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Review article

A systematic review of the prognostic value of motor abnormalities on clinical outcome in psychosis

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ABSTRACT

Schizophrenia spectrum disorders have heterogeneous outcomes and currently no marker predicts the course of illness. Motor abnormalities (MAs) are inherent to psychosis, the risk of psychosis, symptom severity, and brain alterations. However, the prognostic value of MAs is still unresolved. Here, we provide a systematic review of longitudinal studies on the prognostic role of MAs spanning individuals at clinical high risk for psychosis (CHR), patients with first-episode psychosis (FEP), and chronic schizophrenia. We included 68 studies for a total of 23,630 subjects that assessed neurological soft signs (NSS), hypo- or hyperkinetic movement disorders and/or catatonia as a prognostic factor on clinical and functional outcomes. We found increased levels of MAs, in particular NSS, parkinsonism, and dyskinesia, were related to deteriorating symptomatic and poor functional outcome over time. Collectively, the findings emphasize the clinical, prognostic and scientific relevance of MA assessment and detection in individuals with or at risk of psychosis. In the future, instrumental measures of MA are expected to further augment detection, early intervention and treatment strategies in psychosis.

1. Introduction

The outcome of people with schizophrenia spectrum disorders (hereafter: schizophrenia) is very heterogeneous, ranging from full remission to severe chronic states (Lang et al., 2013). To date, readily available and reliable clinical markers that predict illness course in people with schizophrenia, or in individuals at clinical high-risk for psychosis (CHR), are lacking (Fusar-Poli et al., 2013; Owen et al., 2016). Thus, prognostic markers are urgently needed in order to improve staging of the disease process, prediction of symptom course and functional outcome, and development of early intervention and individualized treatment strategies (Klosterkötter et al., 2011). Motor abnormalities (MAs) are frequently observed in CHR and schizophrenia populations and hold promise as objective, easily detectable and clinically available prognostic markers (Van Harten et al., 2017). They can be categorized into four domains: (i) neurological soft signs (NSS), including minor motor and sensory deficits such as integrative sensory function, motor coordination, sequencing of complex motor acts, and primitive reflexes, (ii) hyperkinetic movements such as dyskinesia and akathisia, (iii) hypokinetic movements such as parkinsonism and psychomotor slowing, and (iv) catatonic phenomena (Bombin et al., 2005; Hirjak et al., 2018a,b; Van Harten et al., 2017; Walther et al., 2019a,b).

A steadily growing body of evidence demonstrates that MAs are inherent to the psychotic disease process (Bombin et al., 2005; Hirjak et al., 2018a,b; Mittal et al., 2017; Morrens et al., 2014; Van Harten et al., 2015; Van Harten et al., 2017; Walther et al., 2020b; Walther and Mittal, 2017; Whitty et al., 2009). Aberrant motor functioning was already observed in the pre-antipsychotic era (Kraepelin, 1919), but research interest in MAs diminished after the introduction of antipsychotics, as MAs were primarily interpreted as adverse effects of antipsychotics. Over the past decades, MAs were re-discovered as intrinsic features of the psychosis syndrome, as they were observed in antipsychotic-naïve populations and have been related to psychosis risk and psychopathological symptoms (Van Harten et al., 2017; Walther et al., 2020a,b; Whitty et al., 2009).

Various systematic reviews and meta-analyses have demonstrated elevated levels of MAs in (i) CHR individuals, (ii) unaffected first degree relatives of patients with psychosis, (iii) patients with first episode psychosis (FEP), and (iv) antipsychotic-naïve schizophrenia populations, compared to healthy controls (Bachmann et al., 2014; Bombin et al., 2005; Chan et al., 2010; Hirjak et al., 2018a,b; Koning et al., 2010; Neelam et al., 2011; Pappa and Dazzan, 2009). More importantly, direct

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relationships between spontaneous MAs and psychopathology have been established in CHR individuals and patients with schizophrenia. In antipsychotic-naïve patients with FEP, MAs have been related to positive and negative symptom severity and cognitive dysfunction (Cuesta et al., 2014; Emsley et al., 2017; Peralta et al., 2018; White et al., 2009). Also, in CHR individuals relationships with psychopathology have been found: NSS have been related to negative symptoms, and spontaneous involuntary movements in the upper body to positive, negative and total psychopathology symptoms (Mittal et al., 2014, 2007b). These findings reflect shared etiological pathways of MAs and the psychotic disease process, a notion that is supported by neurobiological findings. Structural and functional neuroimaging studies have related MAs in schizophrenia and CHR individuals to cortical-subcortical dysfunction involving cortico-basal ganglia-thalamocortical and cerebellar circuits (Bernard et al., 2017; Kong et al., 2012; Mittal et al., 2010, 2014; Walther et al., 2017).

Evidence from longitudinal studies suggest that MAs could have predictive value for the risk of transition to psychosis (in CHR) or relapse (in schizophrenia), symptomatic and functional outcome, cognitive impairment and treatment response. In CHR populations, NSS and dyskinesia have been related to transition to psychosis (Callaway et al., 2014; Francesconi et al., 2017; Masucci et al., 2018; Mittal et al., 2007a, b). In patients with FEP, spontaneous MAs have shown predictive value for symptom severity, cognitive functioning and long-term psychosocial outcome (Cuesta et al., 2014, 2018; Minichino et al., 2017; White et al., 2009). In a chronic schizophrenia sample of 2175 participants, tardive dyskinesia was significantly associated with symptom severity, lower remission rates, lower levels of quality of life and psychosocial functioning at 3-year follow-up (Ascher-Svanum et al., 2008).

Despite the increase in literature on the prognostic value of MAs in psychosis, no systematic review to date has attempted to synthesize this evidence. Most systematic reviews on MAs in psychosis have focused on prevalence rates of MAs in first-degree relatives of patients with schizophrenia, CHR individuals, patients with FEP, or patients with chronic schizophrenia (Bachmann et al., 2014; Bombin et al., 2005; Chan et al., 2010; Hirjak et al., 2018a,b; Koning et al., 2010; Neelam et al., 2011; Pappa and Dazzan, 2009). Some of these reviews have related MAs to increased psychotic symptom severity, negative symptoms or cognitive deficits (Bachmann et al., 2014; Bombin et al., 2005; Hirjak et al., 2018a,b; Pappa and Dazzan, 2009). These reviews tentatively conclude that MAs might predict symptom changes and could therefore be of prognostic value. However, most studies included in these reviews were cross-sectional by design and therefore could not address this prognostic question.

Therefore, this systematic review aims to synthesize and evaluate the evidence from longitudinal studies on the prognostic role of MAs on clinical and functional outcomes across the psychosis continuum, including CHR individuals, patients with FEP and chronic schizophrenia. The review of this body of literature could potentially help understanding the prognostic value of MAs in psychosis in the prediction of outcome and treatment response and thereby improve detection, early intervention and treatment strategies.

2. Methods

This systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard (Moher et al., 2009). The protocol for the study was registered under the number CRD42020198127 at PROSPERO international prospective register of systematic reviews.

2.1. Search strategy and study selection

The search strategy aimed to identify studies that examined spontaneous or treatment emergent MAs in relation to clinical or functional outcome at follow-up in patients in the prodromal, early and chronic phase, that is; 1) individuals meeting CHR criteria or with schizotypal personality traits, 2) patients with FEP and 3) patients with (multiple episode) schizophrenia spectrum and other psychotic disorders (e.g., schizoaffective disorder, schizophreniform disorder, other or unspecified schizophrenia spectrum and other psychotic disorder). A systematic literature search was conducted in the databases of MEDLINE and Embase from inception to May 2021 using the following search terms (or their combinations): "psychotic*", "psychos*", "schizophreni*", "Psychotic disorders (MeSH term)", "Schizophrenia (MeSH term)", "extrapyramidal", "parkinsoni*", bradykines*", "hypokines*", "dyskines*", "tremor", "akathisia", "involuntary movement*", "catatoni*", "soft sign*", "follow-up", "longitudinal", "prospective", "retrospective", "prognos*", "predict*", "cohort studies (MeSH term)" and "movement-, motor-, neuromotor-, or psychomotor- "in combination with "disorder*", "abnormalit*", "symptom*", "sign*", "function*", "dysfunction*", "deficit*", "disturbance*", "slowing". The full search strategy is enclosed in the Supplementary material. The automatic search was completed by cross-checking the reference lists of the identified studies and of previous systematic reviews on this topic. There were no language, publication date, or country of origin restrictions (although ultimately 6 studies from a non-western language were excluded). After deduplication, identified records were imported into Covidence (www.covidence.org), an electronic systematic review management system that was used for title/abstract screening, full-text screening, data extraction and risk of bias assessment.

