

# Testing a Motor Score Based on PANSS Ratings: A Proxy for Comprehensive Motor Assessment

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**Background and Hypothesis:** Abnormal psychomotor behavior is a core schizophrenia symptom. However, assessment of motor abnormalities with expert rating scales is challenging. The Positive and Negative Syndrome Scale (PANSS) includes 3 items broadly related to hypokinetic motor behavior. Here, we tested whether a sum score of the PANSS items mannerisms and posturing (G5), motor retardation (G7), and disturbance of volition (G13) corresponds to expert ratings, potentially qualifying as a proxy-marker of motor abnormalities. **Study Design:** Combining baseline datasets ( $n = 196$ ) of 2 clinical trials (OCoPS-P, BrAGG-SoS), we correlated PANSS motor score (PANSS<sub>mot</sub>) and 5 motor rating scales. In addition, we tested whether the cutoff set at  $\geq 3$  on each PANSS motor item, ie, “mild” on G05, G07, and G13 (in total  $\geq 9$  on PANSS<sub>mot</sub>) would differentiate the patients into groups with high vs low scores in motor scales. We further sought for replication in an independent trial (RESIS,  $n = 102$ ), tested the longitudinal stability using week 3 data of OCoPS-P ( $n = 75$ ), and evaluated the validity of PANSS<sub>mot</sub> with instrumental measures of physical activity ( $n = 113$ ). **Study Results:** PANSS<sub>mot</sub> correlated with all motor scales (Spearman-Rho-range 0.19–0.52, all  $P \leq .007$ ). Furthermore, the cutoff set at  $\geq 3$  on each

PANSS motor item was able to distinguish patients with high vs low motor scores in all motor scales except using Abnormal Involuntary Movement Scale (Mann-Whitney-U-Tests: all  $U \geq 580$ ,  $P \leq .017$ ). **Conclusions:** Our findings suggest that PANSS<sub>mot</sub> could be a proxy measure for hypokinetic motor abnormalities. This might help to combine large datasets from clinical trials to explore whether some interventions may hold promise to alleviate hypokinetic motor abnormalities in psychosis.

**Key words:** schizophrenia/psychosis/motor abnormalities/hypokinetic motor disorders/psychopathology/clinical research

## Introduction

Schizophrenia affects approximately 1% of the general population.<sup>1</sup> It is characterized by 8 symptom dimensions, including (1) hallucinations, (2) delusions, (3) negative symptoms, (4) disorganized speech, (5) cognition, (6) depression, (7) mania, and (8) abnormal psychomotor behaviors.<sup>2</sup>

Motor abnormalities have been reported across all stages of schizophrenia spectrum disorders.<sup>3–5</sup> At least

1 motor symptom was observed in drug-naïve first episode psychosis (66%), at hospital admission (59%), and in chronic patients (80%).<sup>3,6,7</sup> Abnormal psychomotor behaviors are associated with lower subjective well-being, poor social functioning, and lower quality of life.<sup>8</sup> Importantly, studies demonstrate that motor abnormalities have predictive value for clinical and functional outcomes.<sup>9–12</sup> Furthermore, hand gestures that are crucial for social interaction are affected by motor abnormalities contributing to stigmatization.<sup>13–15</sup> In sum, motor abnormalities are important sources of information on the course of schizophrenia and might become valuable treatment targets.

Nevertheless, in large-scale studies on the longitudinal course of schizophrenia or in treatment studies, little attention is paid to the assessment of motor symptoms. In prospective trials, motor assessment is often limited to single constructs, such as neurological soft signs, dyskinesia, parkinsonism, or akathisia,<sup>10,16,17</sup> whereas dystonia, catatonia, or psychomotor slowing are not investigated. Comprehensive clinical assessment of multiple motor constructs is time-consuming. Given the interest in motor signs and the longitudinal changes of motor symptoms, it would be most effective to analyze large datasets with a proxy measure of motor abnormalities. Ideally, one would be able to calculate a motor score from existing longitudinal ratings of psychopathology, such as the Positive and Negative Syndrome Scale (PANSS).<sup>18</sup>

