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The association between alterations in motor and cognitive dimensions of schizophrenia-spectrum disorders: A systematic review

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ABSTRACT

Motor and cognitive alterations in schizophrenia-spectrum disorders (SSD) share common neural underpinnings, highlighting the necessity for a thorough exploration of the connections between these areas. This relationship is crucial, as it holds potential significance in unraveling the underlying mechanisms of SSD pathophysiology, ultimately leading to advancements in clinical staging and treatment strategies. The purpose of this review was to characterize the relationship between different hyper and hypokinetic domains of motor alterations and cognition in SSD.

We systematically searched the literature (PROSPERO protocol CRD42019145964) and selected 66 original scientific contributions for review, published between 1987 and 2022. A narrative synthesis of the results was conducted.

Hyper and hypokinetic motor alterations showed weak to moderate negative correlations with cognitive function across different SSD stages, including before antipsychotic treatment. The literature to date shows a diverse set of methodologies and composite cognitive scores hampering a strong conclusion about which specific cognitive domains were more linked to each group of motor alterations. However, executive functions seemed the domain more consistently associated with parkinsonism with the results regarding dyskinesia being less clear. Akathisia and catatonia were scarcely discussed in the reviewed literature.

The present review reinforces the intimate relationship between specific motor alterations and cognition. Identified gaps in the literature challenge the formulation of definitive conclusions. Nevertheless, a discussion of putative underlying mechanisms is included, prompting guidance for future research endeavors.

1. Introduction

Schizophrenia-spectrum disorders (SSD) encompass a vast array of alterations that span different dimensions – most notably psychotic symptoms, but also cognitive and motor alterations (Kirkpatrick et al., 2014). Cognitive alterations have been extensively described in SSD, affecting a wide range of cognitive functions and being related to the extent of recovery after the disorder's onset (Halverson et al., 2019). The National Institute of Mental Health (NIMH) established the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus which identified cognitive subdimensions affected in SSD that appeared as segregated from each other and these

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included: working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing, and social cognition (Green et al., 2004).

Though motor alterations were recognized more than a hundred years before contemporary psychiatry, they were mostly absent from SSD literature until recently (Walther et al., 2020; Whitty et al., 2009). Evidence has shown these alterations are part of the neurodevelopment disorder in SSD and not only side effects of D2-receptor-blocking agents (Koning et al., 2010; Pappa and Dazzan, 2009). Furthermore, specific hyper and hypokinetic motor alterations (formerly referred to as Extrapyramidal Symptoms or EPS) such as tardive dyskinesia (TD) and parkinsonism also seem to have prognostic value for clinical outcome in psychosis (van Harten et al., 2014) while others, such as dystonia, akathisia, and catatonia, have less clear significance (Pieters et al., 2022). Another construct encompassing motor alterations is the group of 'neurological soft signs' (Bachmann et al., 2014). These have also been shown to be associated with worse prognosis (Pieters et al., 2022). However, they are not commonly assessed in clinical practice and incorporate phenomena beyond motor function such as sensory integration and primitive reflexes.

Waddington and Youssef (1986) were among the first to note an association between TD and cognitive impairment in a chronic patient population. This was hypothesized to be caused by some structural neural vulnerability predisposing to both alterations. The understanding of such common factor could potentially unveil the underlying mechanisms implicated in worse outcomes in psychotic disorders. Indeed, more recently, research has shown that brain structures related to motor and cognitive processing, especially the basal ganglia, are anatomically and functionally closely related (Leisman and Shafir, 2016; Obeso et al., 2014). However, the heterogeneity of methodologies to study motor and cognitive alterations, together with changes in prescribing practices of antipsychotic agents over the years, renders a complex picture from which to draw conclusions. Yet, identifying the specific motor and cognitive subdimensions within SSD, as well as understanding their interplay, can be beneficial for two main reasons. Firstly, it can facilitate the development of more clinically informed research, shedding light on the neurobiological mechanisms underlying SSD. Secondly, it can aid in the improvement of diagnosis, staging, and treatment interventions for individuals with SSD.

The primary objectives of this review in patients with SSD are: (i) To examine the associations between motor alterations (hyperkinetic, hypokinetic, and catatonic symptoms) and cognitive alterations; (ii) To identify which motor and cognitive subdimensions alterations are related and to determine the strength of those associations.

We hypothesize that significant associations with cognitive function will be present for all motor alterations subdimensions. These associations should be stronger in relation to executive functions for their role in goal-directed behavior.

2. Material and methods

2.1. Search strategy, study eligibility and selection procedure

Our protocol, based on the PRISMA guidelines (Moher et al., 2009), including its detailed search strategy, is described below and can be retrieved from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019145964. Searches were conducted through MEDLINE, Embase, and PsycINFO online databases and complemented through independent hand searching of reference lists of included full text articles. The searches focused on titles, abstracts, and keywords. Three sets of terms were used in combination, separated by the Boolean term AND, referring to: 1) clinical population (psychosis OR psychotic OR schizophreni* OR schizoaffective OR delusional); 2) cognition (cogniti* OR neurocogniti* OR memory OR attention OR "executive functions" OR "processing speed" OR IQ OR "intelligence quotient" OR reasoning OR learning); and 3) motor alterations (motor OR movement OR EPS OR extrapyramidal OR dyskine* OR akathisi* OR parkinsoni* OR dystonia OR catatonia OR catatoni* OR catalep*). The rationale for the chosen terms was, respectively, the following: 1) terms associated with schizophrenia-spectrum disorders; 2) terms reflecting the MATRICS consensus domains, and general intelligence; and 3) terms covering extrapyramidal and catatonic symptoms. Even though the term 'extrapyramidal symptoms', or EPS, has fallen into disuse, we will employ it as the reviewed articles might still make abundant use of it. The searches were limited to peer reviewed articles, research based on humans, papers written in English and publication date from 1980 (date of DSM-III publication, hence granting higher diagnostic reliability) to December 2022. The results were stored in EndNote. Two researchers, blinded to each other's decisions (B.M. and L.M.), performed the article selection based on the following inclusion criteria: 1) original clinical studies, hence not including reviews; 2) cognition and motor variables assessed by trained professionals, or through computerized tests in the case of cognition; 3) reporting of measures of association between motor and cognitive variables (both measures of strength and significance of association) or any test statistic and level of significance resulting from group comparisons where motor and cognitive variables are used - one to define groups and the other as the variable being compared. Duplicated papers were identified and removed. A final selection of papers was made based on discussion of divergences between the two researchers (B.M. and L.M.) with support from the other co-authors.

2.2. Data extraction

Variables extracted from the final selection of papers included: author names, title, publication year, study type, setting, recruitment dates, diagnostic categories included, number of participants, demographic variables, cognitive subdimensions assessed and specific tools used, motor subdimensions assessed and specific tools used, and statistical analysis (including level of significance).

2.3. Quality assessment

Each paper underwent a quality assessment following the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Institutes of Health, 2014) and obtained score was then transformed into a percentage.

2.4. Registration of review protocol and subsequent changes

The review protocol was registered in advance with the International Prospective Register of Systematic Reviews (PROSPERO), protocol CRD42019145964.

After group discussion, three changes were adopted during the implementation of the protocol and added to PROSPERO. First, articles that solely relied on instrumental measures (e.g., finger-tapping) were also excluded as the association of these methodologies with EPS is not straightforward and also because our search was not designed to cover them. Secondly, quality assessment was changed from Cochrane risk of bias tool to the NIH tool mentioned above as it seemed better fitted for the purpose. Thirdly, Paulsen et al. (1994) extensive review of literature allowed us to use their results instead of reviewing each of the previous papers.

3. Results

We selected 66 articles for narrative synthesis (see Fig. 1 for selection flow diagram). The selected articles are summarized in Tables 1–4, according to motor subdimensions and subgroups of interest (studies in the context of first episode psychosis and spontaneous movement alterations, i.e. non-medicated individuals).