2.2. Study selection and eligibility criteria

Studies of interest were reviewed independently by two authors (L.P. and N.N.) and discrepancies were resolved by discussion. Unresolved disagreements were resolved by discussion with the other authors (P.v. H. and S.W.). Studies were included if they (1) measured MAs (i.e., NSS, hypo- or hyperkinetic movement disorders or catatonia) as a prognostic factor, (2) collected data on clinical or functional outcome, using either continuous measures for psychotic or cognitive symptom severity, psychosocial functioning or quality of life, or dichotomous measures for transition to psychosis, relapse or remission, and (3) included individuals at CHR for psychosis or with schizotypal personality traits, patients with FEP or schizophrenia spectrum and other psychotic disorders. In order to establish the prognostic value of MAs, studies were only included if they associated MAs to clinical or functional outcome at follow-up. In addition, we used the following methodological inclusion criteria: (a) longitudinal studies, (b) studies including only human participants, (c) (English, French, Dutch, German, Italian or Spanish) full-text available, and (d) studies were reported as original articles in peer-reviewed journals. Unpublished studies, conference abstracts or poster presentations were excluded from this review.

2.3. Quality assessment

The risk of various types of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool, an instrument evaluating validity and bias of prognostic factors on six domains: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) study confounding, and (6) statistical analysis and reporting (Hayden et al., 2013). Each domain is being rated on a three-grade scale: low, moderate or high risk of bias. Two authors (L.P. and N.N.) carried out quality control independently and disagreements were resolved by discussion.

2.4. Data extraction and synthesis

Two authors (L.P. and N.N.) conducted independent data extraction in duplicate. We extracted data on study design, patient population and characteristics, treatment components, MAs, clinical or functional outcome measures and effect measures. Depending on the data

available, either the mean and standard deviation, or raw statistics (e.g., Odds ratios, regression coefficients, confidence intervals, Chi-squared statistics and p-values) were extracted. Inconsistencies were resolved by involvement of the other authors (P.v.H. and S.W.). Ideally, a quantitative synthesis of results was conducted in the form of a meta-analysis. We anticipated that there was limited scope for meta-analysis because of the expected heterogeneity in study population, study duration, and measures for MAs as well as clinical outcome. Therefore, we performed a qualitative synthesis to evaluate and synthesize the evidence.

3. Results

Fig. 1 presents a PRISMA flow chart summary of the search and review process, including reasons for study exclusion. The MEDLINE and Embase searches identified a total of 6432 studies. An additional 5 articles were found through cross-referencing. 4733 studies remained after removal of duplicates and 199 remained after title/abstract screening. We screened full-texts of 199 studies and excluded 131 studies, leaving 68 studies for qualitative data synthesis.

3.1. Study characteristics

We identified ten studies on CHR individuals, 28 studies in FEP and 30 studies in chronic schizophrenia. Results are presented in Tables 1–3 and Fig. 2. The identified studies yielded a total of 893 CHR subjects, 2867 FEP patients and 19,870 chronic schizophrenia patients. Studies included the following MAs as predictor for clinical or functional outcome: NSS in 34 studies, dyskinesia in 22, parkinsonism in 21, akathisia in 13, dystonia in six, catatonia in six and other MAs (e.g., psychomotor slowing, akinesia, and electronic measurements of MAs) in eight studies. There were substantial methodological differences between the included studies in terms of sample size, duration of follow-up (ranging from two weeks to ten years), timing of the assessment of MAs

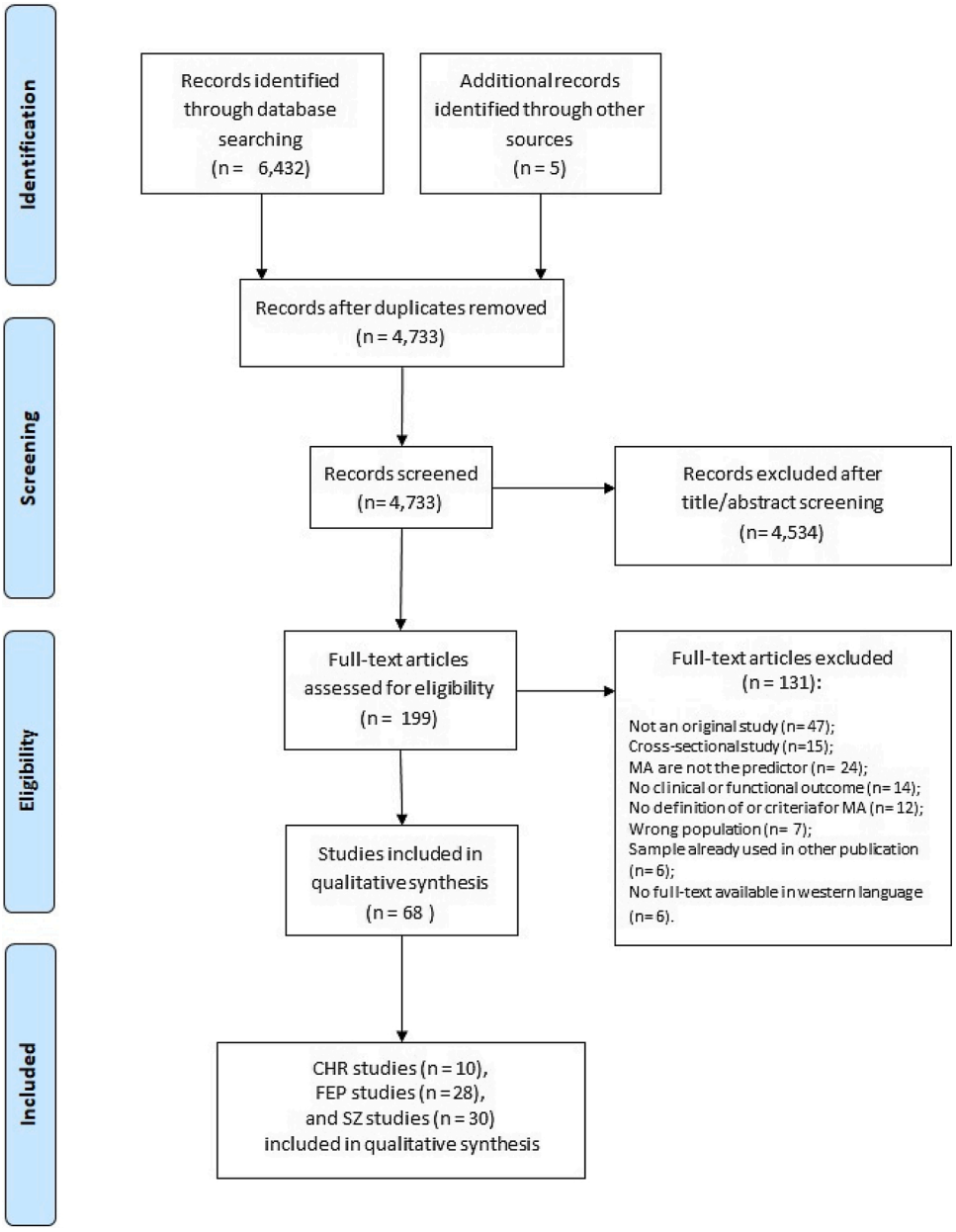

Fig. 1. PRISMA flowchart of systematic review of the prognostic value of motor abnormalities (MA) in Clinical High Risk (CHR) individuals and patients with first episode of psychosis (FEP) and chronic schizophrenia (SZ).

Table 1
Summary of included studies with clinical high-risk individuals.

Authors (year)	*N*	Follow-up, mean (SD)	Age, mean (SD)	Sex (male %)	Antipsychotic-naive	Motor abnormality (scale)	Longitudinal assessment of MAs	Outcome	Results
Callaway et al. (2014)	148	until conversion	19.77 (4.60)	86 (58.1 %)	Yes	Dyskinesia (AIMS)	No	Conversion to psychosis, SIPS	+
Dean et al. (2018)	69	24 months	18.58 (1.78)	40 (58.0 %)	62 (90 %)	NSS (NES), Force stability task, Velocity scaling	No	Conversion to psychosis	+/-
Francesconi et al. (2017)[1]	138	2.2 years	24.3 (3.5)	73 (53.0)	Yes	NSS (NES)	No	Conversion to psychosis, SCID, PANSS, GAF, LSP-39	+
Masucci et al. (2018)	192	2 years (until conversion)	20.03 (3.84)	140 (72.9 %)	161 (84 %)	Motor dysfunction (SIPS G.3)	No	Conversion to psychosis	+
Minichino et al. (2017)[1]	138	2.2 years	24.2 (3.6)	60 (51.7 %)	Yes	NSS (NES)	No	GAF, SOFAS, LSP-39	+
Mittal et al. (2007a,b) [2]	42	1 year	14.12 (1.66)	29 (69.0 %)	NR	Dyskinesia (DISCUS)	No	SIPS	+
Mittal and Walker (2007)[2]	40	4 years	14.48 (1.65)	28 (70 %)	32 (80 %)	Dyskinesia (DISCUS)	No	Conversion to psychosis, SCID	+
Mittal et al. (2011)	40	1 year	16.67 (3.29)	26 (65 %)	29 (72.5 %)	Dyskinesia (DISCUS)	No	Conversion to psychosis, SIPS, GFS-R/S	+
Mittal et al. (2014)	33	1 year	18.52 (2.06)	20 (61 %)	30 (91 %)	NSS (NES)	No	SIPS	+
Tamagni et al. (2013)	53	3 years	26.8 (9.2)	29 (54.7 %)	Yes	NSS (NES)	No	Conversion to psychosis, BPRS	+/-