The PANSS has been frequently used in schizophrenia treatment trials and observational studies. Single PANSS items cover some hypokinetic motor abnormalities, ie, G5 “mannerisms and posturing,” G7 “motor retardation,” and G13 “disturbance of volition.” Item G5 mannerisms and posturing assesses unnatural, awkward, stilted, disorganized, or bizarre body movements or posture, which tap into catatonia symptoms.<sup>19</sup> Item G7 “motor retardation” summarizes reduced motor activity expressed in slow or low-amplitude movements as well as slowed speech, decreased response to stimuli, and poor body tone. This item references to psychomotor slowing.<sup>20</sup> Item G13 “disturbance of volition” involves disruptions in deliberate initiation, maintenance, and regulation of one’s thoughts, behavior, movements, and speech. G13 also taps into core catatonia signs, such as verbigeration, perseveration, or ambitendency. Albeit these items span multiple symptom domains such as disorganization or abnormal psychomotor behavior, they tap predominantly into hypokinetic motor abnormalities, ie, catatonia and psychomotor slowing.<sup>19–21</sup> Studies probing the external validity of single PANSS items to characterize psychomotor abnormalities demonstrated insufficient validity with instrumental measures or brain imaging.<sup>22,23</sup> Alternatively, we sought to test the sum of 3 PANSS motor items creating a PANSS motor score (PANSS<sub>mot</sub>) for hypokinetic motor abnormalities, which may provide better external validity than single items. Similarly, PANSS items P04

“excitement” and G14 “poor impulse control” potentially capture hyperkinetic motor abnormalities, such as dyskinesia, catatonia, or akathisia.<sup>24</sup> Thus, the 2 items could be summarized to a hyperkinetic PANSS<sub>mot</sub>.

Here, we leverage existing well-characterized datasets to test whether a PANSS hypokinetic motor score summing G05, G07, and G13 was associated with expert ratings of motor abnormalities and could be established as a proxy-marker for motor abnormalities. We expect that subjects with high PANSS<sub>mot</sub> scores will have more severe hypokinetic movement disorders, such as catatonia, psychomotor retardation, and parkinsonism. Furthermore, we hypothesize that instrumentally assessed physical activity levels are correlating with PANSS<sub>mot</sub>. Given that participants in these studies were predominantly presenting with hypokinetic motor abnormalities or negative symptoms, we primarily tested the PANSS<sub>mot</sub> on hypokinetic behaviors. In addition, we tested a hyperkinetic motor score from P04 and G14 but expected weak associations with motor rating scales within the existing datasets.

## Methods

### Participants

The current report consists of multiple datasets. The main analysis was based on the baseline data of  $n = 196$  patients, who were recruited in the context of 2 randomized clinical trials, ie, OCoPS-P: *Overcoming Psychomotor Slowing in Psychosis* (ClinicalTrials.gov Identifier: NCT03921450)<sup>11,25–31</sup> and BrAGG-SoS: *Brain stimulation and Group therapy to improve Gesture and Social skills in Psychosis* (ClinicalTrials.gov Identifier: NCT04106427)<sup>32–34</sup> at the in- and outpatient departments of the University Hospital of Psychiatry and Psychotherapy, Bern, Switzerland (hereafter referred to as Bern-sample). All patients were diagnosed with schizophrenia spectrum disorders according to the Structured Clinical Interview for DSM-5 (SCID-5) and they provided written informed consent after receiving a complete description of the study. Both studies complied with the Declaration of Helsinki and were approved by the Bern Ethics Committee (OCoPS-P BASEC-Nr: 2018-02164; BrAGG-SoS BASEC-Nr: 2019-00798). General exclusion criteria included active substance dependence other than nicotine, neurological disorders compromising motor behavior, and traumatic brain injury. Most of the patients were on antipsychotic medication during data acquisition and the mean olanzapine equivalents were computed according to Leucht et al.<sup>35</sup> Assessments were performed by psychiatry residents in training with more than 2 years of experience. All raters were trained by the senior author with regular checks of interrater agreement. All assessments were performed in 1 baseline session including psychopathology and specific motor rating scales.

