These findings of altered white matter-associated gene expression are congruent with several diffusion tensor imaging studies demonstrating aberrant white matter structure in the motor system of schizophrenia patients.

In both first-episode and chronic patients, alterations were found in motor tracts such as the internal capsule or the corpus callosum [142, 206–209], but also in the premotor and motor cortex [210]. Interestingly, in early-onset schizophrenia, white matter maturation is delayed, especially in bilateral frontal lobes and the pyramidal tract [207, 211].

Few studies have linked motor function to white matter structure in schizophrenia. In first-episode patients, impaired motor skills in a pegboard task were related to reduced fractional anisotropy in the anterior thalamic radiation and corticospinal tract [212]. Motor coordination was associated with white matter density in the left inferior frontal gyrus [150] and thalamus [154]. Further-

more, actigraphically assessed motor activity in schizophrenia was linked to white matter integrity underneath the SMA [92]. We have recently found evidence for altered organization of motor pathways in schizophrenia, indicating that motor activity is linearly associated with the structural connectivity of the premotor cortex [213]. In a study on TD in schizophrenia patients, decreased white matter integrity was reported in the external capsule, cingulate, and around the putamen [206]. Despite these findings, the number of specific studies on white matter structures of the motor system in schizophrenia is still limited, and special populations such as elderly or chronic patients or unaffected siblings warrant investigation.

Neurodevelopmental Aspects

Humans have limited postnatal motor abilities. Neuromotor development is a process of learning and training closely linked to brain development. During the 1st year of life, the cerebellum grows extensively. During the 2nd year, the caudate increases gray matter relative to total brain volume [214].

Longitudinal in vivo MRI studies provided valuable insight into region-specific human brain maturation [215]. Gray matter maturation in motor cortices begins early in the primary motor cortex and spreads towards the premotor areas [216], resulting in an early cortical motor network that is further developed until late adolescence [217]. In contrast, white matter density in the bilateral posterior limbs of the internal capsule increases linearly between the ages of 4 and 17 years, indicating maturation in motor pathways such as the corticospinal tract [218, 219].

Schizophrenia has been conceptualized as a lifetime trajectory of neurodevelopmental changes, which, in combination with other causes, eventually lead to the typical course and psychopathology [220, 221]. In motor symptoms in schizophrenia, obstetric complications correlate with spontaneous movement disorders but not with drug-induced motor symptoms [51, 222]. In addition, maternal genital infection was associated with impaired fine motor abilities in adult schizophrenia patients [223].

Neuromotor development is one of the postnatal peculiarities of schizophrenia. Large birth cohort studies indicated delayed gross motor milestones (e.g. standing and walking), as well as impaired motor skills before the age of 11 years in a proportion of children who later developed schizophrenia [224–227]. A combination of delayed neuromotor development and obstetric complications was shown to potentiate the risk of schizophrenia in adulthood [228]. Similarly, deficits in motor coordination at the age of 10 years were found to predict schizophrenia spectrum disorders 35 years later [229]. These findings were corroborated by structured analyses of childhood home videos that revealed increased neuromotor abnormalities and poorer motor skills in subjects who were later diagnosed with schizophrenia compared to their healthy siblings [230]. In fact, abnormal movements were predictive of conversion to psychosis in adolescents at risk (mean age, 14.5 years) [231].

Brain maturation is a dynamic process, and the timeframe of relevant changes is important for the disease process. According to twin theories of motor development and behavior, monozygotic twins discordant for schizophrenia diverged either before the age of 5 years (30%) or between the age of 13 and 17 years (57%) [232]. The age of divergence suggests a temporal effect of dysfunctional processes in motor-relevant brain areas. Consistently, in a birth-cohort study, the proportion of subjects with unusual movements during childhood dropped between the assessments at the age of 8 months, and 4 and 7 years for healthy controls (13, 5, and 5%, respectively) and unaffected siblings (17, 9, and 4%, respectively), but not in schizophrenia patients (19, 15, and 16%, respectively) [227].

Motor developmental changes and abnormalities in childhood have been demonstrated to be predictors of adult schizophrenia. These alterations occur during the maturation of gray matter in the motor cortices [216] and the motor network [217]. During periadolescence, increased pruning of dendritic spines contributes to the gray matter loss in schizophrenia [233]. As schizophrenia is associated with delayed gray and white matter maturation in motor circuits [207], we may speculate that impaired childhood motor performance in schizophrenia is linked to brain maturation delays. One birth cohort study supports this notion: gray matter volume in the motor network and white matter density in the left internal capsule at the age of 33–35 years were associated with earlier infant motor development in healthy subjects, but not in schizophrenia patients [234].

The genetic findings on motor symptoms in schizophrenia remain inconclusive. Some findings point to an association of motor symptoms with the genetic risk of developing schizophrenia, since meta-analyses demonstrated that dyskinesia, NSS, and parkinsonism are more prevalent in unaffected first-degree relatives of patients with schizophrenia than in healthy controls [58, 235].

Summary of Motor System Abnormalities in Schizophrenia

There are several indications linking the neurobiology of the motor system with schizophrenia at the level of neuronal structure, function, and chemistry in the premotor and motor cortices, and the basal ganglia and thalamus, as well as in the connecting white matter pathways. Furthermore, there is converging evidence for a functional and chronological link between the development of the motor system and the trajectory of the disease, congruent with the neurodevelopmental hypothesis of schizophrenia [11, 220, 221].