1,2, same study population.
+, higher levels of MAs predict worse outcome; -, higher levels of MAs predict better outcome +/-, no significant relationship between MAs and outcome at follow-up. **AIMS**, Abnormal Involuntary Movement Scale; **BPRS**, Brief Psychiatric Rating Scale; **DISCUS**, Dyskinesia Identification System Condensed User Scale; **GAF**, Global Assessment of Functioning Scale; **GFS-R/S**, Global Functioning Scale: Role/Social; **LSP-39**; Life Skills Profile-39; **MAs**, motor Abnormalities; **NES**, Neurological Evaluation Scale; **NSS**, Neurological Soft Signs; **PANSS**, Positive and Negative Syndrome Scale; **SCID**, Structural Clinical Interview for DSM-IV; **SIPS**, Structured Interview for Prodromal Syndromes; **SIPS G.3**, Structured Interview for Prodromal Syndromes G.3; **SOFAS**, Social and Occupational Functioning Assessment Scale.

(before or after initiation of antipsychotic treatment), measurement scales and statistical analyses.

3.2. Risk of bias within studies

Overall, the risk of bias within studies as assessed with the QUIPS tool was low to moderate, with the highest ratings for risk of bias on the study attrition items, due to relatively high loss to follow-up, not providing the reasons of loss to follow-up and not comparing completers versus non-completers of the study on key characteristics. In addition, the prognostic factor measurement items were rated with higher risk of bias, if training or experience of raters was unknown, interrater reliability was not reported, the diagnostic criteria to establish a MA were unclear or MAs were not measured on a validated scale. The full risk of bias assessment table can be found in Supplementary Table S1.

3.3. Results in CHR individuals

Out of the ten studies on MAs in CHR individuals, there were five studies on NSS and four studies on (spontaneous) dyskinesia. One study used instrumental measurements (force stability task and velocity scaling) in addition to the assessment of NSS, although they did not identify a significant predictive value of either the instrumental measurements or NSS for conversion to psychosis (Dean et al., 2018). One other study examined motor dysfunction (defined as self-rated clumsiness, awkwardness, or lack of coordination in their movements, and clinician-rated catatonia, motor rituals and dyskinetic movements) in relation to clinical outcome. The latter study found that motor dysfunction at baseline was related to conversion to psychosis in a sample of 192 patients at risk for psychosis and that this relationship was independent of medication status (Masucci et al., 2018).

3.3.1. Symptomatic outcome in CHR individuals

Five studies related MAs, i.e., NSS, dyskinesia and/or motor dysfunction, to higher rates of conversion to psychosis in CHR individuals (Callaway et al., 2014; Francesconi et al., 2017; Masucci et al., 2018; Mittal et al., 2011; Mittal and Walker, 2007). One of these studies followed-up 148 CHR individuals until transition and found that each point increase in the Abnormal Involuntary Movement Scale (AIMS) score at baseline induced more than a doubling of odds (OR = 2.25, 95 %CI = 1.31–3.85) to develop psychosis (Callaway et al., 2014). Two other studies related NSS (Mittal et al., 2014) and dyskinesia (Mittal et al., 2007a,b) to development of negative symptoms over a one year follow-up period. Conversely, two studies did not find a significant association between NSS and conversion to psychosis (Dean et al., 2018; Tamagni et al., 2013). One of them even observed a trend ($p = 0.055$) in the opposite direction: those at-risk mental state individuals who did not transition to psychosis ($n = 16$) displayed a slightly higher prevalence rate of NSS than those who did ($n = 37$) (Tamagni et al., 2013). The other study found that the distribution of CHR individuals who transitioned to psychosis was not significantly different across clusters of impaired motor performance (based on combined NSS assessments and instrumental measurements). They did find cross-sectional correlations between impaired motor performance and more severe negative symptoms, impaired cognition and higher scores on a psychosis risk calculator tool (Dean et al., 2018).

3.3.2. Functional outcome in CHR individuals

One study identified NSS at baseline as a key predictor of low social functioning at one-year follow-up in adolescents with a recent-onset psychiatric disorder (Minichino et al., 2017). Another study related spontaneous dyskinesia at baseline to poor social functioning at two-year follow-up in adolescents at high-risk for psychosis (Mittal et al., 2011).

Table 2
Summary of included studies with first episode psychosis patients.

Authors (year)	*N*	Follow-up, mean (SD)	Age, mean (SD)	Sex (male %)	Antipsychotic-naive	Motor abnormality (scale)	Longitudinal assessment of MAs	Outcome	Results
Bachmann et al. (2005)	39	14.2 (1.6) months	27.0 (7.7)	18 (46.2 %)	8 (20.51 %)	NSS (HS)	Yes	PANSS, SCS	+
Chan et al. (2015)	145	1 year	21.8 (3.8)	69, 48 %	14 (9.66 %)	NSS (CNI)	Yes	PANSS neg	+/- *
Chakos et al. (1992)	70	until remission, min. 14 weeks	24 (-)	39 (56 %)	Yes or 2-week washout period	Parkinsonism (SAS), Akathisia (SAS), Dystonia (SAS)	Yes	Remission, CGI, GAS of SADS, SANS	–
Chatterjee et al. (1995)	89	1 year	25.8 (6.6)	47 (52.8 %)	Yes or 2-week washout period	Parkinsonism (SAS)	Yes	Remission, SADS, SANS, CGI	+
Chen et al. (2005)	93	3 years	31.2 (9.6)	42 (45.2 %)	48 (51.61 %)	NSS (CNI)	Yes	PANSS, HEN, relapse	+/- *
Chiliza et al. (2015) [1]	126	1 year	24.0 (6.6)	93 (73.81 %)	Yes	NSS (NES), Parkinsonism (ESRS)	Yes	Response, PANSS, CGI, CDSS, SOFAS, WHOQOL-BREF	NSS,+; parkinsonism, +/-
Cortese et al. (2005)	39	6 months	23.62 (6.17)	32 (82 %)	Yes	Dyskinesia (ESRS), Parkinsonism (SAS), Force variability, Velocity scaling	Yes	SAPS, SANS	+/-
Cuesta et al. (2014) [2]	77	6 months	30.09 (10)	53 (69 %)	Yes	Parkinsonism (SAS)	Yes	Cognitive functioning	+
Cuesta et al. (2018) [2]	100	10 years	30.09 (10.0)	67 (67 %)	Yes	NSS (NES), Dyskinesia (AIMS), Parkinsonism (SAS), Akathisia (BARS), Catatonia (MRS)	Yes	FAST, DAS-S, GAF	+
Emsley et al. (2005) [3]	66	24 months	28.1 (8.5)	31 (47 %)	62 (92.42 %)	NSS (NES)	Yes	PANSS	+/- *
Emsley et al. (2017) [1]	126	1 year	24.1 (6.6)	93 (74 %)	antipsychotic exposure <4 weeks	NSS (NES)	Yes	PANSS, SOFAS, MCCB	+/- *
Ferruccio et al. (2021)	233	10 years	28.5/29.0 (21−38/ 24−38)**	128 (54.9 %)	No	NSS (NES)	Yes	Remission, SCAN, GAF	+
Johnstone et al. (1990)	253	2 years	NR	137 (57.8 %)	NR	NSS (neurological examination)	No	HMSO, duration of admission	occupational outcome, +/-; duration of admission, +
Kopala et al. (1997)	22	7.1 (3.2) weeks	25.0 (5.9)	17 (77.3 %)	No	Dyskinesia (-), Parkinsonism (-), Akathisia (-), Dystonia (-)	Yes	PANSS, CGI	+/-
Madsen et al. (1999)	18	5 years	28.5 (20−41)	11 (61.1 %)	3 (16.7 %)	NSS (neurological examination)	Yes	Remission, SAPS, SANS	+
Mayoral et al. (2008)	24	2 years	15.70 (1.62)	18 (75 %)	No	NSS (NES)	Yes	PANSS	+
Mayoral et al. (2012)	110	2 years	15.5 (1.8)	74 (67.3 %)	No	NSS (NES)	Yes	PANSS	+
Oosthuizen et al. (2003) [3]	57	12 months	28.2 (8.6)	28 (49.1 %)	antipsychotic exposure < 4 weeks	Dyskinesia (AIMS)	Yes	PANSS	+/-
Peralta and Cuesta (2011)	100	4 weeks	29.6 (10.9)	66 (66 %)	Yes	Dyskinesia (AIMS), Parkinsonism (SAS), Akathisia (BARS), Catatonia (MRS)	No	CASH, CGI	+
Peralta et al. (2018)	189	4 weeks	29.8 (10.3)	126 (66.7 %)	No	Dyskinesia (AIMS), Parkinsonism (SAS), Catatonia (MRS-C)	Yes	SAPS, SANS	+/- *
Prikryl et al. (2007) [4]	92	1 year	25.27 (5.45)	92 (100 %)	No	NSS (NES)	Yes	Remission, PANSS	+
Prikryl et al. (2012) [4]	68	4 years	22.50 (5.00)	68 (100 %)	No	NSS (NES)	Yes	Remission, PANSS	+
Rasmussen et al. (2017)	136	2 weeks	42.06 (1.71)	67 (49.3 %)	38 (28 %)	Dyskinesia (AIMS), Parkinsonism (UPDRS), Akathisia (BARS), Dystonia (own definition)	Yes	Treatment response, BPRS	+
	118		25.2 (6.6)		86 (73 %)		Yes		+