Furthermore, another dataset was used for independent validation. We included baseline data from the clinical trial RESIS: *Repetitive Transcranial Magnetic Stimulation for the Treatment of Negative Symptoms in Schizophrenia* (ClinicalTrials.gov Identifier: NCT00783120; approved by the Ethic Board of the University Medical Center Göttingen (approval number: 23/11/06)).<sup>36</sup> For this study a total of 175 patients were screened and 157 patients completed the baseline (day 0). Patients diagnosed with schizophrenia according to ICD-10 and Mini-International Neuropsychiatric Interview Plus interview<sup>37</sup> with predominant negative symptoms were enrolled in this trial. Additional inclusion criteria were stable antipsychotic medication for at least 2 weeks and a minimum illness duration of 1 year. Chlorpromazine equivalents according to Woods<sup>38</sup> are provided in [table 1](#). Recruitment and data collection were conducted at 3 German university hospital centers, ie, Göttingen, Düsseldorf, and Regensburg (for further information, see Ref. 36). From this sample, we analyzed the data of  $n = 102$  patients completing the PANSS and St. Hans Rating Scale (SHRS) assessments.<sup>39</sup> In this study, PANSS raters were trained by reviewing standardized videotaped interviews.

### Measures

**PANSS and PANSS<sub>mot</sub>** Psychopathology was assessed with the PANSS.<sup>18</sup> We created a PANSS<sub>mot</sub> defined as the sum of the items mannerisms and posturing (G05), motor retardation (G07), and disturbance of volition (G13). The cutoff was set at  $\geq 3$  points (“mild”) on each of the items: G05, G07, and G13. Every patient scoring  $\geq 3$  points on each of these 3 items (total  $\geq 9$  points) was categorized as presenting motor abnormalities. As these 3 items mainly describe hypokinetic motor abnormalities, we performed a second set of analyses on PANSS items describing hyperkinetic motor abnormalities, ie, (P04) excitement and (G14) poor impulse control.

**Motor Abnormalities and Expert Rating Scales** We assessed a range of motor abnormalities using expert rating scales, ie, (1) catatonia using Bush-Francis Catatonia Rating Scale (BFCRS) and Northoff Catatonia Rating Scale (NCRS), (2) parkinsonism using Unified Parkinson’s Disease Rating Scale Part III (UPDRS), (3) psychomotor slowing using Salpêtrière Retardation Rating Scale (SRRS), (4) neurological soft signs using Neurological Evaluation Scale (NES), and (5) dyskinesia using Abnormal Involuntary Movement Scale (AIMS).<sup>40–45</sup>

In RESIS, motor abnormalities were assessed using the SHRS, which provides 9 subscores, ie, objective akathisia, subjective akathisia, dystonia, parkinsonism total, parkinsonism global, active dyskinesia total, active

dyskinesia global, passive dyskinesia total, and passive dyskinesia global.<sup>39</sup>

**Longitudinal Stability in OCoPS-P Study** We investigated the longitudinal stability of correlations between PANSS<sub>mot</sub> and motor abnormalities using week 3 data ( $n = 75$ )<sup>mot</sup> of OCoPS-P.<sup>25</sup> In this randomized, placebo-controlled, double-blinded, 4-arm study, we investigated the effect of add-on repetitive transcranial magnetic stimulation on psychomotor slowing. After 3 weeks of daily treatment, patients completed a series of assessments, including psychopathology assessments comprising PANSS and different motor rating scales (BFCRS, UPDRS, SRRS, and AIMS).

**External Validity with Actigraphy** Gross motor behavior was captured by wearing the tri-axial-accelerometer Move4 (movisens GmbH, Karlsruhe, Germany) on the non-dominant hand. Physical activity levels of waking hours were used for the current analysis by including the baseline data of  $n = 113$  patients from OCoPS-P. For further information, see Refs. 22,31.

