Comprehensive Psychiatry 115 (2022) 152307

Contents lists available at ScienceDirect

Comprehensive Psychiatry

journal homepage: www.elsevier.com/locate/comppsych

Motor abnormalities are associated with poor social and functional outcomes in schizophrenia

Niluja Nadesalingam *, Victoria Chapellier, Stephanie Lefebvre, Anastasia Pavlidou, Katharina Stegmayer, Danai Alexaki, Daniel Baumann Gama, Lydia Maderthaner, Sofie von Känel, Florian Wüthrich, Sebastian Walther

Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern, Switzerland

ARTICLE INFO

Keywords:
Schizophrenia
Psychosis
Motor abnormalities
Functional capacity
Functional outcomes
Global functioning

ABSTRACT

Background: Up to 50% of patients with schizophrenia are suffering from motor abnormalities, which may contribute to decreased quality of life, impaired work capacity, and a reduced life expectancy by 10–20 years. However, the effect of motor abnormalities on social and global functioning, as well as, functional capacity is not clear. We hypothesized, that the presence of motor abnormalities is associated with poorer functional outcomes in patients with schizophrenia.

Methods: We collected data on 5 different motor abnormalities in 156 patients suffering from schizophrenia spectrum disorders: parkinsonism, catatonia, dyskinesia, neurological soft signs and psychomotor slowing (PS). Additionally, we used three different scales to evaluate the functional outcomes in these patients: the Global Assessment of Functioning (GAF) and the Social and Occupational Functioning Assessment Scale (SOFAS) which use clinicians' judgment; and one using a performance-based measure of functional capacity, the brief version of the UCSD Performance-based Skills Assessment (UPSA-B).

Results: Our analysis demonstrated that patients with catatonia (all $F > 4.5$; $p < 0.035$) and parkinsonism (all $F > 4.9$; $p < 0.027$) scored lower on GAF and SOFAS compared to patients without catatonia and parkinsonism. In contrast, no significant difference on functional outcomes between patients with dyskinesia versus without dyskinesia exist in our study. Furthermore, there are statistically significant negative correlations for parkinsonism and PS with GAF, SOFAS and UPSA-B (all tau are at least −0.152, p-value <0.036). We also found significant negative correlations between catatonia and both GAF & SOFAS (all tau are at least −0.203, p-value<0.001) and between NES and SOFAS (tau = −0.137, p-value = 0.033).

Conclusion: Here, we showed that four of the most common motor abnormalities observed in schizophrenia were associated with at least one of the patients' functional outcomes. The stronger the motor impairment was the worse the global and social functioning. Future studies need to test, whether amelioration of motor abnormalities is linked to improved community functioning.

1. Introduction

Common features of schizophrenia are positive symptoms, such as hallucinations and delusions, negative symptoms, such as avolition and affective flattening, formal thought disorder, impaired motor behavior, mood disturbances, cognitive abnormalities, anxiety, and lack of insight [1]. Researchers observed that patients with schizophrenia have a reduced quality of life, an impaired capacity to work, and a reduced life expectancy which is decreased by 10–20 years [2].

Psychiatric disorders critically impact social functioning as mental health problems may compromise the interactions of individuals with their environments including work, social activities, and relationships with partners and family. However, severe mental illnesses including schizophrenia research demonstrated considerable variance in social functioning [3]. Indeed, symptom domains may differentially contribute to poor functioning [4–6]. For example, motor abnormalities, such as peculiar gait, bizarre posture or abnormal involuntary movements of the face [7], may exert problems in global functioning in patients with schizophrenia, including all domains of everyday life. For some decades, motor abnormalities were mainly attributed to side effects of

* Corresponding author at: Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern, Switzerland
E-mail address: niluja.nadesalingam@upd.unibe.ch (N. Nadesalingam).

https://doi.org/10.1016/j.comppsych.2022.152307

Available online 12 March 2022

antipsychotic medication. However, newer reports indicate that motor disturbances are present across all stages of schizophrenia spectrum disorders including clinical high-risk individuals (CHR-individuals) and medication- naïve patients [8–14]. 66% of antipsychotic-naïve first-episode patients showed at least one motor symptom [15]. These motor abnormalities in both medicated and non-medicated patients are suggested to be related to dysfunctional motor cortical inhibition and altered connectivity in the motor circuitry [16–21].

Patients with schizophrenia exhibit different types of motor abnormalities, and clinicians have identified six categories [7,22]. First, abnormal involuntary movements, also known as dyskinesia, are rapid repetitive involuntary contractions of muscles in the face, trunk, and extremities. Second, parkinsonism, which includes akinesia, rigor, and tremor. Third, akathisia, characterized by inner restlessness and the urge to move. Fourth, neurological soft signs (NSS) are distortions in motor sequencing and motor coordination [14]. Fifth, catatonia, a complex psychomotor syndrome that includes hyperkinetic and hypokinetic symptoms in addition to autonomic instability [23]. Lastly, psychomotor slowing, which is observed in fine motor behavior (e.g. writing) as well as in gross motor behavior (e.g. walking) [24]. All these motor abnormalities are quantifiable with reliable motor rating scales or objective instrumentation.

Despite the traditional neglect of the motor abnormalities evaluation in both clinical practice and research, the presence of motor abnormalities seems to be associated with an increased risk of developing schizophrenia as well as with the course of the disorder [13,25]. Moreover, some motor abnormalities are correlated with poorer cognition [26], decreased global functioning [27–29], and poor quality of life [30] in patients with schizophrenia. For example, Sambataro and colleagues (2020) reported that NSS were associated with more negative symptoms and poorer neurocognitive functioning, while catatonia and akathisia predicted reduced cross-sectional global functioning. Furthermore, Ascher-Svanum and colleagues [31] also found that dyskinesia decreased global functioning. In addition, studies in first-episode psychosis (FEP) even suggest that NSS may predict global functioning after 10 years [29], as did catatonia and dyskinesia [27]. Moreover, NSS, akathisia, and parkinsonism at 6 months were linked to global and social functioning at 10 years [27]. In addition, studies with CHR populations point in the same direction. Higher levels of dyskinesia predicted poorer social functioning after one year [32], while higher levels of NSS were associated with lower levels of global functioning at 2-year follow-up [33].

Although previous reports show strong associations between single movement abnormalities and global as well as social functioning, we still struggle to understand the contribution of various motor domains. Thus, the field would benefit from comprehensive analyses covering multiple motor and functional domains. Furthermore, besides their impact on real-world functioning, the association between motor abnormalities and functional capacity needs to be tested. Functional capacity refers to the ability to perform daily tasks, such as counting money, understanding a bill, or rescheduling a doctor's appointment [34]. Accordingly, in the current report, we hypothesized, that the presence of motor abnormalities, measured with diverse motor rating scales as well as a manual dexterity task, is associated with poorer functional outcomes, including global, social, and occupational functioning as well as, poorer functional capacity in patients with schizophrenia spectrum disorders. To test this hypothesis, we pooled the baseline data of three longitudinal studies and conducted correlational analyses between the severity of distinct motor abnormalities and three functional outcome/capacity measures. We expect patients with severe motor impairments to exhibit poorer social functioning and limited functional capacity.

2. Material and methods

2.1. Participants

In the current report, we included 156 patients diagnosed with schizophrenia spectrum disorders according to DSM-5 (Table 1A). Based on the definition of remitted schizophrenia suggested by Andreasen and collaborators in 2005, our sample was divided into remitted ($n = 25$, including 6 first episodes) and non-remitted ($n = 131$, including 18 first episodes) patients [35]. We included patient data from three studies on motor abnormalities or gesture in schizophrenia spectrum disorders [OCoPS-P (Overcoming Psychomotor Slowing in Psychosis) ClinicalTrials.gov Identifier: NCT03921450; GNI (Neural correlates of gesture deficits in schizophrenia) [36,37]; The Brain Stimulation And Group Therapy to Improve Gesture and Social Skills in Psychosis trial (BrAGGSoS, NCT04106427)]. Recruitment was conducted at the in- and outpatient departments of the University Hospital of Psychiatry and Psychotherapy, Bern, Switzerland. All participants provided written informed consent. The study protocols adhered to the declaration of Helsinki and were approved by the local ethics committee. General exclusion criteria were active substance dependence other than nicotine, neurological disorders, which had an impact on motor abilities, and severe brain injury with consecutive loss of consciousness.