(*continued on next page*)

Table 2 (*continued*)

Authors (year)	*N*	Follow-up, mean (SD)	Age, mean (SD)	Sex (male %)	Antipsychotic-naive	Motor abnormality (scale)	Longitudinal assessment of MAs	Outcome	Results
Robinson et al. (1999)		until treatment response, max. 5 years		61 (52 %)		Parkinsonism (SAS), Akathisia (SAS), Dystonia (SAS), motor functioning (neuropsychological testing)		Treatment response, SADS, SANS, CGI, GAS	
Scheffer (2004)	29	6 weeks	22.8 (4.2)	21 (72 %)	Yes	NSS (NES)	Yes	BPRS	+
White et al. (2009)	109	10 years	27.44 (7.63)	62 (56.9 %)	No	NSS (NES)	No	GAF, SADS, SAPS, SANS	+
Whitty et al. (2003) [5]	97	6 months	NR	61 (62.9 %)	33 (34 %)	NSS (NES & CNE)	Yes	PANSS	+
Whitty et al. (2006) [5]	242	4 years	27.5 (11.4)	151 (62 %)	111 (45.9 %)	NSS (CNE)	Yes	SCLFS, PANSS	+

1,2,3,4,5: same study population.
* only cross-sectional correlations between MAs and outcome measures were found; ** median (IQR) for non-remitters ($n = 147$)/remitters ($n = 86$).
+, higher levels of MAs predict worse outcome; -, higher levels of MAs predict better outcome; +/-, no significant relationship between MAs and outcome at follow-up.
AIMS, Abnormal Involuntary Movement Scale; **BARS**, Barnes Akathisia Rating Scale; **BPRS**, Brief Psychiatric Rating Scale; **CASH**, Comprehensive Assessment of Symptoms and History; **CDSS**, Calgary Depression Scale for Schizophrenia; **CGI**, Clinical Global Impression; **CNE**, Condensed Neurological Evaluation; **CNI**, Cambridge Neurological Inventory; **DAS-S**, Short Disability Assessment Schedule; **ESRS**, Extrapyramidal Signs Rating Scale; **FAST**, Functioning Assessment Short Test; **GAF**, Global Assessment of Functioning Scale; **GAS**, Global Assessment Scale; **HEN**, High Royds Evaluation of Negativity; **HMSO**, Registrar Generals Classification of Occupations; **HS**, Heidelberg Scale; **MAs**, motor Abnormalities; **MCCB**, MATRICS Cognitive Consensus Battery; **MRS(-C)**, Modified Rogers Scale(- Catatonia); **NES**, Neurological Evaluation Scale; **NSS**, Neurological Soft Signs; **PANSS**, Positive and Negative Syndrome Scale; **SADS**, Schedule for Affective Disorders and Schizophrenia; **SANS**, Scale for the Assessment of Negative Symptoms; **SAPS**, Scale for the Assessment of Positive Symptoms; **SAS**, Simpson-Angus Scale; **SCAN**, Schedules for Clinical Assessment in Neuropsychiatry; **SCLFS**, Strauss–Carpenter Levels of Functioning Scale; **SCS**, Strauss Carpenter Scale; **SOFAS**, Social and Occupational Functioning Assessment Scale; **UPDRS**, United Parkinson's Disease Rating Scale; **WHOQOL-BREF**, World Health Organization Quality Of Life-BREF Scale.

3.3.3. Other outcome measures in CHR individuals

Two studies performed additional neuroimaging to relate MAs to connective tract abnormalities. One of them found that NSS at baseline were predictive of abnormal white matter tract development on diffusion tension imaging one year later (Mittal et al., 2014), and the other study demonstrated widespread thalamocortical and cortical motor connectivity differences between the CHR cluster groups and healthy controls (Dean et al., 2018).

3.4. Results in patients with FEP

28 longitudinal studies examined MAs in relation to clinical or functional outcome in patients with FEP; 18 of them addressed NSS, 7 dyskinesia, 11 parkinsonism, 6 akathisia, 4 dystonia, and 3 of them addressed catatonia. Among these studies, 19 studies measured only one MA, mostly NSS, while the nine other studies measured two or more MAs. One study used electronic measurements in addition to validated rating scales for parkinsonism and dyskinesia, namely force variability measurement as a proxy for dyskinesia, and velocity scaling for the measurement of bradykinesia in 39 FEP patients with a diagnosis of schizophrenia or schizoaffective disorder (Cortese et al., 2005). Surprisingly, this study found that abnormalities on the pre-treatment instrumental measure of bradykinesia were associated with greater improvement on positive psychosis symptoms ($r = 0.39$, $p = 0.02$) following 6 months of antipsychotic treatment. On the other hand, none of the other baseline motor assessments (Simpson Angus Scale (SAS) for parkinsonism, Extrapyramidal Symptom Rating Scale for Dyskinesia (ESRS-D), and the instrumental measurement of force variability for dyskinesia) were related to change in positive, negative or disorganized symptoms during treatment, although parkinsonism ratings on the SAS were related cross-sectionally to all symptom dimensions ($r = 0.35–0.43$, $p < 0.05$).

3.4.1. Symptomatic outcome in patients with FEP

25 studies examined MAs in relation to symptomatic outcome. Seven studies found a significant relationship between MAs and remission rates or treatment response: either lower levels of NSS at baseline (Chiliza et al., 2015; Ferruccio et al., 2021), a decrease in NSS over time (Madsen et al., 1999; Prikryl et al., 2007, 2012), or lower levels of parkinsonism (Chatterjee et al., 1995; Robinson et al., 1999) were related to higher remission rates or improved treatment response at follow-up (range 1–10 years). Conversely, one other study found that acute dystonia and akathisia were associated with better treatment response in 70 patients with FEP (Chakos et al., 1992). The other 17 studies related MAs to symptom severity levels measured on clinical rating scales: ten of them found that patients with higher levels of MAs had higher scores on overall, positive and negative symptom severity at follow-up. These studies related lower levels of NSS at baseline (White et al., 2009), a reduction of NSS over time (Bachmann et al., 2005; Emsley et al., 2017; Mayoral et al., 2008, 2012; Scheffer, 2004; Whitty et al., 2003, 2006), and lower levels of parkinsonism, dyskinesia and/or catatonia (Peralta and Cuesta, 2011; Rasmussen et al., 2017) to better treatment outcome. Seven studies did not find significant longitudinal relationships between MAs and symptomatic outcome measures (Chan et al., 2015; Chen et al., 2005; Cortese et al., 2005; Emsley et al., 2005; Kopala et al., 1997; Oosthuizen et al., 2003; Peralta et al., 2018), but most studies did establish cross-sectional relationships between MAs and symptom severity: all but one of them (Oosthuizen et al., 2003) found significant cross-sectional relationships between NSS or dyskinesia and negative symptom severity.

3.4.2. Functional outcome in patients with FEP

Of the nine studies that reported functional outcome measures, six reported a significant association between elevated baseline NSS scores (Chiliza et al., 2015; Cuesta et al., 2018; Ferruccio et al., 2021) or stable (versus decreasing) NSS scores over time (Bachmann et al., 2005; Emsley et al., 2017; Whitty et al., 2006) and/or the presence of other MAs (Cuesta et al., 2018) to long-term (range: 1–10 years) poor social functioning at follow-up. One of them also found a significant relationship between elevated NSS scores at baseline and poorer quality of life at one-year follow-up in 126 patients with FEP (Chiliza et al., 2015). Three studies failed to detect significant relationships between NSS and functional outcome over time (Chen et al., 2005; Johnstone et al., 1990; White et al., 2009).

Table 3
Summary of included studies with chronic schizophrenia.