Conclusions and Outlook

Importance of the Motor Domain in Schizophrenia

Motor symptoms were interpreted as an integral part of schizophrenia in the classic and preneuroleptic literature [1, 5, 25]. More recently, various motor symptoms have been reported in never-medicated first-episode patients and in patients at risk for psychosis [10, 13, 34, 62, 236].

Motor symptoms in schizophrenia, however, are not restricted to catatonia or NSS. We have addressed a variety of symptoms, taking into account that further motor disorders have been described, including oculomotor dysfunction [237, 238] or impaired hand gestures [239]. Given that some motor symptoms are present in a majority of patients and that they can be found during the entire course of the disease, we conclude that they form an important domain of schizophrenia pathophysiology [8, 11]. However, the conflicting definitions of motor symptoms in schizophrenia reduce perception and research interest, and render the comparison of the related studies difficult. Furthermore, the debate on whether motor symptoms are an integral part of nosological schizophrenia or whether they are a loosely connected expression of a general neurodevelopmental disorder does not appear to be helpful for a comprehensive view of the manifold phenomena.

The motor domain includes a variety of motor abnormalities with varying degrees of severity. Since the diverse concepts suggest different objects of research and lead to incompatible study results, there is an urgent need for a common descriptive clinical foundation and neurobiological reference. On the basis of this review, we conclude that motor symptoms should be described in objective, concept-independent terms along dimensions such as quantity, sequencing, coordination, goal directedness, intrusion, omission, and negativism. Furthermore, research should be focused on referring these phenomena to the underlying brain systems and their development.

Triggered by articles on the specificity of catatonia [6–8] and on motor symptoms in drug-naïve patients [11, 58, 236], researchers currently debate whether motor symptoms should receive more attention in the DSM-V for schizophrenia. While the majority of researchers may agree that movement disorders are intrinsic to schizophrenia pathobiology [11], serious doubts have been raised about whether movement disorders are specific to schizophrenia, given their prevalence in other endogenous psychoses [60, 62, 236].

We have shown that several components of the motor system are affected by schizophrenia, including white matter and basal ganglia. Motor circuits mature during postnatal brain development [215] and in some instances, motor development is delayed in children who are later diagnosed with schizophrenia [224, 228]. Therefore, the development of motor circuits may be critical in schizophrenia. In particular, deficient migration and function of GABAergic interneurons, as well as impaired mRNA expression related to myelination, are thought to focally alter the brain in schizophrenia [198]. Similar local impairments in motor circuit components may represent the weak link in the chain of this important brain system, rendering it dysfunctional under stress.

The symptoms range from mild and basic disturbances such as hypokinetic and hyperkinetic movement disorders, i.e. parkinsonism and abnormal involuntary movements. In addition, higher motor functions such as coordination, planning, fine-tuning, and learning of motion sequences may be impaired. Finally, schizophrenia patients demonstrate disturbances in intention or will. The latter might originate from both cognitive and motor deficits, but it has also been connected with the function of the pre-SMA and ACC [114]. We suggest that disturbed volition and initiation of movements in schizophrenia may result from dysfunctions of the premotor cortices and of impaired structural connectivity. In addition, bradykinesia may be due to dysfunctional basal ganglion output on thalamocortical pathways.

Finally, the various motor symptoms in schizophrenia have been demonstrated to be important in treatment [34, 240] and rehabilitation [87, 240]. Most importantly, motor symptoms may disturb communication, provoking false signals about one's intentions. The most severe disturbances in communication would be catatonic mutism, negativism, and stupor. However, less pronounced motor disturbances might also affect communication. In

fact, parkinsonism in schizophrenia has been shown to alter speech [241], and negative symptoms have been associated with reduced abilities to imitate emotional face expressions and hand gestures [239]. It is further conceivable that symptoms such as dyskinesia or grimacing may disrupt facial emotion expression. Other motor aspects of nonverbal communication such as posture [15, 34, 35] and gait [34, 35, 88] are also altered in schizophrenia. Thus, communication disturbances in schizophrenia may not only relate to formal thought disorder [242, 243] and affective disturbances [244, 245] but also to motor symptoms.

Assessment of Schizophrenia Motor Symptoms

In recent decades, motor symptoms lost importance in psychiatric assessments. As a result, such symptoms have been increasingly ignored [71]. Renewed awareness of psychomotor symptoms in schizophrenia is necessary to develop comprehensive knowledge about the condition [7, 8, 65]. Operational, unitary, and objective instruments for the assessment of motor disorders are needed, since, compared to rating scales, sensitivity for detecting motor symptoms has been shown to be superior for objective measurements [74, 82].

We propose that single motor symptoms should be investigated descriptively, irrespective of historical concepts, and symptom descriptions should be independent from presumed etiologies. With this strategy, reduced motor activity (or bradykinesia) was quantified [83, 91] and related to abnormal local resting brain perfusion [91], reduced cingulate gray matter [81], and alterations in white matter integrity [92].

Future Directions

We identify three important areas of future research. First, elaborated neuroimaging studies and longitudinal designs are needed to further clarify the impairments in the schizophrenia motor circuitry at different stages of development and in unaffected siblings. Second, further animal models of motor dysfunction are required to elucidate the impact of delayed maturation, as well as the gene-environment interaction on motor function. Third, postmortem brain investigations should clarify the neurochemical and structural role of altered white matter structure as presented in neuroimaging studies. The conceptual work should be addressed to unify the findings on a common basis. We suggest that this basis is the functionality of the motor system. To the best of our current knowledge, these dysfunctions should not be limited by categorical boundaries but rather be described and studied as a dimension linked to neurodevelopmental disorders of schizophrenia.

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