We assessed the severity of psychopathology using the Positive And Negative Syndrome Scale (PANSS) [38]. All patients were on antipsychotic medication at the time of testing and mean olanzapine equivalents (OLZ eq.) were calculated according to Leucht [39] (Table 1B–D).

2.2. Measures

2.2.1. Diagnosis assessment

The diagnosis of the recruited patients was ascertained with the Mini International Neuropsychiatric Interview [40] and Comprehensive Assessment of Symptoms and History [41], or The Structured Clinical Interview for DSM-5® (SCID-5).

2.2.2. Coin rotation

We used the coin rotation task (CR) to assess manual dexterity as a measure of fine motor function. The CR instructions were to rotate a Swiss 50-Rappen coin, comparable to the size of a US dime, between thumb, index, and middle finger of their dominant hand as fast as possible. The participants performed 3 trials of 10s. We videotaped the patients' performance for subsequent blinded scoring. The first trial was considered as a practice. We calculated the CR score for each trial using the following validated formula: CR score = half turns − [(coin drops × 0.10) × half turns] [42,43]. We averaged the CR score of the two last trials to obtain the total CR score.

2.2.3. Motor rating scales

We assessed i) Parkinsonism using the Unified Parkinson's Disease Rating Scale (UPDRS) part III [44] with a total score ranging from 0 to 108; ii) catatonia using the Bush Francis Catatonia Rating Scale (BFCRS), ranging from 0 to 69 [45]; iii) dyskinesia using the Abnormal Involuntary Movement Scale (AIMS), ranging from 0 to 28 [46]; iv) NSS using the Neurological Evaluation Scale (NES) ranging from 0 to 52 [47]. We assessed psychomotor slowing using the Salpêtrière Retardation Rating Scale (SRRS), ranging from 0 to 60 [48]. The SRRS scale also includes items that explore general depressive symptoms. Therefore, we focused the analyses on a modified SRRS (mSRRS) score using the sum of the first five psychomotor items (i.e., slowing of gate/walking, slowing of movements of the trunk/limbs, reduction in facial movement/expression, speech, and voice modulation) and the global rating of the inhibition (item 15) which results in a total score ranging from 0 to 20 [49]. For all the motor rating scales, a higher score indicates more severe motor symptoms. In one of the three involved cohorts, we did not acquire the SRRS scale, resulting in a subset of 104 patients with an mSRRS

Table 1
Demographic table.

1.A Whole group demographic

	Whole group
N	156
Age (years)	37.9 ± 12.1
Gender	88 M
Duration of illness (years)	12.5 ± 11.7
PANSS Total	72.8 ± 20.5
PANSS Positive	16.07 ± 6.3
PANSS Negative	20.2 ± 7.4
OLZ eq.	16.2 ± 11.8
AIMS	1.5 ± 3.7
BFCRS	3.6 ± 4.7
UPDRS III	13.9 ± 11.8
NES	13.5 ± 10.1
CR	11.5 ± 3.5
**mSRRS (*N* = 104)	8.4 ± 4.7
GAF	49.2 ± 15.9
SOFAS	48.6 ± 16.1
**UPSA-B (*N* = 130)	74.9 ± 18.1

1.B. Catatonia classification

	With Catatonia	Without Catatonia	Stats value	*P* value	FDR corrected (for 48 comparisons)
N	61	95	/	/	/
Age (years)	37.7 ± 11.3	38.3 ± 13.3	W = 2890	0.98	1
Gender	35 M	53 M	$\chi^{2=}$0.0009	0.97	1
PANSS Total	84.1 ± 20.7	65.6 ± 16.9	W = 5.82	6E-08	3.375E-07***
PANSS Positive	17.7 ± 6.5	15.4 ± 6.0	W = 2514	0.16	0.225
PANSS Negative	24.8 ± 7.1	17.2 ± 5.9	W = 1198	6.4E-10	5.76E-09***
OLZ eq.	16.9 ± 9.8	15.7 ± 12.7	W = 2499	0.17	0.232
AIMS	2.3 ± 4.7	1.1 ± 2.8	W = 2527	0.11	0.177
BFCRS	7.7 ± 4.8	1.1 ± 2.1	W = 341	2.2E-16	3.3E-15***
UPDRS III	22.7 ± 11.9	8.4 ± 7.2	W = 782	1.4E-14	1.575E-13***
NES	14.4 ± 11.9	13.3 ± 9.8	W = 3125	0.31	0.45
CR	10.6 ± 3.8	11.9 ± 3.3	W = 3267	0.02	0.04*
N	50	54			
mSRRS	11.0 ± 3.6	5.9 ± 4.3	W = 519	5.9E-08	3.375E-07***
GAF	40.7 ± 12.4	54.7 ± 15.6	W = 4141	6E.-06	2.7E-05***
SOFAS	41.2 ± 13.6	53.4 ± 15.8	W = 5.11	1.00E-06	5.0E-06***
N	52	78			
UPSA-B	70.23 ± 17.5	78.0 ± 16.2	W = 2684	0.002	0.006*

1.C. Dyskinesia classification

	With Dyskinesia	Without Dyskinesia	Stats value	P value	FDR corrected (for 48 comparisons)
N	21	135	/	/	/
Age (years)	42.2 ± 13.9	37.7 ± 11.3	W = 1136	0.14	0.203
Gender	16 M	72 M	$\chi^{2=}$2.98	0.09	0.162
PANSS Total	79.0 ± 17.4	71.9 ± 20.9	W = 1056	0.06	0.117
PANSS Positive	16.2 ± 6.3	16.1 ± 6.3	W = 1398	0.92	0.986
PANSS Negative	22.4 ± 7.4	19.9 ± 7.3	W = 1124	0.13	0.195
OLZ eq.	18.2 ± 11.3	15.9 ± 11.4	W = 0.85	0.39	0.450
AIMS	8.4 ± 6.4	0.5 ± 1.1	W = 34	2.2E-16	3.3E-15***
BFCRS	6.7 ± 5.6	3.2 ± 4.4	W = 833	0.001	0.003*
UPDRS III	18.2 ± 13.2	13.3 ± 11.5	W = 1068	0.07	0.131
NES	19.5 ± 10.9	18.5 ± 11.9	W = 1321	0.65	0.80
CR	10.2 ± 3.3	11.6 ± 3.5	W = 1406	0.10	0.173
N	9	95			
mSRRS	10.6 ± 4.9	8.2 ± 4.6	W = 295	0.13	0.195
GAF	44.6 ± 14.7	49.9 ± 16.06	W = 1724	0.11	0.177
SOFAS	44.9 ± 15.2	49.17	W = 1662	0.20	0.250
N	16	114			
UPSA-B	67.7 ± 27.6	75.9 ± 14.9	W = 1662	0.20	0.25

1.D. Parkinsonism classification

	With Parkinsonism	Without Parkinsonism	Stats value	P-value	FDR corrected (for 48 comparisons)
N	88	68	/	/	/
Age (years)	39.2 ± 13.1	36.2 ± 10.4	W = 2636	0.20	0.250
Gender	50 M	38 M	$\chi^{2=}$0	1	1

(*continued on next page*)

Table 1 (*continued*)

