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LEAD ARTICLE

Motor Abnormalities: From Neurodevelopmental to Neurodegenerative Through "Functional" (Neuro)Psychiatric Disorders

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Background: **Motor abnormalities (MAs) of severe mental disorders have been traditionally neglected both in clinical practice and research, although they are an increasing focus of attention because of their clinical and neurobiological relevance. For historical reasons, most of the literature on MAs has been focused to a great extent on schizophrenia, and as a consequence their prevalence and featural properties in other psychiatric or neuropsychiatric disorders are poorly known. In this article, we evaluated the extent to which catatonic, extrapyramidal and neurological soft signs, and their associated clinical features, are present transdiagnostically.** ***Methods:*** **We examined motor-related features in neurodevelopmental (schizophrenia, obsessive compulsive disorder, autism spectrum disorders), "functional" (nonschizophrenic nonaffective psychoses, mood disorders) and neurodegenerative (Alzheimer's disease) disorders. Examination of the literature revealed that there have been very few comparisons of motor-related features across diagnoses and we had to rely mainly in disorder-specific studies to compare it transdiagnostically.** ***Results:*** **One or more motor domains had a substantial prevalence in all the diagnoses examined. In "functional" disorders, MAs, and particularly catatonic signs, appear to be markers of episode severity; in chronic disorders, although with different degree of strength or evidence, all motor domains are indicators of both disorder severity and poor outcome; lastly, in Alzheimer's disease they are also indicators of disorder progression.** ***Conclusions:*** **MAs appear to represent a true transdiagnostic domain putatively sharing neurobiological mechanisms of neurodevelopmental, functional or neurodegenerative origin.**

Key words: schizophrenia/psychosis/mood disorders/obsessive-compulsive disorder/autism spectrum disorders/Alzheimer's disease

Introduction

Motor abnormalities (MAs) of psychiatric disorders have been traditionally a neglected topic in both clinical practice and research, and modern taxonomies of psychopathology continue to ignore them.[1–3] MAs are included among diagnostic criteria of many psychiatric disorders[4] and are present as cardinal or associated features in many others (supplementary table 1); and they also have important implications for the etiology,[5–7] nosology,[5,8,9] pathophysiology,[10–12] and management[13–15] of psychiatric disorders. Furthermore, MAs cut-across many psychiatric, neuropsychiatric and neurological disorders[16] and they have been proposed as a core phenotype dimension of major psychiatric disorders[17,18] and as a putative domain within the NIMH Research Domain Criteria framework (RoDC).[19]

Despite the fact that MAs are a ubiquitous condition of many psychiatric disorders, for historical reasons, most studies on the topic have been mainly focused on psychotic disorders and more specifically on schizophrenia, and only a minority of studies have compared MAs across diagnoses. Thus, the extent to which MAs and their associated clinical features are either disorder-specific or have a transdiagnostic character remains an open question. The present article attempts to meet this challenge through a systematic review of empirical studies examining MAs in several diagnoses. In this article, we consider 3 domains of MAs: catatonic signs, extrapyramidal symptoms (EPS) and neurological soft signs (NSS). Catatonia is a neuropsychiatric psychomotor syndrome characterized not only by a broad range of MAs, but also by affectivity disturbance and complex behaviors including disturbance of will.[15,20,21] Insofar as catatonia does not exclusively affect motility, it can be distinguished from pure MAs such as EPS. EPS may present as either abnormal excess or paucity of movements, and commonly used

terms for the former are dyskinesia, hyperkinesias, and abnormal involuntary movements and for the latter hypokinesia, bradykinesia, and parkinsonism.[22,23] Hereinafter, we use mainly the terms dyskinesia and parkinsonism. The NSS comprise a wide range of subtle abnormalities that are usually grouped into sensory integration, motor coordination and sequencing of complex motor tasks.[24] The rationale for selecting these motor domains was that catatonic and extrapyramidal signs represent well-known phenotypic manifestations of many psychiatric disorders with important clinical and treatment implications. On the contrary, NSS are subclinical features that are not usually assessed in clinical practice, as they need to be elicited by neurological examination; however, they are of research relevance because of their value as endophenotype candidates for many psychiatric disorders.[25]

The goal of this study was 2-fold. We first examined the phenomenology and factor structure of MAs, in order to describe their core clinical phenotype. We next examined the main featured characteristics of MAs across disorders of neurodevelopmental, "functional" or neurodegenerative origin. Among neurodevelopmental disorders we specifically examined the diagnoses of schizophrenia, obsessive-compulsive disorder (OCD) and autism spectrum disorders (ASD); functional disorders included nonschizophrenic nonaffective psychoses (NSNAP) and major mood disorders; lastly, as a neurodegenerative disorder we examined Alzheimer's disease (AD). Neurodevelopmental disorders are a group of conditions with onset, or early manifestations, in the developmental period as a result of early brain dysfunction, which usually follow a chronic course. Neurodegenerative disorders are characterized by late-onset neurodegenerative processes in the brain in which the clinical course is progressive rather than chronic. In opposition to these groups of disorders, "functional" disorders are mainly characterized by onset in early or middle adulthood and by an episodic/remitting course that is putatively tied to a mostly reversible brain dysfunction. The rationale for selecting these diagnoses of varying origin was that they represent major and prevalent psychiatric or neuropsychiatric disorders, in which MAs have been often described. Such an approach may inform on points of commonality and divergence of MAs across diagnostic classes and mechanisms. Before examining these questions, and to illustrate the complexity of motor dysfunction influencing clinical practice and research, it is necessary to address some relevant conceptual and methodological issues.