Authors (year)	*N*	Follow-up, mean (SD)	Age, mean (SD)	Sex (male %)	Antipsychotic-naive	Motor abnormality (scale)	Longitudinal assessment of MAs	Outcome	Results
Ascher-Svanum et al. (2008)	2175	3 years	42.1 (11.2)	1335 (61.4 %)	No	Dyskinesia (AIMS), Parkinsonism (SAS)	Yes	Remission, PANSS, GAF, SF-12, SCAP-HQ	+
Bartkó et al. (1990)	98	28 days	37.5 (19–58)	56 (57.1 %)	No	NSS (neurological examination), Dyskinesia (AIMS)	No	Treatment response	Dyskinesia, +; NSS, +/-
Behere (2013)	17	74.2 (24.2) months	32.7 (7.2)	9 (52 %)	Yes	NSS (modified NES)	Yes	PANSS, SOFS, SCOS	+
Bonnot et al. (2008)	33	20–50 weeks	15.43 (1.5)	30 (91 %)	No	Catatonia (BFCRS)	No	CGI, GAF	+/- *
Buchanan et al. (1994)	31	10 weeks	34.3 (7.9)	21 (67.8 %)	No	NSS (NES)	Yes	BPRS, SANS	+/-
Chen et al. (2000)	43	3 years	48.9 (8.9)	30 (69.77 %)	No	NSS (CNI)	Yes	BPRS	+/-
Chen et al. (2013)	640	1 year	42.9 (12.1)	406 (63.4)	NR	Dyskinesia (AIMS), Parkinsonism (SAS), Akathisia (BARS), MDI (sum of five EPS measures)	Yes	PANSS, SF-36	+
Docx et al. (2014)	105	1 year	31.85 (7.53)	82 (78.1 %)	No	NSS (NES), Parkinsonism (SHRS), Catatonia (BFCRS), Psychomotor slowing (SRRS)	Yes	PANSS	Psychomotor slowing, +; all other MAs, +/-
Dollfus and Petit (1995)	57	2 months (range 10 days-13 months)	40.3 (15.9)	19 (33.3 %)	No	Akinesia (ESRS)	Yes	SAPS, SANS	only outcome measure affective flattening, +
Eberhard et al. (2006)	166	5 years	37.9 (NR)	97 (58.4 %)	No	Dyskinesia (AIMS)	Yes	PANSS	all outcomes except affective flattening, +
Farreny et al. (2018)	275	9 months	42.2 (10.7)	203 (74 %)	No	Parkinsonism (SAS)	Yes	CAINS, PANSS, CDSS	+
Fong et al. (2017)	151	6 months	54.00 (8.40)	80 (54 %)	33 (22 %)	NSS (subscales of NES)	No	PANSS, ADL, IADL	+
Fountoulakis et al. (2019)	133	12 months	33.55 (11.22)	77 (57.9 %)	35 (26.31 %)	NSS (NES)	Yes	PANSS, GAF, CDS, MADRS	+/- *
Hansen et al. (1992)	57	19.2 (8.6) days	45.0 (12.5)	56 (98 %)	42 (74 %) washout period 1 week	Dyskinesia (AIMS), Parkinsonism (SHRS)	Yes	BPRS	+/- *
Haro et al. (2018)	1344	1 year	42.0 (11.4)	953 (70.9 %)	8 (0.6 %)	Dyskinesia (-), Akathisia (-)	No	PANSS, CGI, PSP, SQLS, EQ-5D, number of relapses	+
Mittal et al. (2007a,b)	19	6 weeks	36.3 (5.4)	19 (100 %)	washout period > 6 weeks	NSS (NSSS)	Yes	BPRS	+
Nair et al. (1999)	33	16 weeks	42.4 (NR)	18 (54.5 %)	No	Akathisia (BARS)	Yes	BPRS	+/- *
Park et al. (2016)	484	12 weeks	35.50 (10.40)	234 (48.3 %)	No	Dyskinesia (DIEPSS), Parkinsonism (DIEPSS), Akathisia (DIESPSS), Dystonia (DIEPSS)	Yes	PSP	+
Peralta and Cuesta (1999)	45	4.5 weeks	31.6 (12.8)	28 (63.6 %)	23 (51 %)	Parkinsonism (SAS), Catatonia (MRS)	Yes	SAPS, SANS, CDS	+
Sambataro et al. (2020)	43	7 (6–12) months	37.55 (10.39)	28 (65.1 %)	No	NSS (HS)	Yes	PANSS, BPRS, GAF, B-CATS	+
Schennach-Wolff et al. (2011)	370	2 weeks	34.52 (11.00)	214 (57.8 %)	No	Neurological side effects (UKU)	Yes	Treatment response, PANSS, SCPS, GAF, SOFAS	+
Sevincok and Topaloglu (2006)	10	8 weeks	24.5 (NR)	7 (70 %)	No	NSS (NES)	Yes	PANSS, CGI	+/- *
Siani et al. (2016)	1208	2 years			NR	Akathisia (BARS)	Yes		

(*continued on next page*)

Table 3 (*continued*)

Authors (year)	*N*	Follow-up, mean (SD)	Age, mean (SD)	Sex (male %)	Antipsychotic-naive	Motor abnormality (scale)	Longitudinal assessment of MAs	Outcome	Results
			41.8 (10.88)	761 (63 %)				PANSS, GAF, EQ-5D, SF-6D, CDSS	SF-6D, +; EQ-5D, +/-
Smith et al. (1999)	37	621 (520) days	42.8 (7.6)	25 (67.6 %)	No	NSS (modified NES)	Yes	BPRS, SAPS, SANS	+/-
Tenback et al. (2007)	10,009	12 months	40.1 (13.1)	5775 (57.7 %)	NR	Dyskinesia (own definition)	Yes	CGI	+
Umbricht et al. (2002)	37	29 weeks	41.1 (10.2)	26 (70.3 %)	No	Parkinsonism (SAS), Akathisia (BARS)	No	Treatment response, BPRS, SANS, CGI	+
Van Os et al. (2000)	361	2 years	36 (29–45)	183 (51 %)	NR	Dyskinesia (AIMS)	Yes	SANS	+
Vauth et al. (2021)	1812	6 months	40.1 (12.6)	1086 (59.9 %)	No	Dyskinesia (ESRS), Parkinsonism (ESRS), Akathisia (ESRS), Dystonia (ESRS)	Yes	PSP, SF-36, PANSS, CGI	+
Venkatasubramanian et al. (2013)	36	34.1 (4.1) days	30.28 (7.9)	11 (30.6 %)	Yes	Parkinsonism (SAS)	Yes	SAPS, SANS, CGI	–
Waddington and Youssef (1996)	41	10 years	54.1 (12.5)	22 (53.7 %)	No	Dyskinesia (AIMS)	Yes	Cognitive function	+

* only cross-sectional correlations between MAs and outcome measures were found.
+, higher levels of MAs predict worse outcome; -, higher levels of MAs predict better outcome; +/-, No significant relationship between MAs and outcome at follow-up. **ADL**, Activities of Daily Living Index; **AIMS**, Abnormal Involuntary Movement Scale; **BARS**, Barnes Akathisia Rating Scale; **B-CATS**, Brief Cognitive Assessment Tool for Schizophrenia; **BFCRS**, Bush Francis Catatonia Rating Scale; **BPRS**, Brief Psychiatric Rating Scale; **CAINS**, Clinical Assessment Interview for Negative Symptoms; **CDS**, Calgary Depression Scale; **CDSS**, Calgary Depression Scale for Schizophrenia; **CGI**, Clinical Global Impression; **CNI**, Cambridge Neurological Inventory; **DIEPSS**, Drug-induced Extrapyramidal Symptoms Scale; **EPS**, extrapyramidal symptoms; **ESRS**, Extrapyramidal Signs Rating Scale; ; **EQ-5D**, EuroQol-5 Dimension; **GAF**, Global Assessment of Functioning Scale; **HS**, Heidelberg Scale; **IADL**, Instrumental Activities of Daily Living Scale; **MAs**, Motor Abnormalities; **MADRS**, Montgomery-Asberg Depression Rating Scale; **MDI**, Movement Disorder Index; **MRS**, Modified Rogers Scale; **NES**, Neurological Evaluation Scale; **NSS**, Neurological Soft Signs; **NSSS**, NSS Scale; **PANSS**, Positive and Negative Syndrome Scale; **PSP**, Personal and Social Performance scale; **SANS**, Scale for the Assessment of Negative Symptoms; **SAPS**, Scale for the Assessment of Positive Symptoms; **SAS**, Simpson-Angus Scale; **SCAP-HQ**, Schizophrenia Care and Assessment Program Health Questionnaire; **SCOS**, Strauss Carpenter Outcome Scale; **SCPS**, Strauss-Carpenter-Prognostic Scale; **SF-12**, Short-Form 12-Item Health Survey; **SF-36**, 36-Item Short-Form Health Survey; **SF-6D**, Revision of SF-36; **SHRS**, St. Hans Rating Scale; **SOFS**, Social Occupational Functioning Scale; **SRRS**, Salpêtrière Retardation Rating Scale; **SQLS**, Schizophrenia Quality of Life Scale; **UKU**, Udvalg for Klinske Undersogelser.