1.D. Parkinsonism classification					
	With Parkinsonism	Without Parkinsonism	Stats value	P-value	FDR corrected (for 48 comparisons)
PANSS Total	75.9 ± 22.1	68.9 ± 17.7	W = 2760	0.028	0.06
PANSS Positive	15.9 ± 5.9	16.2 ± 6.6	W = 3024	0.91	0.98
PANSS Negative	21.9 ± 7.65	17.9 ± 6.29	W = 2004	4.10E-04	0.001**
OLZ eq.	16.4 ± 10.7	15.9 ± 13.1	W = 2760	0.47	0.52
AIMS	1.7 ± 3.4	1.3 ± 3.8	W = 2713	0.24	0.29
BFCRS	5.3 ± 5.3	1.5 ± 2.6	W = 1469	2.3E-08	1.725E-07***
UPDRS III	20.8 ± 11.2	5.13 ± 4.3	W = 343	2.2E-16	3.3E-15***
NES	18.2 ± 11.3	19.2 ± 12.6	W = 2283	0.01	0.023*
CR	10.6 ± 3.7	12.6 ± 3.0	W = 3738	2.90E-04	0.001**
N	70	37			
mSRRS	9.7 ± 4.5	5.7 ± 3.9	W = 596	2.5E-05	1.0E-04***
GAF	45.2 ± 14.6	54.4 ± 16.2	W = 4012	2.00E-04	7.5E-04***
SOFAS	45.2 ± 15.5	53.0 ± 15.8	W = 3806	3.50E-03	0.009**
N	77	53			
UPSA-B	71.8 ± 18.1	79.5 ± 14.3	W = 2598	8.17E-03	0.02*

For each measure the mean and standard deviation is indicated. PANSS: Positive And Negative Syndrome Scale; OLZ eq.: olanzapine-equivalent (mg/day); M: male; AIMS: Abnormal Involuntary Movement Scale; BFCRS: Bush Francis Catatonia Rating Scale; UPDRS: Unified Parkinson's Disease Rating Scale; GAF: Global Assessment of Functioning; SOFAS: Social and Occupational Functioning Assessment Scale; UPSA-B: University of California San Diego Performance-Based Assessment; NES: Neurological Evaluation Scale; CR: Coin Rotation; SRRS: Salpêtrière Retardation Rating Scale: mSRRS: Modified SRRS. $\chi^{2=}$chi-square, W=Wilcoxon test.

score.

In this study, we also provide a categorization of the sample for the presence and absence of parkinsonism, catatonia, and dyskinesia using the following cut-off criteria. To be classified into the subgroup with parkinsonism the patients either had to score at least 2 on the items "rest tremor" or "rigidity", or at least 3 on one of the remaining 12 items, or at least 2 on two of the remaining 12 items of the UPDRS III [50]. To be classified into the subgroup with catatonia, the patients had to score at least 1 on two of the 14 items of the BFCRS [45]. (Please refer to Supplement 1 for a stricter and refine "catatonia with psychomotor slowing" classification). To be classified into the subgroup with dyskinesia the patients had to score at least 2 on two items or 3 on one item of the first 7 items of AIMS using the Schooler and Kane criteria [51].

2.2.4. Social and functional outcome measures

We employed three different instruments to measure social and functional outcomes. First, we applied the Global Assessment of Functioning (GAF) [52]. Second, we used the Social and Occupational Functioning Assessment Scale (SOFAS), ranging from 0 to 100 as the GAF [53]. Lastly, we measured the patients' capacity to fulfill tasks encountered in everyday life using the brief version of the UCSD Performance-based Skills Assessment (UPSA-B) [34]. This test includes tasks assessing *financial skills*, like counting money and understanding a utility bill, and *communication skills*, such as how to use a phone to call the emergency services, to ask for a phone number at the call information, and to postpone a doctor's appointment. The total score ranges from 0 to 100. Due to some patients having trouble performing the tasks, we successfully acquired the UPSA-B scale in a subset of 130 patients.

All the assessments were done by trained psychiatrists (KS, DA, LM, DB) during the baseline session of the studies. All raters were extensively trained to achieve high inter-rater reliability (kappa>0.8).

2.3. Analysis

We classified the patients into subgroups based on the presence or absence of parkinsonism, catatonia, and dyskinesia as measured by the UPDRS, BFCRS, and AIMS scales respectively. As the data are not normally distributed, we ran a Wilcoxon rank-sum test with continuity correction to compare the demographics information in the classified subgroups and a chi-square test for gender.

We calculated the mean scores for each functional outcome (GAF, SOFAS, and UPSA-B) separately for each of these subgroups using scripts written in R (version 4.0.2) and used ANCOVAs to calculate the differences in means between patients with and without parkinsonism, catatonia, and dyskinesia for each functional outcome. In addition, we measured the dimensional associations between motor assessments and functional outcomes using partial correlation with the Kendall Tau method. All analyses were co-varied for age, gender, medication (OLZ eq.), and PANSS total score (See supplement 2 for the classification analyses without covariates). All reported *p*-values were corrected for multiple comparisons using false discovery rate (fdr).

3. Results

3.1. Clinical and demographic information

The 156 patients included in this analysis presented moderate to severe symptoms and relevant functional impairment. We classified twenty-one patients with dyskinesia, eighty-eight patients with parkinsonism, and sixty-one with catatonia and summarized the score for each motor and functional outcome according to this classification in Table 1B–D. Global symptom severity as measured by PANSS total score was associated with poorer functioning (PANSS total GAF (tau = −0.35, $p < 0.001$), SOFAS (tau = −0.36, $p < 0.001$), and UPSA-B (tau = −0.29, $p < 0.001$), therefore, we included PANSS total as covariate to all further analyses.

3.2. Categorical differences in functional outcomes across motor abnormalities

We calculated the differences in means between patients with and without parkinsonism, catatonia, and dyskinesia separately for GAF, SOFAS, and UPSA-B to evaluate the effect of motor impairment severity on social and functional outcome (Fig. 1A-C, Table 2), always co-varied for age, gender, medication, and PANSS total score. Patients with parkinsonism (all $F > 4.5$; $p < 0.035$) and catatonia (all $F > 4.9$; $p < 0.027$) scored significantly lower across GAF and SOFAS compared with patients without parkinsonism or catatonia. In contrast, we observed no significant differences in scores between patients with dyskinesia versus patients without dyskinesia (all $F < 0.4$; $p > 0.51$) although, patients without dyskinesia numerically outperformed the ones with dyskinesia in all three functional outcome measures. Similarly, we observed no significant difference in the UPSA-B outcome, due to a strong impact of age on this scale, which is not observed in the other outcomes (Table 2). As demonstrated in the supplement material (Supplement 2) without any covariates or without the PANSS total score both patients with catatonia and parkinsonism scored significantly lower also in UPSA-B.