Conceptual and Methodological Issues

We lack of a unifying theory about normal and abnormal motility and there is no guiding principle of what makes a motor sign or behavior.[26] As a consequence, both the definition and boundaries of abnormal motility have become unclear and changing according to different theoretical backgrounds.[27] For example, we lack universally accepted concepts and assessment tools for catatonia[4,15,16,28–35] and NSS[24,36–40] (supplementary tables 2 and 3), and research is fragmented according to the predefined motor domains, although a comprehensive instrument for rating the 3 motor domains is available.[36]

Daniel Rogers[41] advanced the idea of a "conflict of paradigms" to refer to the psychiatric vs neurologic view of MAs; nonetheless, there are several other conflicting views involving broad vs restrictive definitions, categorical vs dimensional approaches, cross-sectional vs longitudinal views and primary vs drug-induced MAs, issues to which we'll refer briefly. Historically, catatonia was broadly defined as a psychomotor syndrome characterized by the most remarkable signs such as stupor, excitation, negativism, mutism, paratonia and waxy flexibility, but also by less dramatic manifestations including tic- and dyskinesia-like movements, choreo-athetoid movements, rigidity, bradykinesia, release signs and difficulties in motor coordination and balance.[5,42–44] These less dramatic signs are now recognized as EPS or NSS and in general are not included within the catatonia syndrome, which has led to a more restrictive view of the syndrome.[41]

The complexity of the catatonia concept is further highlighted by uncertainty as to whether it is a discrete pathology or a dimensional cluster of symptoms, a question that needs to be framed within the broader context of categorical vs dimensional representations of psychopathology. Dimensions cut-across diagnostic categories, tend to exhibit more predictive value than categories and are an essential component of the RdoC matrix. Catatonia is usually defined as a discrete category and identified with the most striking manifestations; however, catatonia ratings, particularly when scales with broad item coverage are used, tend to follow a continuous distribution in severe mental disorders[18,45–47]; thus, choosing a determined cut-off point to make a diagnosis is a relatively arbitrary question that may reflect underlying severity rather than true categorical distinctions. An additional problem is that current catatonia rating scales and diagnostic criteria essentially define a cross-sectional disorder. Catatonia may vary over time according to specific patterns of symptoms and illness-related factors, by which a longitudinal perspective has been emphasized by all classical[5,42–44] and some modern authors.[48,49] Unlike catatonia, EPS and NSS lacked of nosological formulations, and they are usually rated dimensionally and eventually categorized according to specific cut-off points or criteria. A specific problem of NSS is that they lack a validate criterion to define abnormality, which favors great discrepancy between studies in prevalence rates in healthy controls and those with psychiatric disorders.[24]

Regarding the motor effects of antipsychotic medication, it is worth noting that Steck, who was one of the first in reporting these effects[50] and had been involved

in studying MAs of severe mental disorders in the pre-neuroleptic era,[10] suggested that antipsychotic drugs may be acting by modifying the expression of disease-based motor disorder.[50] This view was ignored by contemporary and subsequent authors and the contribution of drugs to motor disorders was seen as paramount importance. Antipsychotics may cause a broad range of acute and chronic MAs,[51] although it appears that illness-related factors,[52,53] and particularly preexisting MAs[53,54] play also a role. Studies of drug-naïve subjects showed that spontaneous MAs may be an indigenous feature of severe mental disorders tied to the underlying pathophysiology,[53,55–57] and that antipsychotics, in addition to produce drug-emergent MAs in some subjects, they may improve, worsen or left unchanged preexisting catatonic,[58] extrapyramidal[58] and neurological signs.[59] Thus, in subjects on antipsychotics, MAs and particularly NSS and EPS, likely represent a mixture of primary and drug-induced motor features, and currently, a balanced view of MAs in treated subjects is one of antipsychotic medication interacting with or modifying the disease-based motor disorder.[13,57–61]