The quality assessment of the included studies revealed modest scores on average, with half of cross-sectional studies scoring

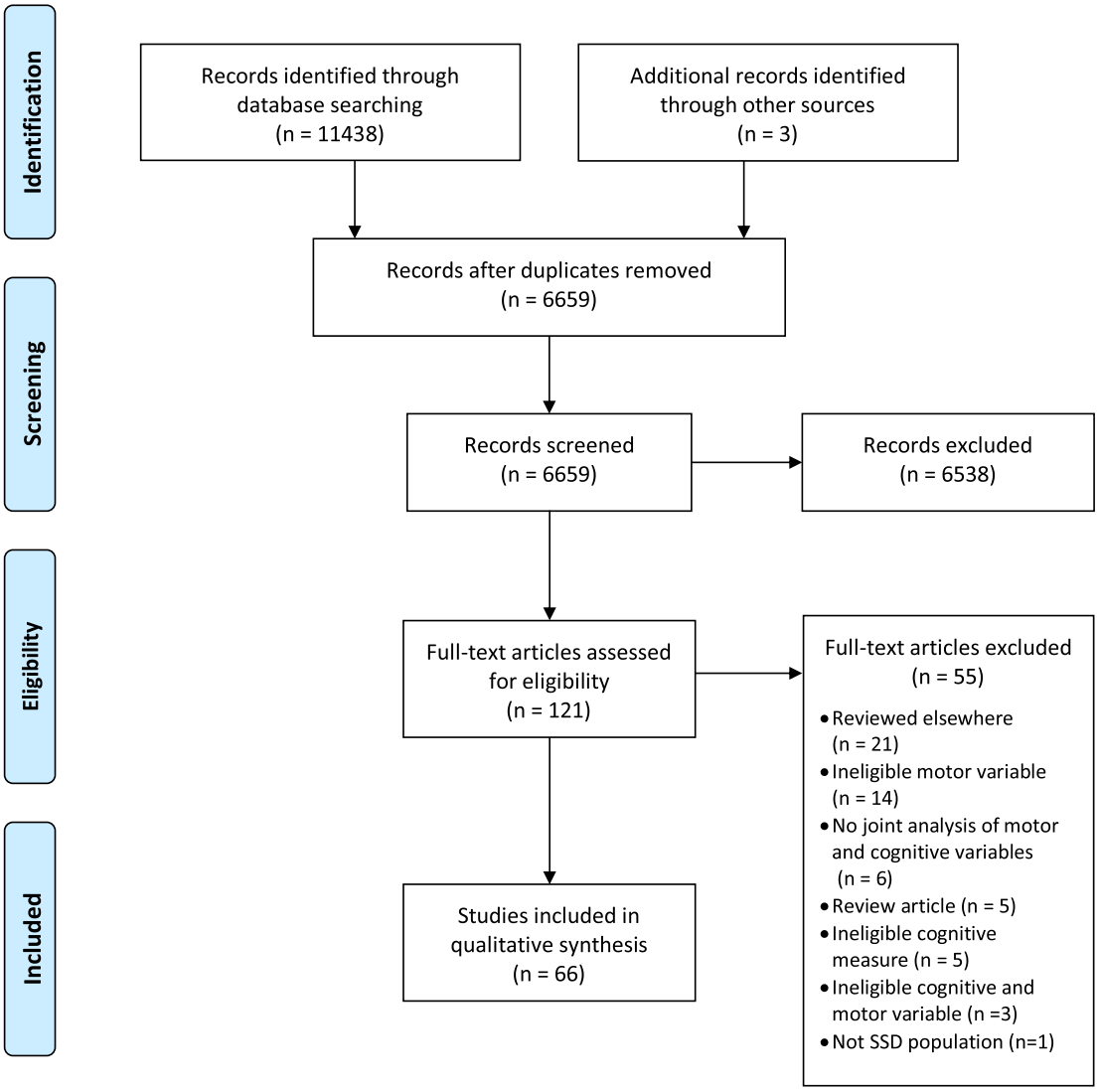

Fig. 1. Article selection flow diagram, adapted from PRISMA.

approximately 5–6 out of 10. The remaining studies were evenly split below and above this range. The main limitations identified were the lack of appropriate control for confounders and absence of blinding for the assessors. Among the selected studies, only seven were considered to have a longitudinal design, and they achieved a slightly better score of 63 % on a 14-point scale. The main limitation for these studies was a loss to follow-up rate exceeding 20 % (see Supplementary Table 1). Sample sizes ranged from 10 to 1310 participants, with an average of 169 (TD and mixed motor alterations studies had the higher average sample sizes – 194 and 197, respectively; parkinsonism and FEP/drug-naïve studies had the lowest average sample sizes – 108 and 75, respectively). Main findings are summarized in Fig. 2.

3.1. Tardive dyskinesia

The review article by Paulsen et al. (1994), which included 21 of the originally selected studies, supported a correlation between TD and cognition. We found 30 subsequent articles focusing on TD that confirmed the same trend (see Table 1), including five studies conducted on a geriatric population (Berry et al., 2007; Byne et al., 1998; Karson et al., 1990; Karson et al., 1993; Quinn et al., 2001).

The instrument used to assess TD was, in most cases, the AIMS, with TD defined according to the Schooler & Kane criteria (Schooler and Kane, 1982). The studies were more heterogeneous regarding how TD was categorized – whether as a continuous or categorical variable – leading to different statistical approaches. The two studies with higher sample sizes were derived from the same clinical trial sample and applied an analysis of covariance (considering TD dichotomously).

The included neuropsychological subdimensions varied across studies. Nevertheless, most research tried to grasp cognitive function in general with the use of tests or batteries covering the main cognitive subdimensions, often relying on the Mini-Mental State Examination (MMSE). A smaller group of studies focused on executive functions and found associations with TD, namely attention, task switching and set-shifting abilities (Spohn and Coyne, 1993; Waddington et al., 1995; Waddington et al., 1993). The larger sample-size studies also indicated a stronger relationship between TD and executive functions (attention and immediate memory) than other neurocognitive domains (Hui et al., 2017; Liang et al., 2022). Another study that specifically assessed executive functions in elderly patients showed this subdimension to be a strong predictor of TD, further adding a topographic nuance to the finding as the result was not applicable to limb-truncal TD (Quinn et al., 2001). Overall, only three studies did not find any association between neuropsychological variables and TD (Barnes et al., 1995; Miller et al., 2005; Pourcher et al., 1993).

Two studies using a longitudinal design were retrieved. A 10-year

Table 1
Studies concerning tardive dyskinesia as the motor alteration of interest.

Study	Study design and setting	Sample	Motor assessment	Cognitive assessment	Analytic approach	Summary of results	Quality check
(Adelufosi and Fadipe, 2012)	Cross-sectional observational, single-center	$N = 20$; institutionalized patients; Dx: scz; Age: not reported	AIMS	MMSE	Between group comparison of means	Patients with TD had lower MMSE score (19.33 vs 23.73).	0.4
(Baribeau et al., 1993)	Cross-sectional observational, single-center	$N = 26$; institutionalized patients; Dx: chronic scz (DSM-III); Age: 31.3	AIMS	Luria-Nebraska Neuropsychological battery (L-N)	Pearson correlation	9/12 items from L-N correlated significantly with the AIMS score ($p < 0.05$), controlling for medication.[a]	0.5
(Barnes et al., 1995)	Cross-sectional observational, single-center	$N = 48$; inpatients; Dx: scz (DSM-III); Age:51	Barnes and Trauer	WAIS-R; Schonell reading test; NART	Between group comparison of means	Patients with and without TD did not differ in terms of current IQ or decline in IQ.	0.4
(Berry et al., 2007)	Cross-sectional observational, multicenter	$N = 50$; outpatients; Dx: psychotic disorders (F20-F29; ICD-10); Age:73.4	AIMS (OTD only)	MMSE, NART, frontal lobe function battery	Between group comparison of means	Patients with OTD had higher premorbid IQ ($p = 0.022$), lower MMSE ($p = 0.012$) and lower verbal fluency in all categories ($p < 0.04$).	0.4
(Brown and White, 1992)	Cross-sectional observational, single-center	$N = 70$; institutionalized inpatients; Dx: scz (DSM-III); Age: 57.9	AIMS	MMSE	stepwise logistic regression	AIMS factor 2 (upper and lower limbs, and truncal movements) showed a trend towards cognitive impairment ($\beta = -0.21$; $p = 0.09$).	0.6
(Byne et al., 1998)	Cross-sectional observational, single-center	$N = 121$; inpatients; Dx: scz (DSM-III-R); Age:74.5	Modified Simpson Dyskinesia Scale	MMSE	Between group comparison of means and MANOVA	OTD (no other topographies) was associated with lower MMSE score ($p < 0.002$), controlling for age.	0.8
(Caroff et al., 2011)	Longitudinal retrospective, multicenter	$N = 1062$; clinical trial, outpatients and inpatients; Dx: scz (DSM-IV); Age: 47.2 (TD group); reanalysis of Miller et al., 2005 data	AIMS	Verbal and working memory, processing speed, vigilance, reasoning (undisclosed tests)	ANCOVA	Cognition composite score was worse in TD patients ($p < 0.001$); TD patients had less improvement in cognition (composite score) over 6 months ($p = 0.011$).	0.64
(Cooper et al., 1993)	Cross-sectional observational, single-center	$N = 185$; institutionalized patients; Dx: scz (DSM-III); Age: not reported	AIMS	Global cognition (Wither and Hinton test)	Regression	No relationship between TD and general cognitive function; in a subgroup of patients, TD severity showed an association with the WCST.[a]	0.3
(Davis et al., 1992)	Cross-sectional observational, single-center	$N = 40$; institutionalized inpatients; Dx: chronic scz (DSM-III); Age: 47.0	AIMS	MMSE	Between group comparison of means and correlation	TD group had worse MMSE score; significant association between severity of OTD and MMSE total score ($r = 0.52$, $p < 0.001$; whole sample).	0.5
(Eberhard et al., 2006)	Longitudinal observational prospective, multicenter	$N = 166$; inpatients and outpatients; Dx: scz spectrum + bipolar; Age: 37.7	AIMS	Automatic Psychological Test	ANOVA	Only BL analysis: TD was associated with worse speed indices in the 3 main cognitive factors (simple tasks, complex tasks, attention and simple decisions) but not in other non-speed indices (e.g. accuracy), except for selective attention.	0.3
(Hui et al., 2017)	Cross-sectional, observational, multicenter	$N = 742$, inpatients ("Han Chinese"); Dx: scz (DSM-IV) >5y illness duration; age: age: 48.0 ± 9.6	AIMS	RBANS (5 age-adjusted index scores and a total score)	ANCOVA	Patients with TD had significant lower attention and immediate memory scores	0.6
(Karson et al., 1990)	Cross-sectional observational, single-center	$N = 49$; institutionalized inpatients; Dx: scz (majority, DSM-III-R) and other chronic psych. dis.; Age:69 ± 6	AIMS	The Neurobehavioral Cognitive Status Examination	Mann-Whitney *U* test; Spearman corr.	TD group had worse memory impairment, calculating ability and reasoning ($p < 0.05$). Within the TD group, no correlation between severity of TD and cognition. No difference	0.4