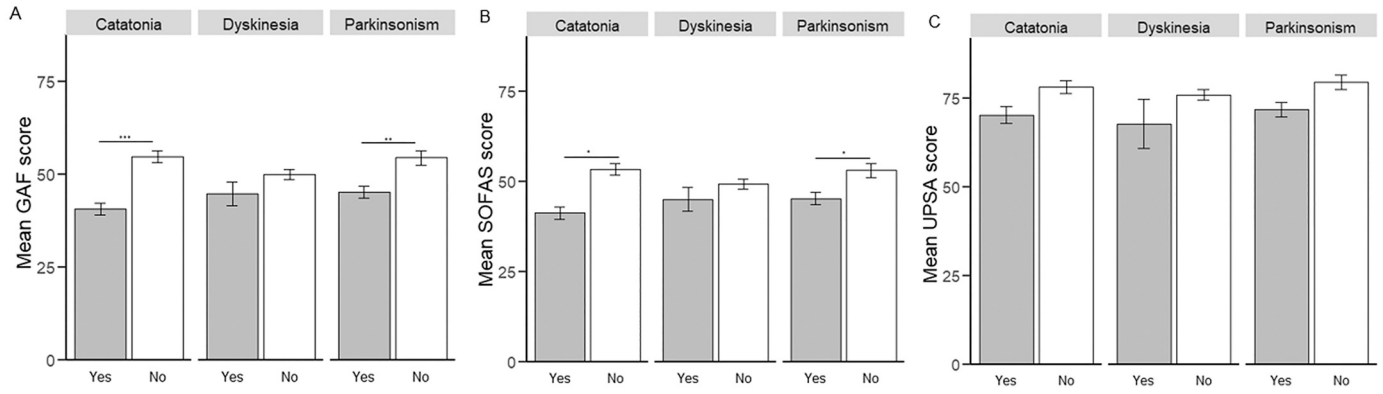

Fig. 1. Severity scores. A) Bar plot represents mean GAF scores for patients that scored high (Yes: grey) vs. low (No: white) in each of the three motor abnormalities categories (Catatonia, Dyskinesia and Parkinsonism) as measured by BFCRS, AIMS and UPDRS respectively. *** denotes a significant difference < 0.001. ** denotes a significant difference < 0.01. Vertical bars represent the standard error of mean. B) Bar plot represents mean SOFAS scores for patients that scored high (Yes: grey) vs. low (No: white) in each of the three motor abnormalities categories (Catatonia, Dyskinesia and Parkinsonism) as measured by BFCRS, AIMS and UPDRS respectively. * denotes a significant difference < 0.05. Vertical bars represent the standard error of mean. C) Bar plot represents mean UPSA-B scores for patients that scored high (Yes: grey) vs. low (No: white) in each of the three motor abnormalities categories (Catatonia, Dyskinesia and Parkinsonism) as measured by BFCRS, AIMS and UPDRS respectively.

Table 2
Effect of motor impairment severity on social and functional outcome for each sub-category.

		GAF			SOFAS			UPSA-B		
		Pr(>F)	p value		Pr(>F)	p value		Pr(>F)	p value	
	age	0.00	0.97		0.30	0.59		6.38	0.01	*
	gender	0.06	0.80		1.92	0.17		0.41	0.52	
Catatonia	Medication_OLZ	2.33	0.13		2.55	0.11		0.32	0.57	
	PANSS_tot	26.33	8.83E-07	***	37.66	7.26E-09	***	24.61	2.28E-06	***
	severity	11.77	7.70E-04	***	4.96	0.03	*	0.22	6.38E-01	***
	age	0.06	0.80		0.14	0.71		5.81	0.02	*
	gender	0.01	0.92		1.64	0.20		0.30	0.58	
Parkinsonism	Medication_OLZ	2.66	0.10		2.80	0.10	.	0.34	0.56	
	PANSS_tot	44.27	5.105E-10	***	54.51	1.01E-11	***	28.75	3.92E-07	***
	severity	8.55	0.004	**	4.51	0.04	*	2.13	0.15	
	age	0.00	0.99		0.38	0.54		5.75	0.02	*
	gender	0.00	0.95		1.68	0.20		0.23	0.64	
Dyskinesia	Medication_OLZ	2.46	0.12		2.72	0.10		0.38	0.54	
	PANSS_tot	48.90	8.44E-11	***	59.72	1.5E-12	***	30.05	2.28E-07	***
	severity	0.42	0.52		0.00	0.99		0.40	0.53	

3.3. Dimensional associations between motor abnormalities and functional outcomes

We found positive correlations between CR score and GAF and SOFAS (all tau>0.13, *p*-value<0.05), suggesting that patients with better CR performance have better functional outcomes. In addition, we observed negative correlations for BFCRS with both GAF (tau = −0.203, *p*-value<0.001) and SOFAS (tau = −0.204, p-value<0.001) but not with the UPSA-B (tau = −0.054, p-value = 0.443) (Table 3). We also detected a negative correlation between NES and SOFAS (tau = −0.137, p-value = 0.033; Table 3). Moreover, both UPDRS and mSRRS correlated negatively with the 3 functional outcomes: GAF, SOFAS and UPSA (all tau<−0.152, p-value<0.036; Table 3). In contrast, no correlations emerged between AIMS and functional outcomes (all tau<0.044, p-value>0.47; Table 3). Taken together, we show that patients with motor abnormalities (higher score in motor evaluation scales) have poorer functional outcomes.

Table 3
Partial correlations of motor assessments with functional outcomes using age, gender, OLZ and PANSS as covariates.

Motor Assessments	GAF (tau; p-value fdr-corrected)	SOFAS (tau; p-value fdr-corrected)	UPSA-B (tau; p-value fdr-corrected)
CRT	0.134; 0.041*	0.131; 0.041*	0.113; 0.088
AIMS	0.011; 0.893	0.044; 0.473	0.006; 0.922
BFCRS	−0.203; <0.001**	−0.204; <0.001**	−0.054; 0.443
UPDRS	−0.272; <0.0001***	−0.232; <0.001**	−0.177; 0.011*
NES	−0.116; 0.092	−0.137; 0.033*	−0.059; 0.218
mSRRS	−0.169; 0.033*	−0.152; 0.036*	−0.159; 0.036*

GAF: Global Assessment of Functioning; SOFAS: Social and Occupational Functioning Assessment Scale; UPSA-B: University of California San Diego Performance-Based Assessment; CRT: Coin Rotation Task; AIMS: Abnormal Involuntary Movement Scale; BFCRS: Bush Francis Catatonia Rating Scale; UPDRS: Unified Parkinson's Disease Rating Scale; NES: Neurological Evaluation Scale; mSRRS: modified Salpêtrière Retardation Rating Scale. P-values are false discovery rate (fdr) corrected. * Denotes a significant correlation.

4. Discussion

The current report aimed to test whether motor abnormalities were associated with global and social functioning, as well as functional capacity in patients with schizophrenia. We examined the effects of multiple motor abnormalities on functional outcomes in 156 patients with schizophrenia spectrum disorders. We divided the sample based on the severity of dyskinesia, parkinsonism and catatonia. Patients with severe parkinsonism and catatonia had poorer social and global functioning. In

contrast, patients with severe dyskinesia did not differ in functional outcomes from patients without dyskinesia. In line with our hypotheses, dimensional ratings of motor abnormalities were broadly linked to poorer functional outcomes at a cross-sectional level.

For example, GAF and SOFAS were negatively correlated UPDRS, mSRRS and BFCRS, while SOFAS was further negatively correlated with NES. Likewise, functional capacity correlated inversely with UPDRS and mSRRS. Finally, the CR score correlated with functional outcome suggesting that better fine motor performance is directly linked to overall better functioning. In sum, our study demonstrates that motor abnormalities are strongly associated with poor community functioning in psychosis.

4.1. Motor abnormalities distinctly impact functioning

While the main finding is a general link between motor abnormalities and measures of functional outcome, the distinction between motor abnormalities requires further elaboration. In addition to GAF and SOFAS, our study also tested functional capacity as measured with the UPSA-B. Functional capacity captures the skills necessary in community function rather than the actual functioning [34,54]. Our data indicate that psychomotor slowing and parkinsonism correlate with inferior functional capacity in patients, while catatonia, dyskinesia, and NSS are unrelated to functional capacity. These findings suggest that hypokinetic motor abnormalities impact the skills more than coordination deficits or hyperkinesia. Previous studies have emphasized the association between neurocognition, negative symptoms, and functional capacity [55–58]. Finally, functional capacity at baseline has proven to be the main determinant of real-life functioning in longitudinal studies [59].

Parkinsonism was linked to poor social and global functioning as well as to poor functional capacity. This is in line with work in FEP [27] but in contrast to others [28]. The different findings between studies may stem from the application of distinct instruments. We applied the UPDRS, which is a comprehensive measure of parkinsonism. Similarly, psychomotor slowing as measured by the mSRRS was linked to all functional outcomes. Psychomotor slowing had been hypothesized to contribute to poor community functioning [24], with reaction times and fine motor performance predicting outcomes [60,61]. However, previous studies using the SRRS in psychosis demonstrated an association between psychomotor slowing and negative symptom severity, but functioning was not tested [62,63]. Still, the current results with the mSRRS (gross motor behavior) and CRT (fine motor skills) both support the notion that psychomotor slowing is linked to poor community functioning [61]. Despite the relevance of fine motor dexterity in psychomotor slowing and by extent in schizophrenia, it is less explored than gross motor function. The present link between manual dexterity and functional outcomes supports the idea that it might be a useful clinical marker [64]. In sum, the hypokinetic motor abnormalities might indicate poor functioning in schizophrenia spectrum disorders.