Systematic Review

We first identified relevant historical literature on MAs in psychiatric and neuropsychiatric disorders. Then we completed an initial search of MeSH terms for "Catatonia" OR "Abnormal involuntary movements" or "Parkinsonism" OR "Extrapyramidal symptoms" OR "Neurological soft signs" AND "Mental disorder" OR "Medical disease" OR "Factor Analysis". Search dates were not constrained, and pertinent cohort studies and review articles were identified. Using this initial information, numerous subsequent searches of specific terms were made in order to examine MAs in the disorders of interest. MeSH terms for specific diagnoses included "Schizophrenia" OR "Psychotic disorder" OR "Mood disorder" OR "Obsessive-compulsive disorder" OR "Autism Spectrum Disorder" OR "Alzheimer's disease". Many variations on each search for the individual diagnoses were also conducted. Exclusion criteria were as follows: studies determining MAs exclusively by instrumental measures, studies of drug-induced motor disorders, and case reports. Studies in English, German, French, Italian or Spanish were included. Because of this study was mainly concerned with primary MA, we tried to prioritize studies including subjects who were drug-naïve, minimally treated, drug-free, or treated subjects in which the antipsychotic medication was controlled for.

The great majority of studies had a focus on schizophrenia spectrum disorders, which can be explained by historical trends. Most of the remaining studies examined MA within specific diagnoses and a total of 46 studies examined MAs in 2 or more diagnoses, one of them usually involving schizophrenia. Of these 46 studies, 22 exclusively addressed the prevalence of catatonia in hospital samples and 24 examined some featural properties of MAs, which should be the main focus of this review[55,62–85] (supplementary table 4). Most of these articles, however, mainly examined the distribution of motor features and were of such variable methodology and quality that we'll refer to some of them in the following narrative review. Thus, we had to rely on findings mainly coming from disorder-specific studies. To maintain a balance between findings in schizophrenia and in other diagnoses, those of schizophrenia were kept at a minimum according to their relevance. Lastly, because of motor dysfunction is a key component of abnormal neurodevelopment and at-risk states, this issue was also briefly addressed.

Phenomenology and Syndromic Structure of MAs

The phenomenology of MAs has been mainly addressed in classical text books[5,42–44] and articles[11,86–91] not included in PubMed. This literature was largely based on close clinical scrutiny of patients followed-up over years and laid the foundation of current descriptions. However, classical and current approaches highly differ in that the former is clinically-based and longitudinally-oriented, and the latter, clinometrically-based and cross-sectionally-oriented. The classical approach is best represented by the Wernicke-Kleist-Leonhard school of psychiatry,[92] which set the MAs at the forefront of psychotic disorders because of their clinical, nosological and neurobiological relevance. Kleist[11] was the first in elaborating a systematic account of catatonic phenomena and in relating them to specific brain circuitry dysfunctions. Leonhard, categorized human motility into spontaneous, expressive, reflex, and reactive movements,[93,94] and articulated the most clinically detailed description and classification of motor phenomena ever produced (supplementary table 5).[5] According to Leonhard, MAs need to be considered in relation to the entire illness course, and distinguished between quantitative increase or decrease of motor activity and qualitatively distinct motor disturbances. Indeed, Leonhard's scheme allows ordering the varied MAs along a continuum of axial characteristics such as bipolarity, bizarreness and complexity of motor behaviors. Leonhard's nosology has been validated to some extent by other authors,[95–101] but it had little international impact mainly due to its complexity. Some attempts have been made to render this classification more simple and operational,[102–104] but with limited success in terms of further use. Notwithstanding this, Leonhard's classification remains of high heuristic value and of potential research interest to address heterogeneity of MAs in psychiatric disorders.[92,101]

When catatonia ratings are examined in the context of other psychopathological symptoms, a catatonia dimension consistently emerges as a highly differentiated

domain.[105] The 15 existing factor analytical studies of catatonia greatly vary about the number of factors obtained (from 2 to 7) and their item composition (supplementary table 6).[18,30,33,63,72,106–115] The mean number of reported factors was 4.1 and the most replicated ones were motor excitement and motor retardation (13 and 11 studies, respectively), followed to a great distance by an involuntary movements factor (5 studies). Variability in the factor structure may be explained by item composition of the rating scales, method for determining the factor solution and sample issues; in fact, a somewhat different factor structure can be obtained by using different rating scales in the same sample[18,113] and by using the same rating scale in different samples.[18,110]

Studies addressing the factor structure of EPS are lacking, but when EPS ratings are analyzed together with ratings of catatonia, they usually form part of overarching hyperkinetic and hypokinetic dimensions.[18] A consistent multidimensionality of NSS has been observed (from 3 to 5 factors) in both exploratory[39,79,116] and confirmatory factor analysis[117] and most studies provided face validity for the 3 predefined NSS domains.[24,118–121] The only study examining conjointly the factor structure of all 3 motor domains resulted in 5 dimensions: motor coordination, movement abnormalities, increased reflexes, dyskinesias, and catatonia.[69]

Strong associations between catatonia and EPS ratings have been reported,[106,122] and to a less degree between these and NSS.[123,124] Most importantly, these associations have also been observed in drug-naïve subjects,[30,53,116] this indicating that associations are genuine and not due to chronicity or drug effects.