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Table 1 (*continued*)

Study	Study design and setting	Sample	Motor assessment	Cognitive assessment	Analytic approach	Summary of results	Quality check
						between OTD vs. limb-truncal TD.	
(Karson et al., 1993)	Cross-sectional observational, multicenter	$N = 107$; institutionalized inpatients and outpatients; Dx: scz (majority, DSM-III-R) and other chronic psych. dis. Age:69 ± 6	AIMS	The Neurobehavioral Cognitive Status Examination	*t*-test; correlation	TD group had worse cognition, except memory. OTD severity correlated negatively with every cognitive function except attention (r: −0.30 to −0.36). The severity of limb-truncal dyskinesia did not correlate with any area of cognition.	0.3
(Krabbendam et al., 2000)	Cross-sectional observational, single-center	$N = 53$; inpatients; Dx: scz (DSM-III); Age: 49.2 ± 8.6	AIMS	Picture learning test, Letter digit Substitution Test, Stroop test	Logistic regression	Delayed recall was associated with the occurrence and severity of OTD (but not limb-truncal); OR:1.55 (95 % CI = 1.05–2.27).	0.7
(Liang et al., 2022)	Cross-sectional, observational, multicenter	$N = 655$, inpatients ("Han Chinese"), Dx: scz (DSM-IV), >5y illness duration; age: 48.0 (likely sample overlap with Hui et al., 2017)	AIMS	RBANS (5 age-adjusted index scores and a total score)	t-test and multiple regression analysis	Significant differences between male TD patients and non-TD patients on the RBANS total score, immediate memory and attention subscales (all $p < 0.05$), multiple regression: attention subscore predictor of AIMS total score (β:-0.12, $p < 0.01$)	0.7
(McCreadie et al., 1997)	Cross-sectional observational, multicenter	$N = 44$; outpatients and institutionalized inpatients (including drug-naïve); Dx: scz (DSM-IV); Age: 62	AIMS	WMS	t-test	Drug-naïve group: no differences in cognition between TD+ and TD-; medicated group: TD+ had lower scores on personal and current information subscale ($p = 0.05$).	0.6
(Miller et al., 2005)	Cross-sectional observational, multicenter	$N = 1310$; clinical trial, outpatients and inpatients; Dx: scz (DSM-IV); Age:43.1	AIMS	DSST, CPT, grooved pegboard, visuospatial working memory, Hopkins Verbal learning test, WCST, category fluency, letter-number span	ANCOVA	Differences in cognition for TD groups were not significant after adjustment for covariates (age, years since first treated with an antipsychotic, use of typical vs atypical antipsychotic, current use of anticholinergic agent).	0.6
(Moore et al., 2004)	Cross-sectional observational, single-center	$N = 161$; outpatients; Dx: scz (DSM-III and IV); Age:56.0 ± 8.7	AIMS	MMSE	Spearman correlation	Significant correlation between MMSE and AIMS ($r = -0.18$, $p = 0.04$).	0.4
(Pantelis et al., 2001)	Cross-sectional observational, single-center	$N = 54$; inpatients; Dx: scz (DSM-III); Age:46.7	tardive dyskinesia rating scale	MMSE, WAIS-R, NART, CANTAB	ANOVA, correlation	Only significant difference was found between higher difficulty spatial working memory tasks between patients with OTD and the others ($p = 0.03$). In the path analysis, OTD was also associated with spatial working memory (span and strategy factors, r: 0.34 and 0.53, respectively).	0.7
(Paulsen et al., 1994)	Cross-sectional observational, single-center	$N = 56$; outpatients; Dx: scz (DSM-III-R); Age: 58.0	AIMS	MMSE, Expanded Halstead-Reitan Neuropsychological Test Battery	ANOVA, correlation	AIMS score correlated negatively with global cognition ($r = -0.42$, $p < 0.001$). Moderate to severe TD patients had worse scores on global cognition and learning. Patients with limb-truncal TD had worse global cognition and attention scores than OTD (but rated higher overall TD score).	0.6

(*continued on next page*)

Table 1 (*continued*)

Study	Study design and setting	Sample	Motor assessment	Cognitive assessment	Analytic approach	Summary of results	Quality check
(Pourcher et al., 1993)	Cross-sectional observational, single-center	*N* = 64; outpatients; Dx: scz, bipolar and others (DSM-III-R); Age: 28.9 ± 4.7	Extrapyramidal Symptoms Rating Scale	DS, CPT, go/no-go test, TMT-B	Stepwise multiple logistic regression	Cognitive impairment was not a predictor of TD.	0.5
(Quinn et al., 2001)	Cross-sectional observational, multicenter	*N* = 128; inpatients; Dx: scz (DSM-IV); Age: 70.0 ± 11.0	AIMS	MMSE; Executive Interview (EXIT)	Multiple logistic or linear regression model	Executive function was a predictor of AIMS score ($r = 0.14$), except for limb-truncal TD patients (where only MMSE score was a predictor; $r = 0.13$). Antipsychotic dosage showed a negative association with TD, but not for all TD criteria.	0.8
(Soni et al., 1993)	Cross-sectional observational, multicenter	N = 40; outpatients; Dx: scz (Research Diagnostic Criteria); Age: 50.7 ± 8.4	AIMS	Bexley Maudsley Automated Psychological screening	t-test; Multiple stepwise regression	Visual spatial memory was worse on TD+, all other cognitive subdimensions did not differ between groups. However, regression analysis did not confirm cognition as predictor of TD.	0.7
(Spohn and Coyne, 1993)	Cross-sectional observational, undisclosed setting	*N* = 84; inpatients; Dx: scz (Research Diagnostic Criteria); Age: 32.8	AIMS	Reaction-time (RT) crossover effect	Hierarchical multiple regression analysis	OTD explained in part RT crossover effect, independently of age and general deficit function ($R^2 = 0.1$; $F = 3.94$).	0.5
(Waddington et al., 1990)	Longitudinal observational, single-center	N = 74; Dx: scz, (Feighner criteria); inpatients (residents); Age: 57.2 ± 13.7	AIMS	Abbreviated custom 10 question test	Linear and logistic regression	Change in cognitive function was the strongest predictor of emergence of TD at FU ($\beta = -0.75$, log. regr.) and of increasing AIMS score ($\beta = -0.59$, lin. regr.); change in current dosage of neuroleptics was the only predictor of limb-truncal TD (not cognition).	0.64
(Waddington et al., 1993)	Cross-sectional observational, single-center	N = 64; Dx: scz (DSM-III); outpatients; Age: 37.7 ± 12.3	AIMS	TMT-A and B	Linear and logistic regression	TMT-B was the strongest predictor of having OTD ($\beta = 0.023$; log. regr.); TMT-A and TMT-B were the only predictors of AIMS score (β: 0.1 and 0.025, respectively; lin. regr.).	0.6
(Waddington et al., 1995)	Cross-sectional observational, single-center	N:47; Dx: scz (DSM-III); outpatients; Age: 35.3 ± 12.3	AIMS	NART, Block design, similarities test, word and face recognition test, unusual views test, WCST, TMT-A and B	Between group comparison of means and correlation	TD+ group had WCST impairment - more perseverative errors and fewer categories ($p = 0.04$); negative correlation between no. of categories and AIMS score ($r = -0.3$; $p < 0.05$).	0.5
(Waddington and Youssef, 1996)	Longitudinal observational, single-center	*N* = 41, residents, Dx: scz (Feighner criteria); age: 54.1 ± 12.5	AIMS	abbreviated custom 10 question test	Comparison of means	On a 5y. follow-up, patients w/ de novo OTD showed cognitive deterioration (contrary to patients w/ TD or without TD at BL; $p = 0.04$).	0.43
(Wade et al., 1993)	Cross-sectional observational, single-center	N = 54; inpatients; Dx: scz Taylor & Adams criteria; "manics" (Feighner criteria); Age:44.9 ± 12.3	AIMS	WAIS, WMS	Multiple regression	TD showed moderate and significant prediction of overall cognitive performance. TD accounted for 8 % of the variance in the cognitive test score of non-timed tasks ($p = 0.03$).	0.6
(Wu et al., 2013)	Cross-sectional observational, single-center	*N* = 206; inpatients; Dx: scz (DSM-IV); Age: 55.2	AIMS	RBANS	Stepwise multivariate regression	AIMS OTD score contributed independently to RBANS total score ($\beta = -0.147$, $p = 0.031$) and attention index of RBANS; AIMS limb and truncal score was detected as an	0.7