Catatonia combines hypokinetic and hyperkinetic features, as well as disturbance of volition and autonomous dysregulation [23]. In line with previous reports, we found that catatonia severity is associated with poor global functioning [27,28]. Furthermore, our data also demonstrate that poor social functioning is linked to catatonia severity. We may speculate that particularly odd movements or disturbances of volition, e.g. withdrawal, may contribute to the deficits in social functioning.

Abnormal involuntary movements or dyskinesia have been suggested to be particularly valuable as marker of the risk for psychosis. Sharing striatal dopaminergic dysfunction with psychosis as one key pathomechanism, dyskinesia points to more severe illness trajectories, cognitive impairment, and poor function [27,32,65,66]. However, our study failed to detect these associations in line with other studies in samples with large ranges of illness duration [28]. The most striking positive findings were detected in subjects at risk for psychosis or first-episode patients, e.g. when baseline dyskinesia predicted global functioning in 10 years [27]. A possible explanation for the lack of an association in our report might be due to the patient selection. We pooled data from three studies, which were not designed to explore dyskinesia, resulting in a low number of patients with severe dyskinesia ($n = 21$) in contrast to the high number of patients without severe dyskinesia ($n = 135$) thus limiting statistical power.

Finally, NSS have been intensively studied as a marker of the psychotic disease process and always seemed to indicate poor outcomes across various stages of psychosis [14]. Supporting this notion, we found soft signs to be correlated with poor social functioning whereas its association with poor global functioning is at trend level. In contrast soft signs were not associated with functional capacity. Indeed, multiple studies reported cross-sectional and longitudinal relationships between NSS and poor social and global functioning in psychosis [27,28,67–69]. Importantly, soft signs were found to predict long-term outcomes in first-episode patients [27,29]. Finally, Minichino et al. (2017) reported that NSS was one of the key predictors for lower functional outcome at two years follow up in CHR-individuals.

Collectively, the current study mainly corroborates previous work and extends towards functional capacity as well as the role of psychomotor slowing. We also observed that functional outcomes are strongly impacted by the severity of illness however, it is worth mentioning that the present results remain the same with and without controlling for the severity of illness, suggesting a specific link between motor and social functioning. While there is considerable overlap between motor abnormalities in both early and chronic psychoses [15], the predictive value of distinct motor abnormalities particularly for the long-term outcome seems to differ [27–29]. NSS, catatonia, and parkinsonism might be particularly suited to identify subjects with poorer functional outcomes.

Studies on longitudinal outcomes in FEP may differ from those with mixed or mainly chronic patients. Indeed, trajectories of FEP are very heterogeneous [71], while limited variability is expected in subjects who have a 5–10 year history of schizophrenia spectrum disorders, particularly as those with favorable courses are less represented in these studies. Some motor signs at 6 months follow-up predicted outcomes while baseline variables failed to correlate [27]. Furthermore, NSS were shown to decrease in a proportion of FEP patients when remission of the psychotic episode is achieved. Importantly, declining NSS scores indicated favorable clinical outcomes in FEP [72–74]. Thus, mixed samples including patients with first and multiple episodes could inform on the associations between motor abnormalities and functional outcomes.

4.2. Potential pathways from motor abnormalities to compromised function

How do motor abnormalities contribute to poor functional outcomes? First, motor abnormalities are readily observable signs, allowing laypersons to perceive subjects with schizophrenia as somebody with severe mental illness. Thus, motor abnormalities might lead to stigmatization of patients suffering from schizophrenia. Critically, such internalized stigma has an indirect negative effect on real-life functioning in patients with schizophrenia [75]. Second, some evidence suggests motor abnormalities to affect the subjective well-being of patients with schizophrenia, leading to poor quality of life [30,76]. Third, multiple studies indicate that motor abnormalities often co-occur with poorer cognition and increased negative symptoms across all stages of schizophrenia [26,28,77–81]. Importantly, both cognitive impairment and negative symptoms may contribute to poor functional outcomes [59] Poorer functional outcome is also related to negative symptoms, including motivational deficits, and poorer social cognition in patients with schizophrenia [82–84]. Finally, motor abnormalities directly impair nonverbal behavior, such as the use and interpretation of hand gestures [37]. Indeed, motor abnormalities can severely hamper the performance of hand gestures, which are important for successful social interactions, and predict mid-term social functioning. [85].

Our study further found that parkinsonism and psychomotor slowing also impair the functional capacity of patients. The performance of everyday skills should be unrelated to stigma, but is likely to be influenced by social interaction deficits, amotivation, or cognitive impairment, all of which correlate with severe motor abnormalities.

First-line treatment for schizophrenia includes antipsychotics, which will improve global functioning but also introduce more motor abnormalities [86,87]. In addition, cognitive remediation therapy has been very effective in improving function in psychosis [88,89]. However, given the strong association of motor abnormalities and functional outcome, it will be important to identify behavioral domains, which can be modulated by further psychiatric treatment efforts. First evidence suggests that repetitive transcranial magnetic stimulation (rTMS) on the supplementary motor area may ameliorate psychomotor slowing in psychosis [90]. However, the effects of this direct mechanistic treatment on function have not been established yet. Likewise, single rTMS treatments have improved hand gesture performance in schizophrenia [91]. While this study warrants replication, the impact on functional outcomes needs to be explored as well. The use of non-invasive brain stimulation techniques has been advocated to treat motor abnormalities in psychosis [22]. We may hope that once these treatments prove to be effective, functional outcomes will improve as motor impairments decline.

4.3. Limitations

First, in the current report, the population combines patients from 3 different studies (including two clinical trials) with heterogeneous samples. Our analysis took medication dosage, age, and psychopathology (PANSS total score) into account, to check for possible confounders. However, we may still have missed potential contributors to variability in the samples. Second, none of the three studies was designed to specifically explore dyskinesia, parkinsonism, or catatonia. This leads to the present small number of patients with dyskinesia. The specific impact of dyskinesia on social and global functioning in schizophrenia should be explored in future studies with dedicated samples. Third, as most of our patients are in psychotic episodes or experience persistent chronic symptoms, the current study cannot conclude on the effect of the course of the illness on the association between NSS and functional outcomes. This question needs to be addressed in studies with a larger group of remitted patients.

Finally, some selection bias might have been introduced as the test of functional capacity was hard to perform for subjects with severe motor signs.

5. Conclusion

Motor abnormalities are associated with poor global and social functioning as well as with poorer functional capacity. All motor domains seem to be important predictors of functional outcome, particularly psychomotor slowing, NSS, parkinsonism, and catatonia. Future studies need to test, whether amelioration of motor abnormalities may improve community functioning.

Fundings

This work was supported by the Swiss National Science Foundation (grants #152619, #l84717 and #182469 to SW, 180022 to KS), the Bangerter Rhyner Foundation (SW), and the Adrian and Simone Frutiger Foundation (KS). The funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Authors' contribution

NN, VC, KS, SV did the recruitments of the patients and ran the experiments. KS, DA, DB, LM, FW, SW performed the psychopathology and motor assessments. NN, AP, SL, and SW wrote the manuscript. AP and SL completed all the analyses and provided the tables and figs. VC, KS, SV, DA, DB, LM, FW reviewed the final version of the manuscript. SW conceived the original idea and supervised the project.