Schizophrenia

NSS and dyskinesias, but not catatonic signs, may appear long before the beginning of the first-episode of psychosis[125–128]; hence, these MAs may be better understood in the context of neurodevelopment deviations, as results of brain insults or dysfunctions during pregnancy and perinatal periods[129] and genetic or epigenetic factors.[130,131] Normal neurodevelopment evolves through a chronological schedule that is closely entwined with the age-associated stage and intrinsically linked to the development of motility, cognitive functions and social behavior.[132–137] Early motor dysfunctions may be a risky step for the development of schizophrenia[138–140] and might predict subsequent negative symptoms[141] and cognitive performance.[142–144] In addition, spontaneous dyskinesias may predict transition to psychosis in at-risk individuals,[145,146] neuromotor dysfunction in children and adolescents may precede the prodrome and onset of schizophrenia,[147] and deviant achievement of motor milestones may serve to recognize individuals at risk of psychosis.[148]

Compared to healthy controls, both dyskinesias[131,149] and NSS[150,151] are significantly more prevalent in subjects with schizotypy or at-risk individuals. Furthermore, meta-analytic evidence indicates that EPS[152–154] and NSS[155] capture a moderate proportion of psychosis proneness, which supports the endophenotype hypothesis of motor dysfunction by associating it with neurodevelopmental deviance. However, some caution is warranted since at-risk individuals are not just for schizophrenia but, more broadly, for other disorders with poor developmental outcomes.[131]

The catatonic subtype of schizophrenia was dropped from DSM-5 due to low diagnostic stability and validity.[156] However; no less important is the poor validity of the DSM schizophrenia concept itself in resolving clinical and etiological heterogeneity,[101] and that motor signs have been de-emphasized in current diagnostic criteria compared with earlier definitions.[157,158] Indeed, Leonhard's and Bleuler's classifications diagnose as much as 2.5 times more catatonias than current consensus diagnoses.[157] Catatonic signs are by no means confined to the catatonic subform of the disorder, and they appear to cut-across schizophrenia subtypes. The Iowa-500 study showed that 32% of people with schizophrenia had catatonia signs and only 6.5% met criteria for the catatonic subtype.[159] From a lifetime perspective, the prevalence of a catatonia syndrome in schizophrenia raises up to 41% (figure 1), and Manschreck[73] noted that most subjects with chronic schizophrenia exhibit mild catatonia-like movements that do not qualify for a catatonia diagnosis.

Converging evidence indicates that catatonia signs are linked to severity of schizophrenia. Most,[160–163] but not all[164] modern outcome studies of schizophrenia examining baseline catatonic signs showed that they were related to a poor outcome, and most subjects with severe impairment present with catatonic symptoms.[41,43,44,165,166] Likewise, motor domains have been consistently linked to negative or deficit schizophrenia,[167] even in drug-naïve subjects,[168] and to poor cognition.[166,169] There is a lack of prospective studies examining catatonia sings across illness stages, but studies using the same rating instrument in samples with differing illness stages, provide indirect evidence for an overall increase of catatonia signs with illness chronicity and severity (supplementary table 7).[18,41,110]

Several systematic reviews have reported prevalence rates for spontaneous dyskinesia between 9%[56] and 13%[56] and for spontaneous parkinsonism between 17%[56] and 25%,[12] although rates up to 30% have been reported using broader definitions of EPS.[18] Both dyskinesias and parkinsonism have been described in about two-thirds of subjects with chronic schizophrenia,[169–171] and although they likely represent a mixture of primary and drug-induced phenomena, the contribution of antipsychotic drugs appears to be of minor relevance, particularly for dyskinesias.[170] An outstanding longitudinal study comparing schizophrenia subjects, who were mostly drug-naïve, with and without spontaneous dyskinesias showed that the group with dyskinesias had poorer premorbid

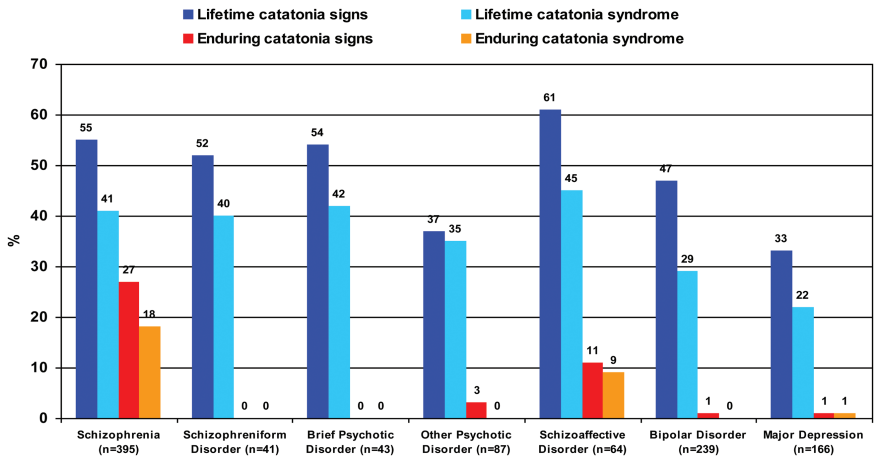

Fig. 1. Data were re-analyzed from Peralta et al.[101] This sample population was derived from a family study comprising 1094 subjects affected with psychotic or mood disorders, who were recruited from out and inpatients facilities in Navarra (Spain) between years 1990 and 2014. Subjects were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition), and catatonia was assessed by means of the Comprehensive Assessment of Symptoms and History (CASH).