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Table 1 (*continued*)

Study	Study design and setting	Sample	Motor assessment	Cognitive assessment	Analytic approach	Summary of results	Quality check
						independent determinant of visuospatial/ constructional index (β = −0.150, $p = 0.04$).	

[a] Correlation/regression coefficient not reported; AIMS – Abnormal Involuntary Movement Scale; BL – baseline; CANTAB – Cambridge Neuropsychological Test Automated Battery; CPT – Continuous Performance Test; DS – Digit Span; DSST – Digit-symbol substitution test; FEP – First Episode Psychosis; IQ – Intelligence Quotient; MMSE – Mini Mental State Examination; NART – National Adult Reading Test; OTD – Orofacial Tardive Dyskinesia; RBANS - Repeatable Battery for the Assessment of Neuropsychological State; scz – schizophrenia; TD – Tardive Dyskinesia; TMT – Trail Making Test; WAIS – Weschler Adult Intelligence Scale; WCST – Wisconsin Card Sorting Test; WMS – Weschler Memory Scale.

Table 2
Studies concerning parkinsonism as the motor alteration of interest.

Study	Study design and setting	Sample	Motor assessment	Cognitive Assessment	Analytic approach	Summary of results	Quality check
(Byne et al., 2000)	Cross-sectional observational, single-center	$N = 79$; institutionalized patients; Dx: scz (DSM-III-R); Age: 74.4	UPDRS	MMSE, CERAD cognitive battery	Pearson's correlation	Bradykinesia was negatively correlated with MMSE, naming and fluency tasks (r: −0.23, −0.25, −0.27, respectively; $p < 0.05$). Cognition was not correlated to tremor, rigidity nor parkinsonism total score.	0.8
(Fervaha et al., 2015)	Cross-sectional observational, multicenter	$N = 325$; post-hoc analysis of RCT; Dx: scz (DSM-IV), patients not receiving antipsychotics or anticholinergics at least in the previous 2 weeks; Age: 41.1	Abbreviated SAS	DSST, grooved pegboard, letter-number sequencing task, visuospatial working memory, Hopkins Verbal learning test, CPT, mazes from Weschler Intelligence Scale for children and WCST	Spearman correlations and multiple regression	Patients with parkinsonism had worse composite cognition score, verbal learning, processing speed and working memory (r: −0.14 to −0.20). But when controlling for motor speed these differences disappeared.	0.7
(Kim et al., 2008)	Cross-sectional observational, single-center	$N = 58$; oupatients; Dx: scz; Age:33.7	SAS	FCQ	MANCOVA	Parkinsonism group scored higher on total FCQ score, and subscales: deterioration of discrimination, psychomotor disorder, and perceptual disorder ($p < 0.005$)	0.44
(Kim and Byun, 2009)	Cross-sectional observational, single-center	N = 58; oupatients; Dx: scz; Age:33.7	SAS	FCQ	Partial correlations	SAS score correlated w/ FCQ's total score and subscores: deterioration of discrimination, psychomotor disorder, perceptual disorder, cognitive floating, automatic behavior disorder (r: 0.23 to 0.32).	0.56
(Krausz et al., 1999)	Cross-sectional observational, single-center	N = 53; inpatients; Dx: scz (DSM-III); Age: 49.2 ± 8.6	SAS	FCQ	Between group comparison of means	Significant difference between high vs. low parkinsonism groups in simple perception, complex perception, thought, motility, lack of automatization, sensory overstimulation and total score ($p < 0.05$).	0.22
(Molina et al., 2018)	Cross-sectional observational, single-center	$N = 22$; Dx: scz (DSM-5); Age:33.9 ± 8.1	SAS	BACS	Spearman correlation	Parkinsonism scores in the patients (but not in controls) were inversely associated to scores in verbal memory, working memory, and performance speed (r: −0.51 to −0.62; $p < 0.05$), but not in motor speed, semantic fluency, or problem solving.	0.6
(Palmer et al., 1999)	Cross-sectional observational, single-center	$N = 96$; outpatients; Dx: scz; Age:58.3	SAS	Halstead-Reitan Battery, CVLT	Stepwise multiple regression	Significant association between parkinsonism severity and learning controlling for the effects of processing speed, AIMS and motor component of cog battery ($r = −0.264$, $p = 0.013$).	0.6

AIMS – Abnormal Involuntary Movement Scale; BACS – Brief Assessment of Cognition in Schizophrenia; CERAD – Consortium to Establish a Registry for Alzheimer's Disease; CPT – Continuous Performance Test; CVLT – California Verbal Learning Test; DSST – Digit-symbol substitution test; FCQ - Frankfurt Complaint Questionnaire; MMSE – Mini Mental State Examination; SAS – Simpson-Angus Scale; scz – schizophrenia; UPDRS – Unified Parkinson's Disease Rating Scale; WCST – Wisconsin Card Sorting Test.

Table 3
Studies concerning akathisia, catatonia or a mixed set of motor symptoms.

Study	Study design and setting	Sample	Motor sub-dimensions	Motor assessment	Cognitive Assessment	Analytic approach	Summary of results	Quality check
(Ahmed, 2013)	Cross-sectional observational; undisclosed setting	$N = 662$; outpatients and inpatients; Dx: scz, schizoaffective, psychotic disorder NOS, mood disorder with psychotic features; Age:?	TD, Parkinsonism and akathisia	Maryland Psychiatric Research Center's Involuntary Movement Scale (MIMS)	Repeatable Battery for the Assessment of Neuropsychological State (RBANS); WAIS-III; Wide-range Achievement Test (WRAT-3)	Canonical correlational analysis	Significant correlation between neurocognition and TD items (rcl = 0.360; Wilk's gamma = 0.643, Chi-square (65); $p < 0.05$); No correlation between neurocognition and parkinsonism. Akathisia not reported.	0.5
(Bark et al., 2005)	Cross-sectional observational, multicenter	$N = 28$; inpatients; Dx: scz (catatonic and paranoid); Age: 36.75	Catatonia	Multiple catatonia rating scales (BFCRS; Northoff Rating Scale)	Iowa Gambling Task, Object Alternation Task, Working memory task, Go-NoGo task and the WCST	ANOVA	Decision-making and behavioral set-shifting deficits in catatonic scz ($p < 0.001$).	0.6
(Chen et al., 2001)	Cross-sectional observational, multicenter	$N = 204$; inpatients; Dx: scz (DSM III-R); Age: 40.5	Neurological soft signs, particularizing EPS, dyskinesia and catatonia subgroups	Cambridge Neurological Inventory	Sustained attention (beep counting)	Partial correlation	Sustained attention had no significant correlation with any of the 3 subgroups of interest (EPS, dyskinesia and catatonia).	0.4
(Docx et al., 2012)	Cross-sectional observational, multicenter	$N = 124$, outpatients and inpatients; Dx: scz & schizoaffective (DSM-IV); age:32.0 ± 8.0	Catatonia and parkinsonism	BFCRS; St Hans rating scale	DSST, CPT, Stroop and Letter Number Sequencing	Correlation analysis	No significant correlation between any cognitive test and catatonia or parkinsonism (dystonia and dyskinesia were not considered because they were very rare).	0.6
(Fritze et al., 2022)	Cross-sectional observational, single-center	N = 131; inpatients; Dx: scz (DSM-IV-TR); age: 38.3 ± 11.7	parkinsonism, TD, akathisia, catatonia	SAS, AIMS, BARS, NCRS	executive functioning, processing speed (TMT-B and DSST)	Cluster analysis, ANCOVA and multiple linear regression	3 clusters according to 'sensorimotor scores'. Worse TMT-B scores in both hyper and hypokinetic clusters. DSST predicted sensorimotor score in the mixed cluster	0.6
(Hoffman et al., 1987)	Cross-sectional observational, multicenter	$N = 21$; inpatients and outpatients; Dx: schizophrenia (DSM-III); age:62.0 ± 6.1	TD and parkinsonism	AIMS; St Hans Rating Scale	Battery divided into 4 factors: verbal, memory, initiation/ cognitive flexibility and visuospatial ability.	Hierarchical multivariate regression analyses	Total parkinsonism accounted for 32 % of the variance in the visuo-spatial factor ($p = 0.008$).	0.5
(Hwang et al., 2012)	Longitudinal observational, single-center	N = 54; outpatients; Dx: scz (DSM-IV); Age:34.2 ± 10.4	EPS	DIEPSS	WAIS, CANTAB subtests (choice reaction time, set-shifting and response inhibition, spatial short-term memory), WCST, Stop-signal task	Partial correlations	On baseline, IQ correlated with bradykinesia, tremor, akathisia and EPS global score (r: −0.27 to −0.35); baseline response inhibition and processing speed measures correlated with FU EPS (r: −0.29 to −0.72).	0.64
(Kim et al., 2002)	Cross-sectional observational, single-center	N = 41; inpatients; Dx: scz (DSM-IV)	Akathisia	BARS	Weschler Memory Scale	ANCOVA and logistic regression	Akathisia group had lower mental control score ($p = 0.02$); on the regression analysis, mental control was associated with global akathisia score ($r = -0.61$, wald score = 9.28, $p = 0.002$).	0.6