### Analysis

All analyses were computed using IBM SPSS Statistics (v29.0.0.0). First, we conducted the main analysis in the Bern-sample. We created 2 groups, ie, high vs low PANSS<sub>mot</sub>, by setting the cutoff at total  $\geq 9$  points, with at least  $\geq 3$  points (“mild”) on each of the following items: G05 mannerisms and posturing, G07 motor retardation, and G13 disturbance of volition. Employing Mann-Whitney-U-Tests, we tested for group differences in motor rating scales, ie, BFCRS, NCRS, UPDRS, SRRS, NES, and AIMS. In addition, we investigated the associations between PANSS<sub>mot</sub> and motor rating scales, including their subscores, ie, BFCRS, NCRS, NCRS affect, NCRS motor, NCRS behavior, UPDRS, SRRS, NES, and AIMS using Spearman correlations. The results of NES subscores are reported in [supplementary tables S1 and S3](#).

Furthermore, we explored how well PANSS<sub>mot</sub> was able to predict the catatonia caseness based on DSM-5 as well as BFCRS criteria using logistic regressions, while controlling for age and current daily dosage of antipsychotic medication. For the DSM-5 diagnosis of catatonia, the presence of 3 or more of the following items is required, ie, catalepsy, waxy flexibility, stupor, agitation, mutism, negativism, posturing, mannerisms, stereotypies, grimacing, echolalia, and echopraxia.<sup>46</sup> BFCRS, on the other hand, requires only the presence of 2 items of the first 14 items of BFCRS for catatonia case definition.<sup>41</sup> Moreover, we analyzed the effectiveness of PANSS<sub>mot</sub> in predicting the catatonia categorization using ROC-curves. We chose to do this analysis only for the motor abnormality catatonia, since there are clear and validated criteria for the diagnosis of catatonia.<sup>19,21</sup>



**Table 1.** Demographic and Clinical Data of the Different Studies

Study	Bern-sample		OCoPS-P		BrAGG-SoS		RESIS		Comparability OCoPS-P, BrAGG- SoS, and RESIS	
	196		125		71		102		Test	P
	N	%	N	%	N	%	N	%		
Number of females (%)	91	46.4	61	48.8	30	42.3	25	24.5	$\chi^2_{(2, N=298)} = 14.4$	.001
Number of inpatients	123	62.8	114	92.8	9	12.7				
No information about antipsychotics	0	0	0	0	0	0	4	3.9	$\chi^2_{(2, N=298)} = 7.8$	.020
Patients with no antipsychotics (n)	10	5.1	3	2.4	7	9.9	1	1.0	$\chi^2_{(2, N=294)} = 10.0$	.007
Monotherapy (n)	90	45.9	61	48.8	29	40.8	23	22.5	$\chi^2_{(2, N=294)} = 15.1$	<.001
Combination therapy with other antipsychotics (n)	34	17.3	29	23.2	5	7.0	22	21.6	$\chi^2_{(2, N=294)} = 8.8$	.012
Combination therapy with other medication <sup>a</sup> (n)	42	21.4	19	15.2	23	32.4	18	17.6	$\chi^2_{(2, N=294)} = 8.6$	.013
Combination therapy with other antipsychotics and medication <sup>a</sup> (n)	20	10.2	13	10.4	7	9.9	34	33.3	$\chi^2_{(2, N=294)} = 26.1$	<.001
Patients with Clozapine-intake (n)	45	23.0	25	20.0	20	28.2	17	16.7	$\chi^2_{(2, N=294)} = 3.1$	.217
Patients with antiparkinsonian medication-intake (n)	1	0.5	0	0	1	1.4	12	11.8	$\chi^2_{(2, N=294)} = 21.5$	<.001
FGA (n)	10	5.1	8	6.4	2	2.8	0	0	$\chi^2_{(2, N=294)} = 6.9$	.031
SGA (n)	155	79.1	98	78.4	57	80.2	74	72.5	$\chi^2_{(2, N=294)} = 0.6$	.749
FGA and SGA (n)	21	10.7	16	12.8	5	7.0	23	22.5	$\chi^2_{(2, N=294)} = 9.5$	.009
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Olanzapine equivalents. in mg	14.6	11.2	16.0	11.3	12.2	10.7	14.5	11.5	$F_{(2, 291)} = 2.6$	.079
Chlorpromazine equivalents. in mg							565	446		
Age in years	37.7	12.5	36.2	12.6	40.3	12.0	34.9	9.3	$F_{(2, 295)} = 5.0$	.008
BMI in kg/m <sup>2</sup>	26.0	5.3	25.1	5.0	27.6	5.6	28.8	6.8	$F_{(2, 269)} = 11.1$	<.001
Duration of illness in years	12.4	11.8	10.3	10.8	16.0	12.5	9.8	9.1	$F_{(2, 271)} = 7.8$	<.001
Number of episodes	5.9	7.2	5.0	6.6	7.5	7.9	5.3 <sup>b</sup>	5.5 <sup>b</sup>	$F_{(2, 262)} = 3.2$	.042
PANSS total	73.0	20.6	77.6	17.9	64.7	22.6	78.9	15.0	$F_{(2, 295)} = 14.9$	<.001
PANSS positive	15.3	5.7	16.2	5.3	13.7	6.0	13.7	4.2	$F_{(2, 295)} = 8.2$	<.001
PANSS negative	20.7	7.4	22.1	6.7	18.2	7.9	25.8	4.4	$F_{(2, 295)} = 30.1$	<.001
PANSS motor score (G5 + G7 + G13)	7.2	3.1	7.8	3.1	6.2	2.8	7.2	2.3	$F_{(2, 295)} = 7.9$	<.001
BFCRS total	4.4	4.6	5.0	4.4	3.5	4.8			$t(194) = -2.2$	.028
NCRS total	8.8	5.2	8.8	5.2						
UPDRS total	16.5	11.1	18.6	11.5	12.8	9.1			$t(174) = -3.9$	<.001
SRRS total	19.4	9.0	20.6	8.5	17.0	9.6			$t(125) = -2.6$	.010
NES total	14.6	9.5	14.4	9.6	15.1	9.2			$t(187) = 0.5$	.622
AIMS total	1.1	2.7	0.8	2.1	1.6	3.5			$t(99) = 1.7$	.101
SHRS Akathisia subjective							0.7	1.3		
SHRS Akathisia objective							0.5	1.0		
SHRS Dystonia							0.1	0.4		
SHRS Parkinsonism total							3.0	4.7		
SHRS Parkinsonism global							0.5	0.8		
SHRS passive Dyskinesia total							0.6	1.7		
SHRS passive Dyskinesia global							0.1	0.4		
SHRS active Dyskinesia total							0.5	1.6		
SHRS active Dyskinesia global							0.1	0.3		