adjustment, earlier illness onset, more severe disorganized and catatonic signs, and much more poor functioning.[172] Another study reported that subjects with chronic schizophrenia and dyskinesias had greater negative and disorganization symptoms, more voluntary MAs, lower premorbid IQ and higher cognitive impairment.[173]

NSS are prominent during the acute exacerbations of schizophrenia and to a less extent during the stabilization phase[174–177]; furthermore, their decreasing during the episode remission runs parallel to remission of symptomatology,[37] even in drug-naïve samples.[176,178] Duration of illness is significantly associated with NSS,[124] and some evidence indicates that NSS are related to both poor cognitive functioning,[179,180] although subscale motor scores may differ in this regard,[74] and poor social functioning.[81]

Nonschizophrenic Nonaffective Psychoses

This diagnostic grouping entails the diagnoses of schizophreniform disorder, schizoaffective disorder, brief psychotic disorder and other unspecified psychotic disorder; and Kalbaum's catatonia original concept mainly corresponds with NSNAP.[181] Within NSNAP, catatonia may appear either in association with other psychotic syndromes or as the main manifestation of the disorder. Disorders with episodic-remitting course in which abnormal motility is the predominant manifestation have been historically acknowledged as periodic psychoses with disturbed motility[43] or motility psychoses,[5,182,183] and more recently as idiopathic or recurrent catatonia.[184–186] Catatonia cut-across all NSNAP with lifetime prevalence rates of 35%–45% (figure 1). Motility psychoses represent the 18% of all NSNAP,[5] and the idiopathic/recurrent catatonias have been described in 4%–46% of case series of subjects with catatonia.[186] When catatonia is the main manifestation of the psychotic disorder, it is usually much more severe than catatonia in other psychiatric conditions.[5,185]

The relevance of catatonia within NSNAP contrasts with the paucity of studies of catatonia and other motor domains within this diagnostic grouping. Only one study reported prevalence rates of spontaneous dyskinesias in schizoaffective (11.4%) and schizophreniform disorder (0%).[55] Consistent evidence indicates that levels of NSS in NSNAP did not differ from those observed in schizophrenia[74,80] or psychotic mood disorder.[74,81]

Mood Disorders

The prevalence of catatonia in manic episodes ranges from 17%[187] to 31%[188] (figure 1), these rates being much higher in mixed mania: between 28%[187] and 61%.[189] The major MAs in mood disorders are psychomotor agitation and retardation, which are closely tied to mood states. Catatonic signs are related to severity of the manic episode[188,190]; and some,[68,189] but not all[190] studies revealed that catatonic manics displayed higher levels of comorbidity and poorer global functioning compared with their noncatatonic counterparts; furthermore, the poor prognosis of manic subjects with catatonia appears to be mediated by the higher comorbidity associated with the mixed states.[191,192]

The only study examining the prevalence of spontaneous dyskinesias in bipolar disorder (BD) reported a figure of 14.3%.[55] Additionally, mood disorders may present a risk factor for developing tardive dyskinesias (TD),[193] and a relationship appears to exist between affective states and TD as increased severity of depression often is coupled with TD worsening and TD often diminish with

mania.[194,195] Bipolar subjects show significantly more NSS than healthy controls,[196–199] though without clear detachment from nonaffective psychoses.[24,74,79–81] NSS occur in decreasing degree in psychotic mania,[77] nonpsychotic mania,[77] euthymic bipolars,[200] unaffected first-degree relatives,[200] and healthy controls.[199,200] Thus, NSS appear to represent both severity and trait deficits in BD.