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Table 3 (*continued*)

Study	Study design and setting	Sample	Motor sub-dimensions	Motor assessment	Cognitive Assessment	Analytic approach	Summary of results	Quality check
(Kim and Byun, 2007)	Cross-sectional observational	$N = 67$; outpatients; Dx: scz (DSM-IV)	Akathisia	BARS	Frankfurt Complaint Questionnaire (FCQ)	ANCOVA	Akathisia group scored significantly higher on total FCQ score ($p = 0.027$) and subtest scores responses (anxiety, disorder of selective attention, deterioration of discrimination, perceptual disorder and coping).	0.56
(Monteleone et al., 2021)	Cross-sectional, observational, multicenter	$N = 875$, Dx: scz (DSM-IV); Age: 40.6	EPS	SHRS	MATRICS, social cognition (FEIT and TASIT)	Stepwise multiple regression, network analysis	Patients with EPS had worse neurocognitive and SC score. However, for SC, network analysis revealed this association might be mediated by neurocognition and/or psychopathology	0.7
(Moura et al., 2021)	Cross-sectional, observational, multicenter	$N = 1007$; Dx: SSD (DSM-IV); age: 27.3 ± 7.4	Parkinsonism, TD, akathisia	UPDRS, AIMS, BARS	IQ (abbreviated WAIS), executive functions, verbal memory, social cognition	Partial correlation network analysis with centrality analysis (gaussian graphical model)	Parkinsonism was directly associated with processing speed (DSST); weaker association between TD and facial recognition. Multiple other associations between motor symptoms and cognition were mediated by psychopathology	0.6
(Potvin et al., 2015)	Cross-sectional observational, multicenter	$N = 82$; outpatients; Dx: scz spectrum dis (DSM-IV); Age: 41.7 ± 10.0	EPS	Extrapyramidal Symptoms Rating Scale	CANTAB, Stroop Color-Word Test	Multiple hierarchical linear regression analysis	Parkinsonism (but not other EPS) accounted for spatial working memory ($t = 3.1$; $p = 0.003$) and stroop color-word score ($t = -2.0$; $p = 0.045$).	0.8
(Sachdev et al., 1996)	Cross-sectional observational, multicenter	N = 100; outpatients; Dx: scz (DSM-III-R); Age: 40.7 ± 9.1	TD and tardive akathisia	AIMS, Akathisia Rating Scale	Symbol-digit modalities test, TMT-A and B	Correlations and stepwise logistic regression	Tardive akathisia was related to Symbol digit modalities test ($r = -0.34$) and TMT-A and B (r: 0.19 and 0.25 respectively).	0.7
(Sambataro et al., 2020)	Longitudinal observational, single-center	$N = 43$; Dx: scz (DSM-IV); Age: 37.6 ± 10.4	Parkinsonism, dyskinesia, akathisia, catatonia	SAS, AIMS, BARS, NCRS	B-CATS (TMT-B, category fluency, DSST)	Multiple regression; cross-sectional and longitudinal analysis	Cognition was predicted by parkinsonism on the cross-sectional analysis (F = 2.35) but not longitudinally.	0.71
(Schäppi et al., 2018)	Cross-sectional observational, single-center	N = 41, outpatients and inpatients, Dx: scz (DSM-5); age: 38.0 ± 11.4	parkinsonism and dyskinesia	AIMS, UPDRS	FAB, DS-backwards	Correlation analysis	UPDRS was sign. Associated with FAB ($r = 0.52$; $p < 0.01$). AIMS was not associated with cognitive functions in patients, but it was in ctrls (w/ FAB).	0.5
(Silver and Shlomo, 2001)	Cross-sectional observational, single-center	$N = 36$, inpatients, Dx: chronic scz (DSM-IV), Age: 40.6 ± 10.7	TD and parkinsonism	AIMS, SAS	Facial Emotion Identification Test; Discrimination of Facial Emotions Test	Correlation analysis	No significant correlation between AIMS or SAS scores and facial emotions perception tests	0.5

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Table 3 (*continued*)

Study	Study design and setting	Sample	Motor sub-dimensions	Motor assessment	Cognitive Assessment	Analytic approach	Summary of results	Quality check
(Sullivan et al., 1994)	Cross-sectional observational, single-center	$N = 34$, Dx:scz (DSM-III-R), Age: 36.9 ± 7.8	dyskinesia and parkinsonism	Gerlach dyskinesia scale	WCST, verbal self-ordered pointing test, letter search task, Brown-Peterson distraction tests, letter fluency, Weschler memory scale	Correlation analysis	No association between total dyskinesia or total parkinsonism with any of the cognitive composites.	0.6
(Tanaka et al., 2012)	Cross-sectional observational, single-center	$N = 61$, Dx: scz (DSM-IV); Age: 40.1 ± 12.2	EPS	DIEPSS	BACS	Correlation analysis	EPS were sig. correlated with attention/speed of processing ($r = -0.45$, $p < 0.01$) and also the cognition composite score (overall score), ($r = -0.41$, $p < 0.05$).	0.6
(Zhornitsky et al., 2011)	Cross-sectional observational, multicenter	$N = 81$, Dx: scz-spectrum (DSM-IV)	EPS (objective and subjective)	Extrapyramidal Symptoms Rating Scale	Subjective Scale to Investigate Cognition in Schizophrenia; CANTAB tasks (motor screening, paired associates learning, spatial working memory)	Linear regression	Weak association between subjective cognition and subjective EPS ($\beta = 0.716$; $p = 0.06$).	0.6

AIMS – Abnormal Involuntary Movement Scale; B-CATS – Brief Cognitive Assessment Tool for Schizophrenia; BARS – Barnes Akathisia rating Scale; BFCRS – Bush-Francis Catatonia Rating Scale; CANTAB – Cambridge Neuropsychological Test Automated Battery; CPT – Continuous Performance Test; DIEPSS – Drug Induced Extrapyramidal Symptoms Scale; DS – Digit Span; DSST – Digit-symbol substitution test; EPS – Extrapyramidal symptoms; FAB – Frontal Assessment Battery; FEIT – Facial Emotion Identification TEST; NCRS – Northoff catatonia Rating Scale; SAS – Simpson-Angus Scale; scz – schizophrenia; TASIT – Awareness of Social Inference Test; TD – tardive dyskinesia; TMT – Trail Making Test; UPDRS – Unified Parkinson's Disease Rating Scale; WAIS – Weschler Adult Intelligence Scale; WCST – Wisconsin Card Sorting Test.

cohort study (Waddington and Youssef, 1996) found that cognitive impairment and TD seemed to develop together within the same time interval and not predict each other (at least within a 5 and 10-year window). Another study, with a 6-month follow-up found that TD was associated with less improvement in cognition over time (Caroff et al., 2011).