Note: BMI, body mass index; FGA, first-generation antipsychotics; SGA, second-generation antipsychotics; PANSS, Positive and Negative Syndrome Scale; BFCRS, Bush-Francis Catatonia Rating Scale; NCRS, Northoff Catatonia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale Part III; SRRS, Salpêtrière Retardation Rating Scale; NES, Neurological Evaluation Scale; AIMS, Abnormal Involuntary Movement Scale; SHRS, St. Hans Rating Scale.

<sup>a</sup>Other medication such as benzodiazepines, antidepressants, and antiepileptics.

<sup>b</sup>Number of inpatient treatments.

Next, we tested these associations in an independent dataset (RESIS), by correlating PANSS<sub>mot</sub> with the 9 subscores of SHRS using Spearman correlations.

In addition, we tested the longitudinal stability of the associations between PANSS<sub>mot</sub> and the motor scales

BFCRS, UPDRS, SRRS, and AIMS using week 3 behavioral data of OCoPS-P. Finally, we verified the external validity by computing Spearman correlations between PANSS<sub>mot</sub> and actigraphic physical activity levels using OCoPS-P baseline data.

As sensitivity analyses, we checked for possible differences in PANSS<sub>mot</sub> between patients receiving first generation vs second<sub>mot</sub> generation antipsychotics with Mann-Whitney-U-Tests in the Bern-sample. Moreover, we tested the correlation of olanzapine equivalents on PANSS<sub>mot</sub>. Furthermore, we conducted further sensitivity analysis by correlating PANSS<sub>mot</sub> with the PANSS subscores, ie, PANSS total, PANSS positive, PANSS negative, and additionally PANSS general excluding the 3 PANSS motor items. Finally, we tested whether a score of 2 items (P04 and G14) would reflect hyperkinetic motor abnormalities by applying the same Spearman correlations with motor rating scales and actigraphy. These results are reported in supplements. All analyses were corrected for multiple comparisons using FDR-correction, except for the logistic regressions and ROC-curves.