As many as 20% of depressed subjects may present with a catatonia syndrome,[201] and compared with noncatatonic depressed they were older, more cognitively impaired and presented more severe depression.[201] Psychomotor retardation indicates episode severity[202] and is central to the melancholic subtype of depression[203]; although it may also appear in mixed states as inhibited mania.[204] Psychomotor agitation in major depression has been reported to be a strong predictor of mood switching.[205]

The prevalence of spontaneous dyskinesias in major depression appears to be as low as 6.3%.[55] The only study specifically addressing parkinsonism in depression reported a 20% prevalence rate, and it was related to older age, severity of depression and cognitive impairment.[206] Levels of NSS in major depression are significantly lower than in psychotic disorders and BD and do not meaningfully differ from those observed in healthy controls[207]; however, psychotic depression exhibit NSS levels comparable to other psychotic disorders.[77]

Obsessive-Compulsive Disorder

Despite poor and nonfunctional motor behavior has been acknowledged in most subjects with OCD,[208,209] only one study has examined catatonia ratings in subjects with this diagnosis[66]; and it reported that OCD subjects had significantly lower catatonia ratings than those with schizophrenia but higher ratings than healthy controls. A phenomenological overlap exists between catatonia and OCD regarding complex repetitive compulsions and catatonic mannerisms and repetitive/perseverative behaviors[210]; and evidence for a relationship between OCD and catatonia comes from the study of the so-called schizo-obsessive disorder.[211] Compared with their schizophrenia counterparts, the majority of schizo-obsessive subjects exhibit both catatonia (83%) and EPS (58%),[210] a clinical picture highly resembling Leonhard's manneristic catatonia.[5] The only study systematically examining catatonia in Tourette's syndrome, a disorder highly comorbid with OCD, found that it was present in 87% of the subjects.[212]

About one-third of subjects with OCD exhibit both dyskinesias other than tics[213] and parkinsonism,[214] although studies differ in their comparative levels in relation to schizophrenia.[66,76] The most common movement disorders comorbid with OCD are tics, now recognized as a diagnostic specifier in DSM5. On a lifetime basis, tics have been reported to co-occur in 22%–44% of subjects with OCD, and inversely, the 20%–40% of subjects with tic disorders have OCD.[215] Subjects with OCD and comorbid tics exhibit earlier age of onset, male preponderance, greater likelihood of family members also having OCD, chronic course of symptoms and a poorer response to treatment.[216] Furthermore, subjects with OCD, and particularly those with tic disorder, are more likely to have comorbid conditions characterized by abnormal motility such as attention deficit hyperactivity disorder (ADHD),[217] ASD,[218] and basal ganglia disorders.[219,220]

Subjects with OCD and parkinsonism differ from those without parkinsonism in having more severe compulsions, lower IQ scores and poorer cognitive performance.[214] A subgroup of severely impaired OCD subjects present obsessional slowness,[221,222] a concept highly overlapping with parkinsonism.[223,224] The majority of subjects with obsessional slowness (76%) also present with a broad range of mild catatonia-like signs, EPS and NSS.[222] Subjects with OCD consistently exhibit lower NSS ratings than those with schizophrenia,[66,76,84] but higher ratings than their first-degree relatives[225] and healthy controls.[66,224,226]

Autism Spectrum Disorders

As a typical neurodevelopmental disorder, the majority of children with ASD exhibit varying degrees of MAs. The association of ASD with psychosis and catatonia has long been recognized,[227,228] since they share many abnormal patterns of movement. In their study of 117 cases of catatonic schizophrenia in children, Leonhard held that they "correspond to many of the autistic children studied by Kanner".[229] Based on this overlap, some modern authors conceptualize catatonia in ASDs as a deterioration of the previous level of motor behavior or the emergence of "new" motor signs.[45,230,231] Although up to 20% of subjects with ASD develop a catatonia syndrome,[231] this syndrome is poorly recognized in the clinical practice as there is a general bias to diagnose catatonia in its severe form.[231] For example, Wing and Shah[45] examined 28 catatonia-like behaviors and reported that the lifetime prevalence of at least 1 motor sign in subjects with ASDs, learning disabilities and typically developing children was 100%, 93%, and 33%, respectively. The finding of catatonia signs in typically developing children is of interest and may reflect age-dependent reversible developmental traits. Levels of catatonia in ASD are inversely related to IQ,[45,230–232] a finding in line with the frequently reported association between catatonia and intellectual disability.[233–236]

The only studies examining EPS in autism reported prevalence rates of 25% for parkinsonism[237] and 18% for dyskinesias.[238] Levels of NSS in ASD are similar to those reported in early-onset schizophrenia,[82,83] and are related to low IQ or cognitive impairment.[239–241]

Alzheimer's Disease

A broad range of catatonia-like signs, which are generally described as neurological or EPS, have been extensively documented in AD.[242,243] However, these MAs have

been often poorly described,[244] and no single study has addressed the prevalence of catatonia in AD. Nevertheless, factor-analytical studies of the neuropsychiatric inventory, which comprises some catatonia-like signs within the "aberrant behavior" item, have consistently identified a psychomotor factor, which has been reported to be as clinically significant in 11% of newly diagnosed subjects with AD[245] and in 32% of subjects with varying severity of the disorder[246]; furthermore, this factor has been related to poor functional outcome, rapidity of evolution and severity of AD.[245] On the other hand, in the neurological literature, the single most recognized catatonic feature in AD is paratonia (*gegenhalten*), which was first described by Dupré[247] in subjects with intellectual disability and afterwards by Kleist in dementia.[89] Paratonia usually occurs with other catatonia signs such as automatic obedience, motor perseveration, echopraxia and frontal release signs.[248] Paratonia has been found in 10% of early stages and in 90% of late stages of AD,[249] and it is a robust independent indicator of severity and progression of the illness.[250] Thus, if we consider aberrant motor behavior and paratonia as proxy indicators of catatonia, the prevalence of a catatonia syndrome in AD appears to be substantial and of most clinical relevance.