3.2. Parkinsonism

While some studies focused specifically on parkinsonism (see Table 2), this motor subdimension was often assessed together with other movement disorders (see Table 3; first episode psychosis and spontaneous movement-disorders studies are addressed separately). Six studies reported no significant association between parkinsonism and any of the cognitive subdimensions assessed (Ahmed, 2013; Byne et al., 2000; Chen et al., 2001; Docx et al., 2012; Silver and Shlomo, 2001; Sullivan et al., 1994). Studies with positive findings reported correlations between parkinsonism and different cognitive outcomes which varied according to the study's methodology (i.e. general cognition score, verbal learning, visuo-spatial abilities, spatial working memory and frontal lobe functions). The only longitudinal study in chronic SSD (Hwang et al., 2012) showed that parkinsonian symptoms were cross-sectionally associated to IQ and were predicted on a 6-month follow-up by a baseline response inhibition task ($r = 0.72$, $p < 0.001$).

3.3. Akathisia, catatonia and mixed motor alterations studies

Only 4 studies reported clinician rated scores of akathisia in relation to cognitive performance. The study with the largest sample did not report any association between akathisia and cognition (Ahmed, 2013). Hwang et al. (2012) found a cross-sectional link between akathisia and IQ but no associations between baseline cognition and follow-up akathisia. The study by Sachdev et al. (1996) identified an association between akathisia and a symbol-substitution task. Kim et al. (2002) found that individuals with akathisia (or higher akathisia scores) had worse mental control (a very sensitive measure of attentional dysfunction).

We only selected three studies that addressed catatonia in chronic medicated patients (Bark et al., 2005; Chen et al., 2001; Docx et al., 2012). The only significant association was found in the study by Bark et al. (2005) which examined set-shifting ability differences between a group with 8 patients diagnosed with catatonic schizophrenia and a group of patients with paranoid schizophrenia.

Kim et al. conducted a series of studies analyzing objective EPS in relation to subjective cognitive dysfunction. In three separate articles they showed that akathisia and parkinsonism are related to the overall score and specific sub-dimensions of a subjective cognitive-perceptual dysfunction scale. Zhornitsky et al. (2011) also showed an association between subjective cognitive capacities and subjective motor alterations.

A group of studies, predominantly more recent, investigated different motor subdimensions together, sometimes employing a single combined scale for the assessment of extrapyramidal symptoms such as the EPS rating scale or the Drug-induced EPS scale (DIEPSS). These studies on mixed motor alterations more frequently reported a lack of association between motor and cognitive variables (Chen et al., 2001; Silver and Shlomo, 2001; Sullivan et al., 1994).

3.4. First episode psychosis and spontaneous movement alterations studies

Seven articles presented studies on the first episode psychosis (FEP) population, dealing with a range of different movement disturbances. Cuesta et al. (2014) and Pareek et al. (2010) investigated spontaneous parkinsonism in FEP in relation to a mixed group of cognitive sub-dimensions in the former and executive functions in the latter. Cuesta et al., using a longitudinal design, found a predictive value of baseline spontaneous parkinsonism over cognitive dysfunction on a 6-month follow up, but found no cross-sectional differences at baseline between patients with and without spontaneous parkinsonism. A notable 21-year

Table 4
Studies concerning first episode psychosis or drug-naïve samples (spontaneous movement disorder).

Study	Study design and setting	Sample	Motor subdimensions	Motor assessment	Cognitive Assessment	Analytic approach	Summary of results	Quality check
(Colomer et al., 2017)	Longitudinal observational, single-center	N = 21; inpatients; Dx: First episode scz and non-affective psychoses; Age: 26.8; drug-naïve	Catatonia	BFCRS	MCCB	Spearman correlation	Negative correlation between BFCRS baseline score and working memory and visual learning ($r = -0.44$ and -0.50, respectively; $p < 0.05$).	0.57
(Compton et al., 2015)	Cross-sectional observational, multicenter	*N* = 47; inpatients; Dx: first episode of non-affective psychosis; Age: 24.3	Dyskinesia and catatonia	Dyskinesia Identification System Condensed User Scale (DISCUS); Catatonia Rating scale	Symbol coding in Brief Assessment of Cognition in Schizophrenia; mazes from the Neuropsychological Assessment Battery; Hopkins Verbal Learning Test-revised; Brief Visuospatial Memory test-revised; WMS; WAIS letter number sequencing	Correlations	No significant correlation was found between abnormal movements and neurocognition.	0.6
(Cuesta et al., 2014)	Longitudinal observational prospective, undisclosed setting	*N* = 77; inpatiens and outpatients; Dx: first episode of non-affective psychosis (drug-naïve); Age: 30.1	Spontaneous parkinsonism (SP)	SAS	Test of Non-verbal Intelligence-2, computerized reaction time, vigilance and span of apprehension tasks, executive verbal fluency (animals), WCST, TMT-B, WMS	Linear mixed models	No neurocognition differences on baseline between patients w/ or without SP; parkinsonism showed a significant longitudinal association with memory, executive functioning and attention impairments (1 and 6 months; β: −0.04 to −0-59); baseline SP had a 6-month predictive value for cognitive impairment.	0.79
(Cuesta et al., 2018)	Cross-sectional observational, single-center	N = 50; inpatients; Dx: first episode of non-affective psychosis; Age: 25.5	Extrapyramidal symptoms and catatonia	SAS; BARS; BFCRS	MCCB (based)	Regression model	Parkinsonism (SAS total score) was significantly associated with visual memory (β =0.66, $p = 0.006$); akathisia was significantly associated with visual memory (β =0.11, $p = 0.03$) and speed of processing (β = −0.34, $p = 0.02$).	0.6
(Fenton et al., 1994)	Retrospective, single-center	N = 100; inpatients; Dx: scz (DSM-III); Age: 28	Spontaneous (oral) dyskinesia	No formal instrument - retrieved from clinical records	WBIS or WAIS	Between group comparison of means	Patients with orofacial dyskinesia had lower IQ ($p < 0.002$)	0.3
(Kindler et al., 2019)	Cross-sectional observational, single-center	N = 10; outpatients; Dx: FEP; age:17.7 ± 1.7	Dyskinesia	AIMS	Premorbid IQ (Peabody Picture Vocabulary Test)	Spearman rank correlation	No significant correlation between premorbid IQ and dyskinesia in the FEP group. Significance reached for the whole sample (CHR and controls included).	0.7
(Lindgren et al., 2022)	longitudinal observational, multicenter	*N* = 113, FEP (18 % affective psychosis), ICD-10	Parkinsonism (park.)	SAS	WAIS, WMS, TMT, verbal fluency test, theory of mind (hinting task)	Linear regression models	Non-affective psychosis BL park was associated with lower BL and 1y. follow-up verbal, visuomotor and composite scores). Follow-up park. only predicted follow-up visuomotor factor. No associations	0.64

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Table 4 (*continued*)

Study	Study design and setting	Sample	Motor subdimensions	Motor assessment	Cognitive Assessment	Analytic approach	Summary of results	Quality check
							between park. and social cognition	
(Molina et al., 2016)	Cross-sectional observational, multicenter	$N = 76$, outpatients (and 66 siblings); Dx: scz (DSM-IV); Age: 29	Spontaneous parkinsonism (SP)	UPDRS-3	Purdue pegboard test, Luria Manual sequences, Symbol Digit modalities test, Weschler words list II; Weschler spatial span; five-digit test, Raven progressive matrices, WCST, oral trails test	Linear regression	SP was a predictor of cognition (β =0.41; $p < 0.001$; sample included patients and siblings).	0.8
(Pareek et al., 2010)	Cross-sectional observational, single-center	$n = 178$, outpatients and inpatients; Dx: FEP, scz, schizoaffective and 'other psychoses'; Age: 24.8	Spontaneous dyskinesia	AIMS	WCST	Spearman correlation	AIMS total score was positively correlated with perseverative errors on the WCST ($r = 0.19$, $p = 0.04$).	0.5
(Peralta et al., 2024)	Longitudinal, observational, single-center	$N = 243$; antipsychotic naïve on baseline; Dx: psychotic disorder (DSM-5); Age (at follow-up): 48.5 ± 10.4	Parkinsonism (park.), dyskinesia, catatonia	SAS, AIMS, CASH	Screen for Cognitive Impairment in Psychiatry (SCIP)	hierarchical linear regression models	Motor alterations did not predict 21y. follow-up cognition; baseline premorbid IQ predicted follow-up motor alterations. Park. was strongly associated with cognition (cross-sectional at follow-up; $r = -0.57$)	0.79

AIMS – Abnormal Involuntary Movement Scale; BARS – Barnes Akathisia rating Scale; BFCRS – Bush-Francis Catatonia Rating Scale; BL – baseline; CHR- Clinical High Risk; FEP – First-episode Psychosis; MCCB – MATRICS Consensus Cognitive Battery; SAS – Simpson-Angus Scale; scz – schizophrenia; TMT – Trail Making Test; UPDRS – Unified Parkinson's Disease Rating Scale; WAIS – Weschler Adult Intelligence Scale; WBIS – Weschler Bellevue Intelligence Scale; WCST – Wisconsin Card Sorting Test; WMS – Weschler Memory Scale.