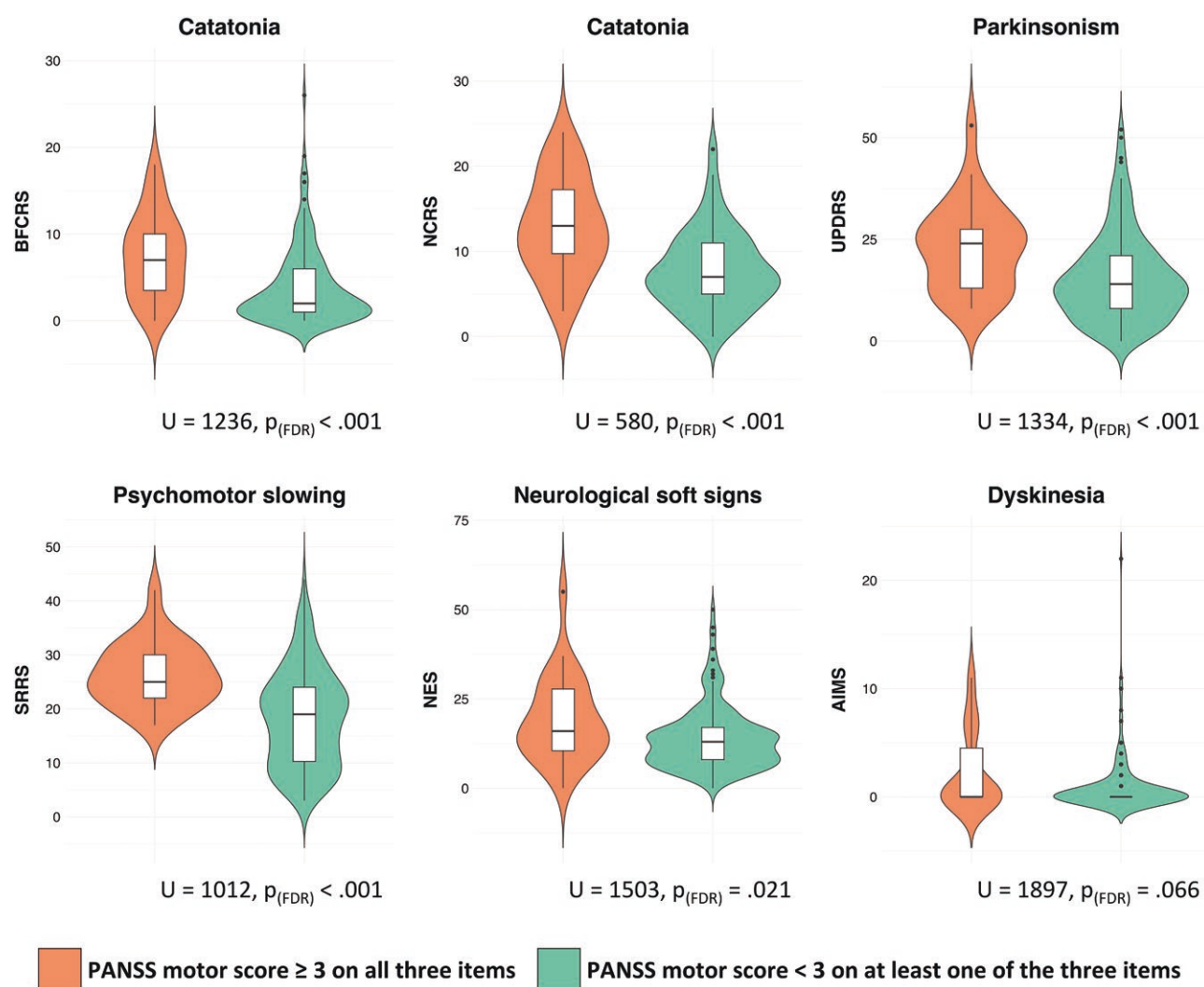
## Results

### Demographic and Clinical Information

The Bern-sample consisted of patients with moderate to severe psychopathology, including pronounced motor symptoms. Mean age was  $37.7 \pm 12.5$  years and mean duration of illness was  $12.4 \pm 11.8$  years. All but 10 subjects were on antipsychotics. Table 1 gives more information.