Although cognitive impairment is the signature feature of AD, EPS are extremely common with a prevalence rate ranging from 12% in mild stages[251] up to 92% in severe stages,[252] with parkinsonism being much more prevalent than dyskinesias.[253] Furthermore, mild parkinsonism in the elderly has been reported as a risk factor for developing dementia.[254] Based on the presence or absence of EPS 2 AD subphenotypes can be recognized: "cognitive/pure" and "cognitive/motor," mirroring the classification of Parkinson disease (PD) into "motor" and "motor/cognitive" forms. Such distinction is extremely important, as individuals with AD and EPS show a faster course of the disorder.[253,255] Furthermore, EPS share a pattern of presentation similar to that seen in PD, suggesting common pathogenic mechanisms across the 2 neurodegenerative disorders.[256]

There are few studies of NSS in AD, but they consistently show that AD exhibit higher NSS compared with mild cognitive impairment[257] and healthy old controls.[257,258] Furthermore, NSS appear to increase with progression of AD and cognitive deterioration.[258]

Discussion

This revision raised some relevant findings that could eventually inform the transdiagnostic issue of MAs in psychiatric disorders. First, MAs represent an overarching concept entailing inter-related motor domains, which in turn can be further differentiated into several subdomains. Of particular concern was the lack of a consistent syndromic structure of catatonia beyond the excitement and retarded factors, which poorly account for the multidimensional structure of this motor domain. Given that highly differentiated symptoms tend to display a hierarchical arrangement,[259,260] likely the catatonia syndrome may be viewed as a higher-order dimension with 2 middle-order dimensions and various lower-order dimensions that are close to the item level. This view appears to fit well how catatonia is currently approached, since on the one side, it is considered as an unspecific syndrome with similar phenomenological presentation in psychiatric, medical and neurological conditions[15,261–263]; and on the other side, clinical lore and distribution of signs across diagnoses indicates that lower-order dimensions are to some extent disorder-specific.

Second, one or more motor domains had a substantial prevalence across all the examined diagnoses. Notwithstanding this, prevalence rates are highly contingent on the methodological issues described above. Catatonic signs had a substantial prevalence in all diagnoses excepting OCD, a diagnosis in which they have been poorly examined. Particularly high rates of catatonic signs were observed across all classes of psychotic disorders, although enduring signs were mainly confined to schizophrenia; this suggesting that non-enduring catatonia signs are a hallmark transdiagnostic feature of psychotic illness, while enduring catatonic signs are specific to schizophrenia. EPS had a substantial prevalence in disorders of neurodevelopmental or neurodegenerative origin; and NSS showed similar high levels across diagnoses excepting OCD and depression. The transdiagnostic prevalence of MAs is in a small part definitional since only catatonic signs are included in the diagnostic criteria of psychotic and ASD.

Third, MAs were a severity marker of either the illness episode or the disorder. In "functional" disorders, MAs, and particularly catatonia, appear to be markers of episode severity. In neurodevelopmental and neurodegenerative (ie, chronic) disorders, but with different degree of strength or evidence, all motor domains were indicators of both illness severity and poor outcome. Dementia is an interesting case in relation to transdiagnostic mechanisms, since it has an established neuropathology. In AD, abnormal motility in addition to being a marker of severity was also a marker of illness progression.

A subordinate but interesting finding was that one or more motor domains were consistently related with poor cognition in neurodevelopmental disorders; furthermore, in schizophrenia both motor and cognitive dysfunctions appear to be stable traits long before illness onset. Motor and cognitive dysfunctions are also inextricably linked in AD and other widespread neurodegenerative disorders such as PD[256]; thus, it could be argued that the 2 domains are intimately related in both neurodevelopmental and neurodegenerative disorders, which further support the transdiagnostic character of MAs. Interestingly, in schizophrenia, dyskinesias may appear long before illness onset as a manifestation of deviant

neurodevelopment[125–128] (see Schiffman, this issue), and they increase with age,[55] particularly after age 65,[264] this suggesting that for this particular motor domain 2 overlapping and age-dependent neurobiological mechanisms are possible.