Declaration of Competing Interest

SW has received honoraria from Mepha, Neurolite, Janssen, Lundbeck, Otsuka, and Sunovion. KS has received honoraria from Lundbeck and Sunovion. NN, VC, AP, SL, DA, DB, LM, SV, FW, reported no biomedical financial interests or potential conflicts of interest.

Acknowledgements

We would like to thank all the participants of the studies and the clinical personnel of the wards for their help and support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2022.152307.

References

[1] Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "Just the facts" 4. Clinical features and conceptualization. Schizophr Res 2009. https://doi.org/10.1016/j.schres.2009.03.005.
[2] Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet 2016;388:86–97. https://doi.org/10.1016/S0140-6736(15)01121-6.
[3] Velthorst E, Fett AKJ, Reichenberg A, Perlman G, Van Os J, Bromet EJ, et al. The 20-year longitudinal trajectories of social functioning in individuals with psychotic disorders. Am J Psychiatry 2017;174:1075–85. https://doi.org/10.1176/appi.ajp.2016.15111419.
[4] Grau N, Rubio-Abadal E, Usall J, Barajas A, Butjosa A, Dolz M, et al. Influence of cognition, premorbid adjustment and psychotic symptoms on psycho-social functioning in first-episode psychosis. Psychiatry Res 2016. https://doi.org/10.1016/j.psychres.2016.04.121.
[5] Addington J, Addington D. Social and cognitive functioning in psychosis. Schizophr Res 2008. https://doi.org/10.1016/j.schres.2007.07.004.
[6] Hunter R, Barry S. Negative symptoms and psychosocial functioning in schizophrenia: neglected but important targets for treatment. Eur Psychiatry 2012. https://doi.org/10.1016/j.eurpsy.2011.02.015.
[7] Walther S, Strik W. Motor symptoms and schizophrenia. Neuropsychobiology 2012. https://doi.org/10.1159/000339456.
[8] Kindler J, Schultze-Lutter F, Michel C, Martz-Irngartinger A, Linder C, Schmidt SJ, et al. Abnormal involuntary movements are linked to psychosis-risk in children and adolescents: results of a population-based study. Schizophr Res 2016;174:58–64. https://doi.org/10.1016/j.schres.2016.04.032.
[9] Mittal VA, Neumann C, Saczawa M, Walker EF. Longitudinal progression of movement abnormalities in relation to psychotic symptoms in adolescents at high risk of schizophrenia. Arch Gen Psychiatry 2008;65:165–71. https://doi.org/10.1001/archgenpsychiatry.2007.23.
[10] Pappa S, Dazzan P. Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review. Psychol Med 2009;39:1065–76. https://doi.org/10.1017/S0033291708004716.
[11] van Harten PN, Walther S, Kent JS, Sponheim SR, Mittal VA. The clinical and prognostic value of motor abnormalities in psychosis, and the importance of instrumental assessment. Neurosci Biobehav Rev 2017;80:476–87. https://doi.org/10.1016/j.neubiorev.2017.06.007.
[12] Walther S, van Harten PN, Waddington JL, Cuesta MJ, Peralta V, Dupin L, et al. Movement disorder and sensorimotor abnormalities in schizophrenia and other psychoses - European consensus on assessment and perspectives. Eur Neuropsychopharmacol 2020;38:25–39. https://doi.org/10.1016/j.euroneuro.2020.07.003.
[13] Walther S, Mittal VA. Motor system pathology in psychosis. Curr Psychiatry Rep 2017;19. https://doi.org/10.1007/s11920-017-0856-9.
[14] Whitty PF, Owoeye O, Waddington JL. Neurological signs and involuntary movements in schizophrenia: intrinsic to and informative on systems pathobiology. Schizophr Bull 2009;35:415–24. https://doi.org/10.1093/schbul/sbn126.
[15] Peralta V, Campos MS, De Jalón EG, Cuesta MJ. Motor behavior abnormalities in drug-naïve patients with schizophrenia spectrum disorders. Mov Disord 2010;25:1068–76. https://doi.org/10.1002/mds.23050.

[16] Carment L, Dupin L, Guedj L, Térémetz M, Cuenca M, Krebs MO, et al. Neural noise and cortical inhibition in schizophrenia. Brain Stimul 2020;13:1298–304. https://doi.org/10.1016/j.brs.2020.06.015.

[17] Teremetz M, Amado I, Bendjemaa N, Krebs MO, Lindberg PG, Maier MA. Deficient grip force control in schizophrenia: behavioral and modeling evidence for altered motor inhibition and motor noise. PLoS One 2014;9:111853. https://doi.org/10.1371/journal.pone.0111853.

[18] Walther S, Stegmayer K, Federspiel A, Bohlhalter S, Wiest R, Viher PV. Aberrant hyperconnectivity in the motor system at rest is linked to motor abnormalities in schizophrenia spectrum disorders. Schizophr Bull 2017;43:982–92. https://doi.org/10.1093/schbul/sbx091.

[19] Walther S, Schäppi L, Federspiel A, Bohlhalter S, Wiest R, Strik W, et al. Resting-state hyperperfusion of the supplementary motor area in catatonia. Schizophr Bull 2017;43:972–81. https://doi.org/10.1093/schbul/sbw140.

[20] Viher PV, Stegmayer K, Bracht T, Federspiel A, Bohlhalter S, Strik W, et al. Neurological soft signs are associated with altered white matter in patients with schizophrenia. Schizophr Bull 2022;48:220–30. https://doi.org/10.1093/schbul/sbab089.

[21] Viher PV, Stegmayer K, Federspiel A, Bohlhalter S, Wiest R, Walther S. Altered diffusion in motor white matter tracts in psychosis patients with catatonia. Schizophr Res 2020;220:210–7. https://doi.org/10.1016/j.schres.2020.03.017.

[22] Lefebvre S, Pavlidou A, Walther S. What is the potential of neurostimulation in the treatment of motor symptoms in schizophrenia? Expert Rev Neurother 2020. https://doi.org/10.1080/14737175.2020.1775586.

[23] Walther S, Stegmayer K, Wilson JE, Heckers S. Structure and neural mechanisms of catatonia. Lancet Psychiatry 2019;6:610–9. https://doi.org/10.1016/S2215-0366(18)30474-7.

[24] Osborne KJ, Walther S, Shankman SA, Mittal VA. Psychomotor slowing in schizophrenia: implications for endophenotype and biomarker development. Biomarkers Neuropsych 2020. https://doi.org/10.1016/j.bionps.2020.100016.

[25] Peralta V, Cuesta MJ. Motor abnormalities: from neurodevelopmental to neurodegenerative through "functional" (neuro)psychiatric disorders. Schizophr Bull 2017;43:956–71. https://doi.org/10.1093/schbul/sbx089.

[26] Cuesta MJ, Sánchez-Torres AM, De Jalón EG, Campos MS, Ibáñez B, Moreno-Izco L, et al. Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naive patients with first-episode psychosis: a 6-month follow-up study. Schizophr Bull 2014. https://doi.org/10.1093/schbul/sbt125.

[27] Cuesta MJ, García de Jalón E, Campos MS, Moreno-Izco L, Lorente-Omeñaca R, Sánchez-Torres AM, et al. Motor abnormalities in first-episode psychosis patients and long-term psychosocial functioning. Schizophr Res 2018;200:97–103. https://doi.org/10.1016/j.schres.2017.08.050.

[28] Sambataro F, Fritze S, Rashidi M, Topor CE, Kubera KM, Wolf RC, et al. Moving forward: distinct sensorimotor abnormalities predict clinical outcome after 6 months in patients with schizophrenia. Eur Neuropsychopharmacol 2020;36:72–82. https://doi.org/10.1016/j.euroneuro.2020.05.002.

[29] Ferruccio NP, Tosato S, Lappin JM, Heslin M, Donoghue K, Giordano A, et al. Neurological signs at the first psychotic episode as correlates of long-term outcome: results from the AESOP-10 study. Schizophr Bull 2021;47:118–27. https://doi.org/10.1093/schbul/sbaa089.