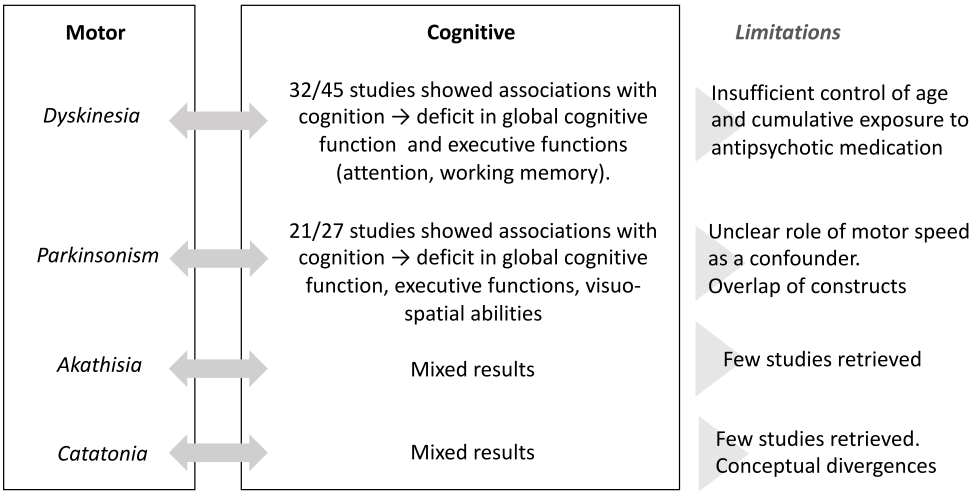

Fig. 2. Summary of main results.

follow-up study (Peralta et al., 2024) found no predictive value of spontaneous motor alterations over cognition, but conversely found premorbid IQ to predict follow-up motor alterations. With a medicated FEP sample, Lindgren et al. (2022) also found baseline parkinsonism to predict 1 year global, verbal and visuomotor cognition. Pareek et al., using a cross-sectional design, exclusively investigated executive functions through the Wisconsin Card Sorting Test and found a significant positive correlation between spontaneous parkinsonism and perseverative errors. Compton et al. (2015) and Kindler et al. (2019) investigated dyskinesia in FEP. Neither study found a significant association between dyskinesia and cognition (a neurocognitive battery was used in the former study and pre-morbid IQ assessment in the latter). As a side note, the study by Kindler et al. enrolled only 10 patients with FEP, but included 45 subjects with Clinical High Risk (CHR) for psychosis. In that subgroup, a trend was found for the negative association between dyskinesia and premorbid IQ. The studies by Colomer et al. (2017), Cuesta et al. (2018), and Compton et al. (2015) investigated the associations between catatonic symptoms and cognition in FEP patients. Only the study by Colomer et al. – with a drug-naïve sample – found catatonia to be negatively correlated with cognition (working memory and visual learning), with statistical significance. Cuesta et al., with a similar approach, were not able to find an association. Conversely, these authors found significant associations between EPS and cognition - parkinsonism with visual memory, and akathisia with visual memory

and speed of processing.

Two other studies investigated spontaneous movement disorders in patients with longer durations of psychotic disorders (Fenton et al., 1994; Molina et al., 2016). These studies investigated treatment naïve-patients and found worse general cognition in patients with spontaneous dyskinesia (orofacial) and parkinsonism, respectively.

4. Discussion

In this review, we analyzed 66 articles that investigated clinical assessments of hyper and hypokinetic motor alterations, including catatonia, in relation to neuropsychological variables within the context of SSD. Most of the reviewed studies reported significant associations between the included motor subdimensions and cognition. Most reported correlations fall within the weak or moderate range. Cognition is still frequently approached as a single entity, limiting the ability to conduct a more in-depth analysis of the specific cognitive subdimensions that correlate with motor alterations. The contribution of antipsychotics or other medications as a potential confounding factor to the reported correlations is still not completely addressed, but evidence from well controlled studies and medication-naïve samples indicates an effect that extends beyond confounding.

Overall, our findings support cognition and the array of motor alterations in SSD as fundamental components that span from phenomenological to neurobiological approaches to these disorders. This perspective aligns with the systems neuroscience theory of disconnectivity in corticobasal circuits in SSD, particularly in relation to the parallel loops connecting the basal ganglia, cerebral cortex, and cerebellum, which are implicated in affective, cognitive, and motor functions (Bernard et al., 2017; Obeso et al., 2014). This formulation might, however, be too imprecise to be informative for effective translation into clinical impact. In fact, the array of motor alterations encompasses a range of phenomena which, despite sharing certain neural substrates, are likely characterized by distinct interactions with cognitive function. We will delve into these nuanced interactions in the subsequent discussion.

4.1. Tardive dyskinesia

The association between TD and cognition gathered significant attention as a research topic in the 1980s and early 1990s. The review article published in 1994 by Paulsen et al. (1994) shed light on the methodological limitations of the previously published articles, including poorly defined samples, inadequate neuropsychological assessments, inadequate statistical testing, poor control for confounders, and excessive use of cross-sectional designs. The analysis of subsequent studies conducted in the present review revealed that although there has been an improvement in methodological quality over the years, there is still a lack of high-quality studies dedicated to addressing this question, and many of the limitations identified in the 1994 review still apply. Significant issues related to the samples used in the studies need to be addressed, which compromises the generalizability of the results to the SSD population. A considerable number of studies primarily relied on acute inpatients or even chronically institutionalized patients, potentially selecting a population with a worse prognosis. Furthermore, the choice of cognition subdimensions and the instruments used to assess them often involved simplistic assessments (e.g. MMSE), which might have limited the sensitivity to capture cognitive variability associated with TD.

Research into the pathophysiology of dyskinesia in SSD helps understanding its association with cognitive alterations. Emerging evidence underscores thalamo-cortical hyperconnectivity as a pivotal factor for this motor alteration, exhibiting a notable correlation with aggravated cognitive deficits, particularly pertaining to attention and processing speed (Chen et al., 2019; Walther et al., 2017). Structural neuroimaging investigations have revealed a noteworthy diminution in the volume of both the putamen and the cerebellum in association with tardive dyskinesia (Sakreida et al., 2022), both of which have long been regarded as quintessential motor-regulating structures, yet their involvement in cognitive functions is increasingly apparent.

We observed a trend in more recent studies, which consistently demonstrated negative results regarding the association between TD and cognition, particularly when other motor alterations were also assessed. Interestingly, these studies tended to report a higher frequency of associations between cognition and parkinsonism rather than dyskinesia. This shift could stem from earlier research that predominantly focused on TD in older patients, often treated with typical antipsychotics. Age and antipsychotic dosage are acknowledged confounders when examining motor-cognitive associations. The distinction between typical and atypical antipsychotics' effects on this link remains unclear. Yet, it is plausible that increased use of atypical antipsychotics, coupled with shorter treatment durations, reduced TD severity while maintaining observable parkinsonism in more recent samples. Additionally, potential publication bias may underlie studies concentrating solely on TD, favoring statistically significant results for publication.

4.2. Topographic distinctions

Considering the somatotopic organization of the basal ganglia (Nambu, 2011), it is important to explore the potential variations in the associations between TD and cognitive function based on the topography of the dyskinesia – orofacial TD (OTD) vs. limb-truncal TD. The finding that OTD is more associated with cognition may be biased due to the higher occurrence of OTD compared to limb-truncal TD in the reviewed literature. Notably, two high-quality studies from the reviewed pool indicate that both OTD and limb-truncal TD may be associated with cognitive alterations but through different subdimensions (Quinn et al., 2001; Wu et al., 2013). In the future, a more precise understanding of how the basal ganglia contribute to cognitive functions may help elucidate the distinct associations with altered movement in different body parts.

4.3. Parkinsonism

Most studies assessing parkinsonism have found a weak to moderate association with worse cognitive outcomes in different subdomains. Across studies, deficits in executive functions, learning, and visuospatial abilities were associated with higher parkinsonism levels. Interestingly, one large-sample negative study did not include the assessment of executive functions (Ahmed, 2013). Consistent with these findings, the literature on Parkinson's disease suggests a rationale for an association between parkinsonism and frontal lobe functions (Rodriguez-Oroz et al., 2009). Despite their scarcity, studies on parkinsonism within SSD also reveal the implication of structures with active roles in cognitive processes involved in goal-directed behavior. Molina et al. (2018) not only described an association between parkinsonism and a set of cognitive skills but also investigated how parkinsonism related to structural connectivity alterations. Their results pointed to prefrontal cortex-caudate dysconnectivity (higher fractional anisotropy) being related to parkinsonism score. This association held true even in patients with limited exposure to antipsychotic medication. A recent imaging study also pointed to an association between parkinsonism and volume reduction of the left caudate nucleus and the motor cortex in medicated patients with schizophrenia, a pattern that differed from dyskinesia, as noted above (Sakreida et al., 2022). Hence, at least in a subgroup of patients with SSD, alterations to the caudate nucleus development might give rise to both parkinsonian symptoms and difficulties in planning goal-directed behavior. It is important to note, however, that the association between executive functions and motor output such as parkinsonism (but potentially other motor categories) might in part be caused by an overlap of these constructs (motor planning). These new insights into the distinct associations of parkinsonism and dyskinesia with

specific brain structures in SSD might help understand their correlations with particular cognitive functions. However, studies designed to investigate this question further are still warranted.