Although not object of this review, some etiological, therapeutic and neurobiological questions can also illustrate the transdiagnostic issue of MAs. Regarding familial-genetic factors, catatonic schizophrenia appears to exhibit higher familial loading of psychotic disorders than noncatatonic schizophrenia,[265,266] and Leonhard's periodic catatonia has been consistently considered as highly familial[5,97] with a morbidity risk of 26.9% and major gene effect and anticipation.[267] As showed in this review, compared to healthy controls, higher levels of NSS have been found in the first-degree relatives of subjects with schizophrenia, BD, and OCD, while in the other diagnoses there was a lack of studies thereof. Thus, familiality of catatonia may be disorder-specific, while that of NSS cut-across several diagnoses. Regarding treatment, lorazepam and electroconvulsive therapy are highly effective in treating acute catatonia regardless the underlying etiology, with response rates of 70%–90%.[268,269] Although these treatments appear to be somewhat less effective in neurodevelopmental and medical conditions,[270] their overall effectiveness for catatonia is one of the major arguments for considering this syndrome transdiagnostically.

Lastly, given the transdiagnostic character of MAs in most of the realms addressed in this review, it could be argued that they share abnormal brain circuitry functioning involving the motor system, which may be viewed as common pathway of the various motor loop networks related to different disorders and brain mechanisms. In this regard, some plausible models of brain dysfunction underlying motor domains have been proposed[271–273] (also see Pantelis and Mittal et al, this issue). For example, Northoff,[271] attempted to explain catatonic and extrapyramidal signs by integrating dysfunction of brain circuitry and neurotransmission; to explain catatonia, he suggested a deranged "top-down" modulation of cortical-subcortical connections (as reflected, eg, in the modulation of basal ganglia by lateral orbito-frontal cortex) related to cortical GABAergic-mediated dysfunction; and to explain EPS, he suggested a "bottom-up" modulation of cortical-subcortical connections related to basal ganglia dopamine dysfunction. More recently, Hiryak[272] developed a 3-stage severity model of catatonic, extrapyramidal and neurological signs in schizophrenia on the basis of a graded dysfunction of the cortico-cerebelar-thalamo-cortical loop. The 2 models appear to work well across the 3 neurobiological mechanisms involved in the diagnoses examined: stable dysfunction in neurodevelopmental disorders, reversible dysfunction in functional disorders, and progressive dysfunction in AD.

Limitations

Several limitations apply to the present study. First, while our study covered the major clinical domains of MAs observed in psychiatric disorders, we excluded studies using instrumental measures[274,275] and experimental paradigms[276,277] of motor dysfunction. These measures and paradigms are increasingly used to disentangle mechanisms underlying abnormal motility and ideally they should be used together with clinical ratings of MAs. Second, some disorders defined by abnormal motility such as ADHD and tic disorders were not included in this review; these diagnoses, however, are important targets for transdiagnostic research that should be examined in future studies. Third, we largely relied on articles focused on specific disorders, which had a highly variable methodology; therefore, some subjectivity in selecting the most informative articles cannot be excluded; furthermore, the range of MAs-related features reviewed here was necessarily limited and highly dependent on the quality of individual studies. Fourth, in analyzing the existing data we mainly focused on general measures of catatonic, extrapyramidal and neurological signs, and it is possible that focusing on more specific dimensions of MAs might reveal a somewhat different pattern of MAs-related features across disorders. Lastly, the studies reviewed adopted widely varying measures and designs, and further progress in transdiagnostic comparison of MAs arguably requires consistency of measures across the groups studied.

Conclusions and Future Directions

Despite their clinical and neurobiological relevance, MAs continue to be a neglected area in clinical practice and research. Domains of MAs cut-across neurodevelopmental, "functional" and neurodegenerative disorders, although with different expressivity or prevalence. They are markers of episode or illness severity across diagnoses, and in AD are also indicators of illness progression. MAs appear to represent a true transdiagnostic domain putatively sharing neurobiological mechanisms of neurodevelopmental, functional or neurodegenerative origin, this being a strong argument for studying MAs on their own, irrespective of diagnostic categories. MAs are closely tied to neurobiological mechanisms, and thus, they are a window to the brain mechanisms of psychiatric and neuropsychiatric disorders, but we know virtually nothing about the shared and disorder-specific mechanisms. Thus, unraveling these mechanisms may share light on the nature of both motor dysfunction and the underlying diagnoses.

Given the complexities surrounding the definition and assessment of abnormal motility in psychiatry, we first need a unified theory and assessment tool for MAs, and the 3 motor domains should be examined concurrently along with instrumental measures of motor function. The

ideal methodological requirements would be the prospective, independent screening and evaluation of MAs in a large sample with mixed diagnoses, coupled with risk factors, neurobiological measures, treatment response, and follow-up studies. This endeavor is undoubtedly arduous and may seem insurmountable; however, it appears to be a necessary step for unraveling the transdiagnostic and disorder-specific features of motor dysfunction in (neuro) psychiatric disorders. Indeed, MAs fit good the criteria for RDoC[277] (also see Garvey and Cuthbert and Mittal et al, this issue); thus, they should be incorporated as an additional RDoC domain, which undoubtedly would boost knowledge of that under-researched clinical phenotype.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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