[30] Putzhammer A, Perfahl M, Pfeiff L, Hajak G. Correlation of subjective well-being in schizophrenic patients with gait parameters, expert-rated motor disturbances, and psychopathological status. Pharmacopsychiatry 2005. https://doi.org/10.1055/s-2005-864125.

[31] Ascher-Svanum H, Zhu B, Faries D, Peng X, Kinon BJ, Tohen M. Tardive dyskinesia and the 3-year course of schizophrenia: results from a large, prospective, naturalistic study. J Clin Psychiatry 2008;69:1580–8. https://doi.org/10.4088/JCP.v69n1008.

[32] Mittal VA, Jalbrzikowski M, Daley M, Roman C, Bearden CE, Cannon TD. Abnormal movements are associated with poor psychosocial functioning in adolescents at high risk for psychosis. Schizophr Res 2011;130:164–9. https://doi.org/10.1016/j.schres.2011.05.007.

[33] Minichino A, Francesconi M, Carrión RE, Bevilacqua A, Parisi M, Rullo S, et al. Prediction of functional outcome in young patients with a recent-onset psychiatric disorder: beyond the traditional diagnostic classification system. Schizophr Res 2017;185:114–21. https://doi.org/10.1016/j.schres.2016.12.019.

[34] Mausbach BT, Depp CA, Bowie CR, Harvey PD, McGrath JA, Thronquist MH, et al. Sensitivity and specificity of the UCSD performance-based skills assessment (UPSA-B) for identifying functional milestones in schizophrenia. Schizophr Res 2011;132:165–70. https://doi.org/10.1016/j.schres.2011.07.022.

[35] Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry 2005;162:441–9. https://doi.org/10.1176/appi.ajp.162.3.441.

[36] Wüthrich F, Viher PV, Stegmayer K, Federspiel A, Bohlhalter S, Vanbellingen T, et al. Dysbalanced resting-state functional connectivity within the praxis network is linked to gesture deficits in schizophrenia. Schizophr Bull 2020;46:905–15. https://doi.org/10.1093/schbul/sbaa008.

[37] Walther S, Stegmayer K, Sulzbacher J, Vanbellingen T, Müri R, Strik W, et al. Nonverbal social communication and gesture control in schizophrenia. Schizophr Bull 2015;41:338–45. https://doi.org/10.1093/schbul/sbu222.

[38] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987. https://doi.org/10.1093/schbul/13.2.261.

[39] Leucht S, Samara M, Heres S, Patel MX, Furukawa T, Cipriani A, et al. Dose equivalents for second-generation antipsychotic drugs: the classical mean dose method. Schizophr Bull 2015. https://doi.org/10.1093/schbul/sbv037.

[40] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59. 0–0.

[41] Andreasen NC, Flaum M, Arndt S. The comprehensive assessment of symptoms and history (CASH): An instrument for assessing diagnosis and psychopathology. Arch gen psychiatry. 1992. https://doi.org/10.1001/archpsyc.1992.01820080023004.

[42] Barkemeyer CA, Maria MPS, Browndyke JN, Callon EB, Dunn AM. The coin rotation task: a convenient and sensitive measure of fine motor control. Arch Clin Neuropsychol 1998. https://doi.org/10.1093/arclin/13.1.18a.

[43] Walther S, Vanbellingen T, Müri R, Strik W, Bohlhalter S. Impaired pantomime in schizophrenia: association with frontal lobe function. Cortex 2013;49:520–7. https://doi.org/10.1016/J.CORTEX.2011.12.008.

[44] Fahn S. Elton RM of the UDC. The unified Parkinson's disease rating scale. Recent Dev Park Dis 1987;Vol 2.

[45] Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. I. Rating scale and standardized examination. Acta Psychiatr Scand 1996;93:129–36. https://doi.org/10.1111/j.1600-0447.1996.tb09814.x.

[46] Guy W. Abnormal Involuntary Movement Scale (117-AIMS). In: Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: National Institute of Mental Health. DHEW publication 1976;76-338:534–7.

[47] Buchanan RW, Heinrichs DW. The neurological evaluation scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res 1989;27:335–50. https://doi.org/10.1016/0165-1781(89)90148-0.

[48] Widlocher D, Ghozlan A. The measurement of retardation in depression. In: Hindmarch I, Hum Sotnier PD, editors. Psychopharmacol Meas Methods. Vol 2. Wiley; 1989.

[49] Docx L, Morrens M, Bervoets C, Hulstijn W, Fransen E, De Hert M, et al. Parsing the components of the psychomotor syndrome in schizophrenia. Acta Psychiatr Scand 2012;126:256–65. https://doi.org/10.1111/j.1600-0447.2012.01846.x.

[50] Van Harten PN, Matroos GE, Hoek HW, Kahn RS. The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia: the Curaçao extrapyramidal syndromes study: I. Schizophr Res 1996;19:195–203. https://doi.org/10.1016/0920-9964(95)00096-8.

[51] Johnson GFS, Hunt GE, Rey JM. Incidence and severity of tardive dyskinesia increase with age. Arch Gen Psychiatry 1982;39:486. https://doi.org/10.1001/archpsyc.1982.04290040080012.

[52] Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976;33:766–71. https://doi.org/10.1001/archpsyc.1976.01770060086012.

[53] Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. Am J Psychiatry 1992;149:1148–56. https://doi.org/10.1176/ajp.149.9.1148.

[54] Harvey PD, Velligan DI, Bellack AS. Performance-based measures of functional skills: usefulness in clinical treatment studies. Schizophr Bull 2007;33:1138–48. https://doi.org/10.1093/schbul/sbm040.

[55] Harvey PD, Isner EC. Cognition, social cognition, and functional capacity in early-onset schizophrenia. Child Adolesc Psychiatr Clin N Am 2020;29:171–82. https://doi.org/10.1016/j.chc.2019.08.008.

[56] Mahmood Z, Burton CZ, Vella L, Twamley EW. Neuropsychological predictors of performance-based measures of functional capacity and social skills in individuals with severe mental illness. J Psychiatr Res 2018;102:201–6. https://doi.org/10.1016/j.jpsychires.2018.04.011.

[57] Yang Z, Lee SH, Abdul Rashid NA, See YM, Dauwels J, Tan BL, et al. Predicting real-world functioning in schizophrenia: the relative contributions of neurocognition, functional capacity, and negative symptoms. Front Psych 2021;12:219. https://doi.org/10.3389/fpsyt.2021.639536.

[58] Bowie CR, Harvey PD. Cognitive deficits and functional outcome in schizophrenia. Neuropsychiatr Dis Treat 2006;2:531–6. https://doi.org/10.2147/nedt.2006.2.4.531.

[59] Mucci A, Galderisi S, Gibertoni D, Rossi A, Rocca P, Bertolino A, et al. Factors associated with real-life functioning in persons with schizophrenia in a 4-year follow-up study of the Italian network for research on psychoses. JAMA Psychiat 2021;78:550–9. https://doi.org/10.1001/jamapsychiatry.2020.4614.

[60] Lehoux C, Everett J, Laplante L, Émond C, Trépanier J, Brassard A, et al. Fine motor dexterity is correlated to social functioning in schizophrenia. Schizophr Res 2003;62:269–73. https://doi.org/10.1016/S0920-9964(02)00327-4.

[61] Morrens M, Hulstijn W, Sabbe B. Psychomotor slowing in schizophrenia. In: Schizophr. Bull. vol. 33. Schizophr Bull; 2007. p. 1038–53. https://doi.org/10.1093/schbul/sbl051.

[62] Bervoets C, Docx L, Sabbe B, Vermeylen S, Van Den Bossche MJ, Morsel A, et al. The nature of the relationship of psychomotor slowing with negative symptomatology in schizophrenia. Cogn Neuropsychiatry 2014;19:36–46. https://doi.org/10.1080/13546805.2013.779578.