The evidence from the few longitudinal studies retrieved, combining medicated and non-medicated samples, suggests that under antipsychotic medication, parkinsonism primarily correlates cross-sectionally with cognition. However, the same motor alteration in drug-naïve samples might hold prognostic value by predicting cognition upon follow-up (Cuesta et al., 2014). Nevertheless, conflicting evidence exists. Interestingly, in a 21-year follow-up, spontaneous parkinsonism did not predict cognition, but baseline IQ predicted follow-up parkinsonism (Peralta et al., 2024). This highlights the complexity of the correlations at hand, in close proximity with other mediating and moderating variables over time.

The role of motor speed bias in the association between cognition and parkinsonism does not appear to be consistently supported. Two separate studies that controlled for this factor yielded opposite results (Fervaha et al., 2015; Palmer et al., 1999). Moreover, since certain neurocognitive assessments rely on motor speed, further research is needed to evaluate potential effect modification and/or bias. This factor may also be relevant in regard to dyskinesia (Eberhard et al., 2006). Additionally, assessments of parkinsonism may be influenced by other clinical factors such as negative symptoms or other causes of psychomotor retardation. Properly controlling for these in the clinical setting can prove challenging as the constructs themselves are ill-defined (Walther and Strik, 2012). Consequently, the use of instrumental and objective assessments for motor outcomes could be particularly advantageous in this field (van Harten et al., 2017).

There was a lack of studies addressing social cognition. Parkinsonism seemed the motor alteration potentially with stronger negative correlations with that cognitive domain, but – as recent network analysis studies suggest – with the mediation of neurocognition (Monteleone et al., 2021; Moura et al., 2021; Silver and Shlomo, 2001). Despite the accumulating evidence regarding the interconnectedness of social cognition and motor function during human development (Kenny et al., 2016), this area remains understudied in the field of psychosis.

4.4. Akathisia

The mechanisms underlying this hyperkinetic syndrome are still poorly understood (Musco et al., 2020). Simultaneously, the subjective discomfort that is part of the presentation of akathisia makes it more challenging to interpret cognitive dysfunction in this context. The reviewed articles exhibited significant variations in cognitive assessments, which limited the comprehensive interpretation of results. However, discrepancies were evident (e.g. attentional deficits were found in one-third of the studies assessing attention). Overall, further clarification is needed on this topic.

4.5. Catatonia

According to Bark et al. (2005), the association between catatonic symptoms and impairment in set-shifting abilities could be attributed to dysfunction in the ventral prefrontal cortex. Consistent with this finding, a study assessing stereotypies (not included in this systematic review due to the device-assisted assessment) found a positive correlation between perseverative errors on the WCST and the severity of stereotypies (Morrens et al., 2006). Studies specifically designed to investigate this question are warranted as the cited evidence is based on exploratory research. Dean et al. (2020) conducted a study on patients with SSD and a previous history of catatonia. They included a broader range of cognitive assessments and hypothesized that cognitive functions relying more on motor performance, such as verbal fluency and processing speed, would be significantly more impaired in these patients compared to those without a history of catatonia, which was the case.

The different approaches mentioned above highlight the heterogeneity of conceptualizations of catatonia, with an impact in research questions (i.e. catatonia as a disorder of will vs. a motor disorder; Walther et al., 2019).

4.6. First episode psychosis and spontaneous movement alterations studies

Studies conducted during the early stages of psychosis show the presence of interrelated motor (parkinsonism, akathisia, catatonic symptoms) and cognitive symptoms (executive functions, memory, and attention), in medicated and non-medicated individuals. These symptoms may reflect early pathophysiological processes involving cortical-striatal circuits with aberrant dopaminergic transmission (Howes et al., 2009).

Overall, parkinsonism appears to be the motor syndrome most consistently associated with cognition in the early stages of psychotic disorders. However, the number of studies retrieved was very limited, with a modest total number of participants.

Spontaneous dyskinesia and parkinsonism in antipsychotic-naïve samples are variables of interest for further studies. Our findings suggest an association between motor and cognitive alterations in this subgroup of patients, which aligns with a previous review on spontaneous movement disorders in first episode psychoses (Pappa and Dazzan, 2009). Spontaneous motor alterations have mixed evidence of predicting cognition on follow-up studies. However, it is challenging to find unmedicated individuals with established SSD, so the field is gaining traction in the at-risk population (not reviewed in the present article). For example, Mittal et al. (2010) reported a correlation between dyskinetic movements and cognitive alterations (verbal comprehension, perceptual organization, and auditory memory), with these symptoms predicting at-risk individuals transitioning to psychotic disorders on follow-up. In the present review, our findings suggest that the relationship between hyper and hypokinetic motor changes and cognitive alterations is independent of medication use. Nonetheless, medication might influence this connection in certain vulnerable individuals later on. Exploring these factors in early psychosis could shed light on distinguishing primary pathological processes from medication-related effects, offering valuable insights for diagnosis and prognosis.

4.7. Subjective reports of cognitive and motor dysfunction

A weak relationship emerged between subjective motor (parkinsonism and akathisia) and cognitive alterations indicating that also in the context of insight motor and cognitive (specific) alterations might be correlated. Very few studies were however retrieved on this topic. Subjective motor alterations seemed strongly related to objective motor alterations. The opposite apparently happens between subjective and objective cognition (Medalia and Thysen, 2008). Of note, there have been recent developments in the study of subjective experiences of catatonia (Brandt et al., 2024), which could, perhaps in the future, also integrate subjective and objective appraisals of cognitive function.

4.8. Limitations

This study is limited by the lack of a meta-analytic approach. Given the considerable heterogeneity among the studies, the use of meta-analytic statistics would have been challenging to apply. Therefore, we opted for a narrative synthesis following a systematic search.

The exclusion of certain research fields also limits the scope of the present review. We did not include other types of motor symptoms and assessments (e.g., neurological soft signs, oculomotor studies) nor studies that focused on the ‘at-risk-mental state’ for psychosis. This choice was made to maintain a concise analysis. Additionally, the term ‘sensorimotor’ (whose relevance stems from the use within the RDoC initiative) was not a search term, which could have excluded articles of interest from this review.

An important limitation, intrinsic to the topics at hand, concerns the

construct overlap between different motor alterations. Thus, the precise delineation of motor alterations should be approached with caution, as these motor syndromes may not be entirely distinct from one another due to conceptual or neurobiological overlaps (Peralta et al., 2010). Another limitation from the included studies is the insufficient explanation regarding the persistence of motor alterations termed as 'tardive.' Although 'tardive' is commonly associated with dyskinesia, it is not consistently applied to describe other motor syndromes which may not always resolve following the discontinuation of the causative medication (Aquino and Lang, 2014). Moreover, in most samples the response of motor alterations to the reduction of antipsychotic medication was not assessed. This lack of information could obscure the differentiation between tardive and non-tardive motor alterations, particularly concerning their cognitive consequences.

5. Conclusions and recommendations for future studies

The reviewed studies point to significant connections between specific motor subdimensions and cognition in SSD, regardless of medication. Further in-depth research is necessary to elucidate detailed information on the specific cognitive and motor subdomains that are associated. Investigating these associations longitudinally would provide insight into their prognostic value and variations over the course of the disorder alongside with (dis)continuous medication use. Furthermore, we emphasize the following points as suggestions for enhancing future studies: (i) incorporating assessments that encompass clinician ratings, instrumental evaluations, and subjective accounts of motor alterations, this way contributing to more comprehensive and valid assessments of the motor domain; (ii) formulating hypotheses that guide the selection of cognitive assessments. Drawing from the current review, it seems important to include a comprehensive set of assessments evaluating executive functions, as well as processing speed and motor speed. Addressing the presented gaps in the literature and suggestions to overcome them could yield a more profound understanding of the interactions between specific motor and cognitive functions within SSD.

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CRediT authorship contribution statement

Bernardo Melo Moura: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Luís Madeira:** Formal analysis, Supervision, Writing – review & editing. **P. Roberto Bakker:** Conceptualization, Supervision, Writing – review & editing. **Peter van Harten:** Writing – review & editing. **Machteld Marcelis:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

None.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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