3.4.3. Other outcome measures in patients with FEP

Two studies related MAs to cognitive functioning over time. One of them significantly related lower NSS endpoint scores and a reduction in NSS over time to improved cognitive performance, specifically in working memory, at one-year follow-up in 126 patients with FEP (Emsley et al., 2017). The other study showed that elevated spontaneous parkinsonism scores were significantly associated with impairment in memory, executive functioning, and attention over a 6-month follow-up period (Cuesta et al., 2014).

3.5. Results in patients with schizophrenia

Of the 30 studies that were identified in patients with (chronic) schizophrenia, 19 assessed one MA, mainly NSS or dyskinesia, and the other 11 studies assessed multiple MAs. One study did not differentiate between the different MAs and used the Udvalg for Klinske Undersogelser (UKU) Side Effect Rating Scale to score neurological side effects altogether (i.e., dystonia, rigidity, hypokinesia/akinesia, hyperkinesia, tremor, akathisia, epileptic seizures, paresthesia) in 370 hospitalized patients with an acute psychotic episode (Schennach-Wolff et al., 2011). They found that less extrapyramidal side-effects at admission and during the first two weeks of treatment were significant predictors for early improvement, independent of type and dosage of the antipsychotic treatment.

3.5.1. Symptomatic outcome in patients with schizophrenia

27 studies related MAs to symptomatic outcome in terms of treatment response, symptomatic remission, relapse or symptom severity. Three studies related elevated scores of dyskinesia, parkinsonism and/or akathisia to lower treatment response or remission rates (Ascher-Svanum et al., 2008; Umbricht et al., 2002) or higher relapse rates (Haro et al., 2018). Conversely, one study found a significant link between elevated baseline scores of dyskinesia and higher response rates after four weeks of antipsychotic treatment ($r = 0.26$, $p < 0.01$) in 98 medicated patients with schizophrenia, but found no significant relationships between NSS and treatment response (Bartkó et al., 1990). The other 23 studies related MAs to symptom severity measured on clinical evaluation scales: 13 of them, with samples ranging from 17 to 10,000, found a significant relationship between MAs and more severe positive, negative and/or overall symptom severity. This applies for elevated baseline scores of NSS (Behere, 2013; Fong et al., 2017; Mittal et al., 2007a; Sambataro et al., 2020), presence or development of tardive dyskinesia (Eberhard et al., 2006; Tenback et al., 2007; van Os et al., 2000), and/or (a combination of) other MAs, such as parkinsonism, akinesia, akathisia, dyskinesia, dystonia, and catatonia (L. Chen et al., 2013; Dollfus and Petit, 1995; Farreny et al., 2018; Peralta and Cuesta, 1999; Schennach-Wolff et al., 2011; Vauth et al., 2021). One study found results that indicated a relationship in the opposite direction between MAs and symptomatic outcome: an open-label trial with risperidone in 36 antipsychotic-naïve patients with schizophrenia significantly related development of parkinsonism to clinical improvement over five weeks (Venkatasubramanian et al., 2013). The remaining nine studies with samples ranging from 10 to 640 did not find a significant relationship between the presence or development of MAs and

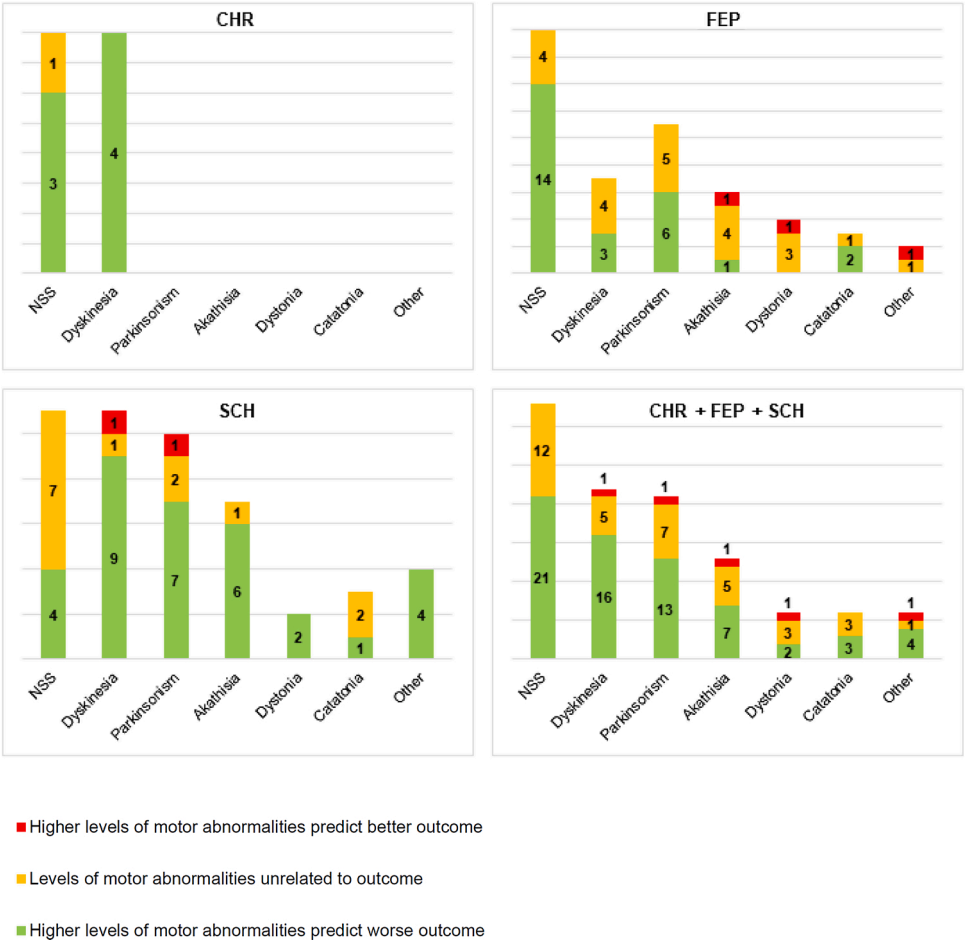

Fig. 2. Overview of results of the included studies in clinical high risk (CHR) individuals and subjects with first episode psychosis (FEP) and chronic schizophrenia (SCH).

symptomatic outcome at follow-up (Bonnot et al., 2008; Buchanan et al., 1994; Chen et al., 2000; Docx et al., 2014; Fountoulakis et al., 2019; Hansen et al., 1992; Nair et al., 1999; Sevincok and Topaloglu, 2006; Smith et al., 1999). Although Docx et al. (2014) did not identify changes in NSS, parkinsonism and catatonia as significant predictors of symptomatic outcome, they did find significant correlations between the course of psychomotor slowing on the Salpêtrière Retardation Rating Scale and the course of negative symptoms. Two other studies that failed to detect longitudinal relationships between MAs and symptomatic outcome, identified cross-sectional correlations between akathisia and global psychopathology (Nair et al., 1999) and catatonia and global symptom severity (Bonnot et al., 2008).

3.5.2. *Functional outcome in patients with schizophrenia*

Eight studies related MAs to social functioning and/or quality of life at follow-up. Six of these studies found that MAs, including NSS, dyskinesia, parkinsonism, akathisia and dystonia, were linked to poor (psycho)social functioning at follow-up (Ascher-Svanum et al., 2008; Behere, 2013; Chen et al., 2013; Fong et al., 2017; Park et al., 2016; Vauth et al., 2021). One study showed that akathisia scores contributed to poor general health on the six-dimensional health state short form (SF-6D) (Siani et al., 2016). Another study did not find a significant relationship between catatonia and social functioning (Bonnot et al., 2008).

3.5.3. *Other outcome measures in patients with schizophrenia*

One study tested the association between orofacial dyskinesia and cognitive functioning over time in 41 patients with chronic schizophrenia over a period of 10 years (Waddington and Youssef, 1996). They showed that patients with persistent orofacial dyskinesia have poorer cognitive function than patients without orofacial dyskinesia and that patients who develop orofacial dyskinesia over time show a deterioration of cognitive functioning. Another study analysing the relationship between MAs, including dyskinesia, parkinsonism, and akathisia and poor clinical and functional outcome in 640 patients with schizophrenia also found that these MAs were related to higher rates of hospitalization (Chen et al., 2013).