### High vs Low PANSS<sub>mot</sub> in the Bern-Sample

Mann-Whitney-U-tests revealed that the cutoff set at 3 points on each PANSS motor item was able to distinguish between low and high motor scores in all motor rating scales (all  $U \geq 580$ ,  $P \leq .017$ ,  $P_{(FDR)} \leq .021$ ) excluding AIMS (see figure 1, supplementary tables S1 and S2).



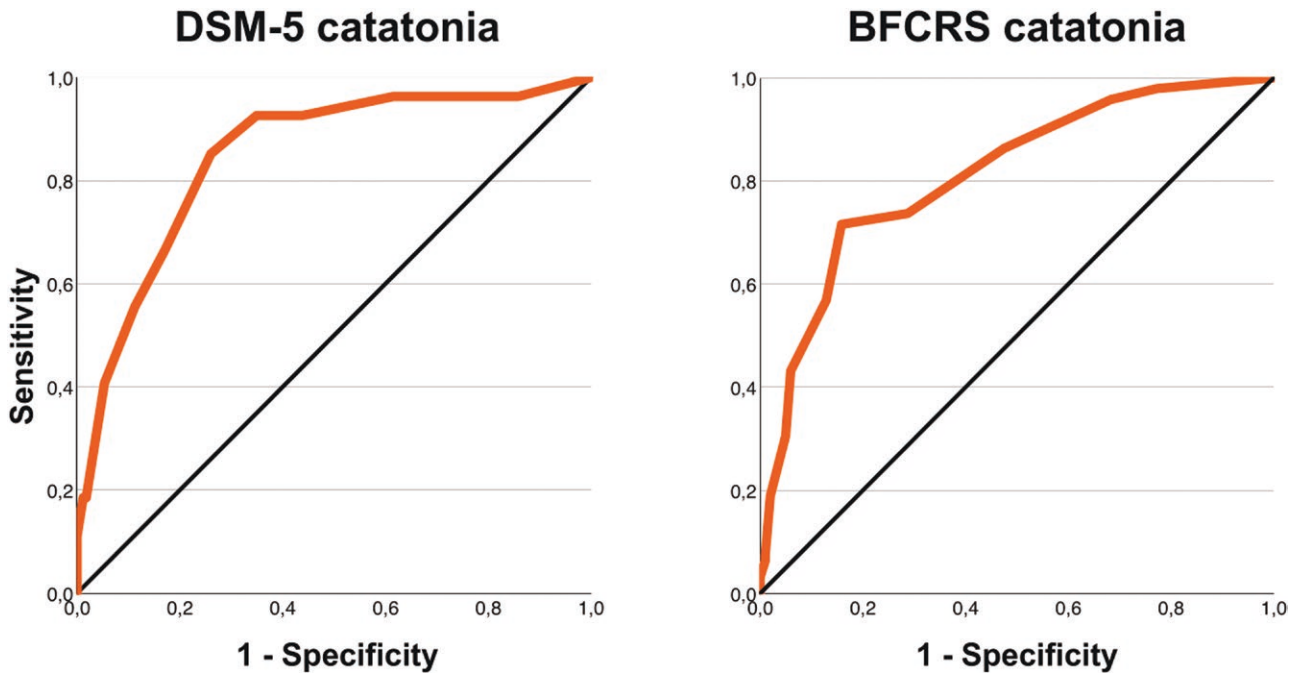
**Fig. 1.** Difference in motor rating scales based on PANSS motor score in the Bern-sample.

*Note:* The categorization of patients into high and low PANSS motor score resulted in differences especially in hypokinetic motor abnormalities catatonia, parkinsonism, and psychomotor slowing. Within the boxplots, the lower and upper whiskers represent the minimum/lowest value and the maximum/highest value, respectively. Dots are outliers. The box displays the interquartile range between 1 and 3 quartile. The middle line inside the box is the median.