[63] Docx L, Sabbe B, Fransen E, Bervoets C, Hulstijn W, Van Den Bossche MJA, et al. Longitudinal evaluation of the psychomotor syndrome in schizophrenia. J Neuropsychiatry Clin Neurosci 2014;26:359–68. https://doi.org/10.1176/appi.neuropsych.13020027.

[64] Térémetz M, Carment L, Brénugat-Herne L, Croca M, Bleton JP, Krebs MO, et al. Manual dexterity in schizophrenia-a neglected clinical marker? Front Psych 2017;8:120. https://doi.org/10.3389/fpsyt.2017.00120.

[65] Quinn J, Meagher D, Murphy P, Kinsella A, Mullaney J, Waddington JL. Vulnerability to involuntary movements over a lifetime trajectory of schizophrenia approaches 100%, in association with executive (frontal) dysfunction. Schizophr Res 2001;49:79–87. https://doi.org/10.1016/S0920-9964(99)00220-0.

[66] Waddington JL, Youssef HA, Dolphin C, Kinsella A. Cognitive dysfunction, negative symptoms, and tardive dyskinesia in schizophrenia: their association in relation to topography of involuntary movements and criterion of their abnormality. Arch Gen

Psychiatry 1987;44:907–12. https://doi.org/10.1001/archpsyc.1987.01800220077011.
[67] Whitty P, Clarke M, McTigue O, Browne S, Gervin M, Kamali M, et al. Diagnostic specificity and predictors of neurological soft signs in schizophrenia, bipolar disorder and other psychoses over the first 4 years of illness. Schizophr Res 2006;86:110–7. https://doi.org/10.1016/j.schres.2006.04.012.
[68] White C, Stirling J, Hopkins R, Morris J, Montague L, Tantam D, et al. Predictors of 10-year outcome of first-episode psychosis. 2021. https://doi.org/10.1017/S003329170800514X.
[69] Behere RV. Dorsolateral prefrontal lobe volume and neurological soft signs as predictors of clinical social and functional outcome in schizophrenia: a longitudinal study. Indian J Psychiatry 2013;55:111–6. https://doi.org/10.4103/0019-5545.111445.
[71] Morgan C, Dazzan P, Lappin J, Heslin M, Donoghue K, Fearon P, et al. Rethinking the course of psychotic disorders: modelling long-term symptom trajectories. Psychol Med 2021:1–10. https://doi.org/10.1017/S0033291720004705.
[72] Bachmann S, Bottmer C, Schröder J. Neurological soft signs in first-episode schizophrenia: a follow-up study. Am J Psychiatry 2005;162:2337–43. https://doi.org/10.1176/appi.ajp.162.12.2337.
[73] Bachmann S, Degen C, Geider FJ, Schröder J. Neurological soft signs in the clinical course of schizophrenia: results of a meta-analysis. Front Psych 2014;5. https://doi.org/10.3389/fpsyt.2014.00185.
[74] Kong L, Bachmann S, Thomann PA, Essig M, Schröder J. Neurological soft signs and gray matter changes: a longitudinal analysis in first-episode schizophrenia. Schizophr Res 2012;134:27–32. https://doi.org/10.1016/j.schres.2011.09.015.
[75] Galderisi S, Rossi A, Rocca P, Bertolino A, Mucci A, Bucci P, et al. The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. World Psychiatry 2014;13:275–87. https://doi.org/10.1002/wps.20167.
[76] Kao YC, Liu YP, Chou MK, Cheng TH. Subjective quality of life in patients with chronic schizophrenia: relationships between psychosocial and clinical characteristics. Compr Psychiatry 2011;52:171–80. https://doi.org/10.1016/j.comppsych.2010.05.008.
[77] Peralta V, de Jalón EG, Campos MS, Cuesta MJ. Covariation between motor signs and negative symptoms in drug-naive subjects with schizophrenia-spectrum disorders before and after antipsychotic treatment. Schizophr Res 2018;200:85–91. https://doi.org/10.1016/J.SCHRES.2017.08.039.
[78] Mittal VA, Dean DJ, Bernard JA, Orr JM, Pelletier-Baldelli A, Carol EE, et al. Neurological soft signs predict abnormal cerebellar-thalamic tract development and negative symptoms in adolescents at high risk for psychosis: a longitudinal perspective. Schizophr Bull 2014;40:1204–15. https://doi.org/10.1093/schbul/sbt199.
[79] Chan RCK, Geng F, Lui SSY, Wang Y, Ho KKY, Hung KSY, et al. Course of neurological soft signs in first-episode schizophrenia: relationship with negative symptoms and cognitive performances. Sci Reports 2015 2015;51(5):1–11. https://doi.org/10.1038/srep11053.
[80] Peralta V, Cuesta MJ. Negative, parkinsonian, depressive and catatonic symptoms in schizophrenia: a conflict of paradigms revisited. Schizophr Res 1999;40:245–53. https://doi.org/10.1016/S0920-9964(99)00047-X.
[81] Carment L, Dupin L, Guedj L, Térémetz M, Krebs MO, Cuenca M, et al. Impaired attentional modulation of sensorimotor control and cortical excitability in schizophrenia. Brain 2019;142:2149–64. https://doi.org/10.1093/brain/awz127.
[82] Ventura J, Hellemann GS, Thames AD, Koellner V, Nuechterlein KH. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. Schizophr Res 2009;113:189–99. https://doi.org/10.1016/j.schres.2009.03.035.
[83] Fervaha G, Foussias G, Agid O, Remington G. Motivational deficits in early schizophrenia: prevalent, persistent, and key determinants of functional outcome. Schizophr Res 2015;166:9–16. https://doi.org/10.1016/j.schres.2015.04.040.
[84] Green MF, Horan WP, Lee J. Social cognition in schizophrenia. Nat Rev Neurosci 2015;16:620–31. https://doi.org/10.1038/NRN4005.
[85] Walther S, Eisenhardt S, Bohlhalter S, Vanbellingen T, Müri R, Strik W, et al. Gesture performance in schizophrenia predicts functional outcome after 6 months. Schizophr Bull 2016;42:1326–33. https://doi.org/10.1093/schbul/sbw124.
[86] Ceraso A, Lin JJ, Schneider-Thoma J, Siafis S, Tardy M, Komossa K, et al. Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev 2020;2020. https://doi.org/10.1002/14651858.CD008016.pub3.
[87] Leucht S, Leucht C, Huhn M, Chaimani A, Mavridis D, Helfer B, et al. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. Am J Psychiatry 2017;174:927–42. https://doi.org/10.1176/appi.ajp.2017.16121358.
[88] Ventura J, Subotnik KL, Gretchen-Doorly D, Casaus L, Boucher M, Medalia A, et al. Cognitive remediation can improve negative symptoms and social functioning in first-episode schizophrenia: a randomized controlled trial. Schizophr Res 2019;203:24–31. https://doi.org/10.1016/j.schres.2017.10.005.
[89] Mueller DR, Khalesi Z, Benzing V, Castiglione CI, Roder V. Does integrated neurocognitive therapy (INT) reduce severe negative symptoms in schizophrenia outpatients? Schizophr Res 2017;188:92–7. https://doi.org/10.1016/j.schres.2017.01.037.
[90] Walther S, Alexaki D, Schoretsanitis G, Weiss F, Vladimirova I, Stegmayer K, et al. Inhibitory repetitive transcranial magnetic stimulation to treat psychomotor slowing: a transdiagnostic, mechanism-based randomized double-blind controlled trial. Schizophr Bull Open 2020;1. https://doi.org/10.1093/schizbullopen/sgaa020.
[91] Walther S, Kunz M, Müller M, Zürcher C, Vladimirova I, Bachofner H, et al. Single session transcranial magnetic stimulation ameliorates hand gesture deficits in schizophrenia. Schizophr Bull 2020;46:286–93. https://doi.org/10.1093/schbul/sbz078.