4. Discussion

We systematically reviewed the prognostic value of MAs on clinical and functional outcome across the psychosis spectrum, including CHR individuals and patients with FEP and chronic schizophrenia. Our main finding was that in general, increased levels of MAs, in particular NSS, parkinsonism, and dyskinesia, were related to deteriorating symptomatic and poor functional outcome over time across the prodromal, early and chronic stages of psychosis. The amount and consistency of evidence differed per MA and study population (Fig. 2). Taken together, the current systematic review indicates that: (1) most evidence was found for NSS, where results indicate a predictive value of NSS for poor clinical and functional outcome. These findings were most consistent in in the CHR and FEP group. (2) Dyskinesia was addressed in all three study populations and related to poorer clinical and functional outcomes at follow-up, especially in the CHR and chronic schizophrenia group. (3) Parkinsonism was assessed in FEP and chronic schizophrenia populations, and in both groups predicted poor clinical and functional

outcome. (4) The evidence supporting the prognostic value of akathisia and dystonia in patients with schizophrenia was weak and inconclusive, as the majority of studies did not evaluate dystonia or akathisia separately but related combined ratings of MAs (dyskinesia, parkinsonism, akathisia and dystonia) to clinical and functional outcomes at follow-up. (5) There was limited evidence on the prognostic role of catatonia on psychosis trajectories. The included studies suggest that catatonia, when measured at the antipsychotic-naïve state, could be of predictive value for clinical and functional outcome over time. (6) Most studies that failed to detect a prognostic value of MAs on outcome measures at follow-up still found cross-sectional correlations between MAs and global and negative symptom severity. (7) Only very few studies found an opposite relationship indicating that MA were related to better treatment outcomes, although these findings were not replicated in comparable studies.

The findings of this systematic review relating MAs to poor prognosis in all stages of the psychosis spectrum, stresses the clinical value of MAs in psychotic disorders. MAs are prognostic markers that may predict the development and course of schizophrenia. Given the enormous burden of illness of schizophrenia, a clinically relevant marker is of great importance. The clinical value is further strengthened by the fact that MAs are early-detectable and objective signs that can be easily measured at low cost. Their predictive value can be used for detection, staging and prediction of the illness. With so much consistent evidence for the role of MAs in the prognosis of psychotic disorders it can be considered to add MAs as a criterion in classification systems such as DSM, as suggested previously (Van Harten and Tenback, 2009). This would contribute to the development of early detection and intervention strategies, predictive models for the course of illness and treatment response, and it may improve precision medicine. The importance of MAs as potential biomarkers in psychosis is supported by earlier findings showing that MAs are (i) elevated in psychosis populations compared to healthy controls, (ii) already present before illness onset, (iii) cross-sectionally related to psychopathological symptoms and to structural and functional brain alterations (Bachmann et al., 2014; Bombin et al., 2005; Chan et al., 2010; Hirjak et al., 2018a,b; Koning et al., 2010; Neelam et al., 2011; Pappa and Dazzan, 2009). As motor abnormalities often persist despite of effective antipsychotic treatment, they should be viewed as intrinsic to psychosis. Hereafter, we discuss our findings on the different MAs in light of previous research and provide background on the assumed underlying pathophysiological mechanisms.

4.1. Findings on NSS

NSS predicted poor clinical or functional outcome in CHR and first- or multiple episode schizophrenia populations, which is in line with previous systematic reviews relating NSS to psychopathology (Bachmann et al., 2014; Bombin et al., 2005; Hirjak et al., 2018a,b). Hirjak et al. (2018a,b) demonstrated that individuals with schizotypal personality traits and CHR individuals and unaffected first-degree relatives of schizophrenia patients exhibited higher levels of spontaneous MAs, including NSS, than healthy controls, and thereby related spontaneous MAs to psychosis risk. The systematic review of Bombin et al. (Bombin et al., 2005) demonstrated higher levels of NSS in patients with schizophrenia than in healthy controls and in patients with other psychiatric disorders and related NSS to greater symptom severity and cognitive dysfunction. Bachmann et al. (2014) specifically focused on the course of NSS in patients with schizophrenia and therefore only included longitudinal studies. Their findings indicate that NSS in schizophrenia comprise both state- and trait-features, as NSS scores decreased with remission of psychopathological symptoms (state-related) and that even after remission of the acute illness, NSS scores remained significantly higher than in healthy controls (trait-related). Although our primary outcome was not the course of MAs or comparison of levels of NSS between different populations, the current systematic review found similar results. We found longitudinal associations between NSS and symptom course, cross-sectional correlations between NSS and symptom severity, and higher levels of NSS in patient populations compared to healthy controls. However, some studies related a decrease in NSS to symptomatic improvement over time, while others found that NSS were relatively stable, not varying with the severity of illness. For establishing the prognostic value of NSS, it is essential to have a deeper understanding of these trait- and state-features of NSS. Future studies should therefore repeatedly measure NSS, before, after and during antipsychotic treatment, especially in patients during acute episodes of psychosis.

4.2. Findings on dyskinesia

Our finding that spontaneous dyskinesia was related to psychopathology in psychosis corroborates previous systematic reviews indicating spontaneous dyskinesia to be more prevalent in antipsychotic-naïve patients with first-episode psychosis and psychosis risk populations compared to healthy controls (Hirjak et al., 2018a,b; Koning et al., 2010; Pappa and Dazzan, 2009). The current systematic review extends this prior knowledge by including longitudinal studies that relate dyskinesia to the course of illness in psychosis populations with and without previous exposure to antipsychotics. Our results indicate that the presence of dyskinesia is of prognostic value in antipsychotic-naïve populations and that the presence or development of dyskinesia was predictive for more severe psychopathology in patients with chronic schizophrenia exposed to long-term antipsychotic treatment.

4.3. Findings on parkinsonism

The current systematic review suggests a prognostic value of parkinsonism for greater symptom severity, social dysfunction and cognitive deficits. In a previous systematic review, parkinsonism has mainly been associated with negative symptoms, which can be explained by either overlapping definitions among constructs or shared pathological mechanisms (Pappa and Dazzan, 2009). Assessments for parkinsonism and negative symptoms could partially measure the same construct, as there are phenomenological similarities between parkinsonian symptoms (akinesia, psychomotor slowing) and negative symptoms (affective flattening, alogia, apathy) (Peralta and Cuesta, 1999). Alternatively, parkinsonism in patients with schizophrenia may reflect shared etiological pathways, involving dopaminergic pathways (Cuesta et al., 2014). Findings from the current review support this second notion that parkinsonism and negative symptoms might reflect shared pathophysiological mechanisms, as we found a predictive value of parkinsonism for global and negative symptom severity and cognitive deficits, and not merely cross-sectional correlations between parkinsonism scores and negative symptoms.

4.4. Findings on catatonia

Our findings suggest that catatonia, when measured at the antipsychotic-naïve state, could be predictive for treatment response, symptom severity and functional outcome over time, although the number of relevant studies are limited. Catatonia is described as a psychomotor syndrome composed of hyper- and hypokinetic motor signs and behavioral and affective symptoms (Rasmussen et al., 2016; Rogers et al., 2019; Walther et al., 2019a,b). Based on the phenomenology of catatonia, this syndrome indicates a link between motor and non-motor symptoms by itself. An association between catatonic signs and the development of psychotic symptoms would therefore be expected and needs to be examined in future studies.

4.5. Findings on dystonia and akathisia

There was limited evidence that supported the prognostic value of

akathisia and dystonia. Most studies that included dystonia and/or akathisia combined these ratings together with other MAs (dyskinesia and parkinsonism) and related them to poor clinical outcome. Only a few studies evaluated the prognostic value of dystonia and akathisia separately and the results were inconsistent. In addition, the systematic review of Pappa and Dazzan (2009) reported a limited number of studies describing variable and low prevalence rates of akathisia (0–8 %) and dystonia (0–2.4 %) in patients at the antipsychotic-naïve state. Especially the estimates of the akathisia prevalence rates need to be interpreted with caution, as these are often not measured on the preferred Barnes Akathisia Rating Scale (Barnes, 1989), but on other general extrapyramidal symptom rating scales. This may lead to misinterpretation of (psychosis-induced) motor agitation as akathisia.

4.6. Motor abnormalities and neural mechanisms

The findings from this review suggest that there is a genuine relationship between MAs and the pathobiology of psychosis. These findings have been supported by structural and functional MRI studies that suggested a common vulnerability for MAs and schizophrenia. Currently there is no pathophysiological model integrating the relationship between all MAs and psychotic disorders, but several pathophysiological mechanisms have been proposed. For the occurrence of NSS and spontaneous dyskinesia in CHR individuals, dysfunctions in cerebello-thalamo-cortical, fronto-parietal, and cortico-subcortical networks have been demonstrated (Bernard and Mittal, 2014; Mittal et al., 2010, 2014). These networks are important for sensorimotor functioning and mature from infancy to adulthood. Abnormal neurodevelopment in these networks could therefore lead to age-related differences in the sensorimotor system (Kipping et al., 2017). The findings linking early deficits in motor development with adult schizophrenia, support the neurodevelopmental hypothesis of psychosis (Murray et al., 2017). Likewise in catatonia, neuroimaging studies suggested the involvement of cerebello-thalamo-cortical motor networks, explaining the link between catatonia motor symptoms and psychopathology (Hirjak et al., 2019; Sambataro et al., 2021; Viher et al., 2020; Walther et al., 2016, 2017, 2019a,b).

Finally, multiple neurotransmitter systems have been proposed to be involved in the development of MAs and psychosis. The well-known dopamine hypothesis for schizophrenia provides a possible explanation for the common occurrence of psychotic signs and MAs, in particular parkinsonism and dyskinesia. This hypothesis, revised by Howes and Kapur, postulates that presynaptic striatal hyperdopaminergic activity might mediate psychotic symptoms and hypodopaminergic activity in striatal or subcortical areas (Howes and Kapur, 2009). This hyperdopaminergic activity in the ascending striatal pathways may lead to hyperkinetic movements, as the hypodopaminergic activity in striatal or subcortical areas may result in cognitive dysfunction and hypokinetic parkinsonian signs (Cuesta et al., 2014; Mittal et al., 2007a,b). As the striatal circuitry matures during adolescence some individuals may show MA as the first signs of aberrant functioning in the cortico–striato–pallido–thalamic circuit, moderated by dopaminergic function, that may later give rise to psychotic symptoms (Mittal et al., 2007a,b). However, there are multiple other potential etiologies to motor abnormalities in psychoses including neuroinflammation or dysfunctions of GABAergic, glutamatergic, and serotonergic neurotransmission (Hagemeyer et al., 2012; Hirjak et al., 2019; Janova et al., 2017; Martino et al., 2020; Northoff et al., 2021). Some of the suggested pathways may explain single signs, such as psychomotor slowing or posturing/freezing. However, most of the suggested etiologies still require replication both in humans and animal models, as well as further neuroimaging studies in patients.

4.7. Motor abnormalities and antipsychotics

The results suggest that MAs are predictive for poor clinical and functional outcome, irrespective of antipsychotic treatment status, as this relationship is demonstrated in antipsychotic-naïve CHR and FEP populations as well as (long-term) medicated patients with schizophrenia. This is in line with the notion that MAs can be considered as intrinsic to the disease process that can be modulated by antipsychotics, where antipsychotics may both improve or unmask MAs (Peralta et al., 2013; Van Harten et al., 2015). However, the evidence for the prognostic value of akathisia and dystonia in this review was weak and inconclusive. These MAs may be more specifically drug-induced, as they are directly related to the dopamine D2 affinity of antipsychotic agents (Loonen and Ivanova, 2021; Musco et al., 2020). Therefore, akathisia and dystonia may be considered as treatment-induced phenomena rather than “genuine” MAs that are directly linked to the pathophysiology of psychosis. For dyskinesia, we found a predictive value on clinical outcome in both antipsychotic-naïve subjects and long-term medicated patients with schizophrenia, although the underlying mechanism may differ in both groups. The link between dyskinesia and psychopathology becomes more complex in patients with chronic schizophrenia, as antipsychotics, ageing and neurodegeneration contribute to the emergence of dyskinesia (Pappa and Dazzan, 2009). In this population, the association between dyskinesia and psychotic symptom severity could be explained by the dopamine supersensitivity psychosis hypothesis (Yin et al., 2017). This concept proposes increased sensitivity of dopamine receptors in the mesolimbic dopamine system producing psychotic symptoms, that might extend to the nigrostriatal dopamine system associated with tardive dyskinesia. This theory, supported by experimental animal models and neuroimaging studies, may explain the development of tolerance to antipsychotics, the presence of tardive dyskinesia and “rebound psychosis”, i.e., the acute relapse of psychosis during or after treatment discontinuation (Yin et al., 2017). Thus, the presence of dyskinesia in patients with schizophrenia and individuals at risk for schizophrenia constitutes a complex and heterogeneous phenomenon, where some abnormal involuntary movements seem to be intrinsic to the pathogenesis of the psychotic illness and can be moderated or induced by the use of antipsychotics.

Very little is known on the specific treatment effects of antipsychotics on MA. Therefore, we cannot promote motor abnormalities as treatment markers currently. In fact, the concurrence of genuine or spontaneous motor abnormalities with drug induced motor abnormalities has made research in this area extremely difficult. For example, reports on the incidence of motor abnormalities in the large CATIE trial neglected the prevalence of pre-existing motor abnormalities or effects of illness chronicity, reporting no specific effect on motor abnormalities of the antipsychotics tested (Miller et al., 2008). The only comprehensive trial to date noted that antipsychotic drug treatment had variable effects on pre-existing motor abnormalities in drug-naïve first episode psychosis (Peralta and Cuesta, 2010). The current perspective on schizophrenia treatment includes two concurrent strategies: optimizing the antipsychotic treatment to reduce drug induced motor abnormalities and specific add-on interventions targeting motor abnormalities, such as repetitive transcranial magnetic stimulation (Lefebvre et al., 2020; Walther et al., 2020a, 2019a).

4.8. Strengths and limitations

While previous systematic reviews have focused on cross-sectional studies relating spontaneous MAs to psychosis risk and symptomatology in early psychosis and CHR populations, this systematic review extends the current knowledge by providing an overview of longitudinal studies that evaluated the prognostic role of MAs on functional and clinical outcomes across the whole psychosis spectrum. By including all domains of MAs, including NSS, hypokinetic and hyperkinetic movements, and catatonic phenomena in subjects from the prodromal, early and chronic phase of psychosis, we aimed at providing a comprehensive state-of-the-art review on the existing evidence on the prognostic value of MAs in psychosis. However, some limitations should be noted. First of

all, the included studies highly differed in their methodology, assessment methods for MAs and clinical outcome measures, therefore a quantitative synthesis of evidence in the form of a meta-analysis could not be performed. Secondly, many of the reviewed studies were affected by some methodological limitations: small sample size, a short duration of follow-up or a relatively high, and possibly selective, loss-to-follow-up, and/or no reporting of training or experience of raters or inter-rater reliability for the measurement of MAs. On the other hand, almost all studies used validated scales for the assessment of MAs and the majority of studies (73.5 %) measured MAs longitudinally. Despite the aforementioned limitations, the amount and consistency of evidence strongly indicates a prognostic value of MAs for poor clinical and functional outcome.

4.9. Future directions

Further research may reveal the clinical value of MAs in clinical practice of psychotic disorders and could unravel the role of MAs in the psychopathological process and in the development and course of the psychotic illness. Based on the methodological shortcomings of the reviewed studies we suggest that future studies: (i) Have a longer duration of follow-up in large samples. Such studies would evaluate the relationship between the course of MAs and other psychotic symptoms and the prognostic value of MAs on long-term clinical and functional outcome. Short-term clinical trials are less suitable for this purpose, as other variables, such as treatment effects, antipsychotic adherence and acute antipsychotic-induced extrapyramidal symptoms, may be important in predicting short-term outcome and information on long-term outcome is missing. (ii) Assess all domains of MAs, including NSS, hyper- and hypokinetic movements and catatonic phenomena. This accounts especially for the CHR population, for which only studies were found assessing NSS and dyskinesia. Furthermore, more evidence on the clinical value of catatonia in psychosis is needed, as the literature on catatonia was scarce in our review. (iii) Repeatedly measure MAs in different phases of the psychotic process, preferably before and after the start of antipsychotic treatment. Studies performed in antipsychotic-naïve subjects could provide the most valuable information about the relation between genuine MAs and psychopathology. (iv) Measure MAs on validated clinical rating scales, used by experienced and trained raters. Recent developments of electronic assessment of MAs, such as instrumental tasks like force stability and velocity scaling, balance assessments and computerized handwriting technology, could contribute to more precise, less rater-biased information about MAs (Mittal, 2016; Van Harten et al., 2017). Furthermore, wearable sensors and smartphone applications offer the possibility for the collection of real-life, ecologically valid (semi-)continuous data on motor patterns and psychopathology. Previous studies have found that with actigraphy and ecological momentary assessment the severity of motor patterns could be related to the severity of positive and/or negative symptoms (Kluge et al., 2018; Pieters et al., 2021; Walther et al., 2014). (v) Include structural and functional neuroimaging techniques, preferably longitudinally, to gain deeper knowledge regarding the pathobiology of motor abnormalities in psychosis.

5. Conclusion

To date, the recognition of MAs as an intrinsic factor of the psychosis continuum has been well-established (Walther et al., 2020a,b). This review extends the current knowledge in the field by establishing the prognostic value of MAs for the development and course of psychosis. These findings highlight the clinical and scientific relevance of recognition and assessment of MAs in subjects with, or at risk for, psychosis. In the future, a deeper understanding of the relationship between MAs and psychopathology could contribute to better detection, early intervention and treatment strategies, to improve the outcome of this debilitating illness.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.11.027.

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