**Table 2.** Correlations Between PANSS Motor Score and Motor Rating Scales in the Bern-Sample

		BFCRS	NCRS	NCRSm	NCRSb	NCRSa	UPDRS	SRRS	NES	AIMS
PANSS <sub>mot</sub>	Rho	0.52	0.67	0.57	0.47	0.57	0.48	0.69	0.34	0.19
	$P_{(FDR)}$	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	.007

Note: Displayed are Spearman-Rho-values. PANSS, Positive and Negative Syndrome Scale; PANSS<sub>mot</sub>, PANSS motor score; BFCRS, Bush-Francis Catatonia Rating Scale; NCRS, Northoff Catatonia Rating Scale; NCRSm, NCRS motor; NCRSb, NCRS behavior; NCRSa, NCRS affect; UPDRS, Unified Parkinson’s Disease Rating Scale Part III; SRRS, Salpêtrière Retardation Rating Scale; NES, Neurological Evaluation Scale; AIMS, Abnormal Involuntary Movement Scale.



**Fig. 2.** ROC-curves catatonia.

Note: The effectiveness of PANSS<sub>mot</sub> in predicting patients with catatonia vs without catatonia.

*Association Between PANSS<sub>mot</sub> and Motor Rating Scales in the Bern-Sample*

Spearman correlations revealed that the PANSS<sub>mot</sub> was associated most strongly with hypokinetic motor abnormalities (all  $Rho \geq 0.48$ ,  $P < .001$ ,  $P_{(FDR)} < .001$ , see [supplementary figures S1–S5](#)). In contrast, hyperkinetic motor abnormalities and coordination had lower correlation values (see [table 2](#) AIMS and NES, [supplementary table S3](#) NES subscores). Sensitivity analyses indicated no significant association between PANSS<sub>mot</sub> and current daily dosage of antipsychotics or class of antipsychotics (see [supplementary material](#)). Furthermore, PANSS<sub>mot</sub> had higher correlation coefficients with motor rating scales than the PANSS positive or general subscore (see [supplementary table S4](#)). Finally, PANSS<sub>mot</sub> correlated with PANSS negative ( $Rho = 0.65$ ,  $P_{(FDR)} < .001$ ) and PANSS general ( $Rho = 0.50$ ,  $P_{(FDR)} < .001$ ) (see [supplementary tables S5–S6](#)).

*Logistic Regressions and ROC-Curves for Catatonia in the Bern-Sample*

PANSS<sub>mot</sub> predicted catatonia according to DMS-5 and BFCRS criteria with an accuracy of 87.8% (Wald- $\chi^2 = 26.3$ ,  $df = 1$ ,  $P < .001$ ) and 76.0% (Wald- $\chi^2 = 42.8$ ,  $df = 1$ ,  $P < .001$ ), respectively, while controlling for age and current daily dosage of antipsychotic medication. The analysis on the effectiveness of PANSS<sub>mot</sub> in predicting the categorization into patients with catatonia vs without catatonia according to DSM-5 as well as BFCRS indicated an AUC of 0.847 and 0.811, respectively (see [figure 2](#)).

*Replication: PANSS<sub>mot</sub> in RESIS*

This analysis is based on the baseline data of patients ( $n = 102$ ) who completed PANSS and SHRS assessments at day 0. Demographic and clinical information is depicted in [table 1](#). In this sample, PANSS<sub>mot</sub> correlated only

**Table 3.** Correlations Between PANSS Motor Score and Subscores of the St. Hans Rating Scale in RESIS

		AKA s	AKA o	DYT	PAR t	PAR g	DYK ta	DYK ga	DYK tp	DYK gp
PANSS <sub>mot</sub>	Rho	0.05	0.04	0.02	0.22	0.28	0.05	0.04	0.03	0.07
	<i>P</i> -value	.619	.684	.822	.024	.005	.625	.670	.727	.473
	<i>P</i> <sub>(FDR)</sub>	.818	.818	.822	.107	.042	.818	.818	.818	.818

Note: Displayed are Spearman-Rho-values. PANSS, Positive and Negative Syndrome Scale; PANSS<sub>mot</sub>, PANSS motor score; AKA s, Akathisia subjective; AKA o, Akathisia objective; DYT, Dystonia; PAR t, Parkinsonism total; PAR g, Parkinsonism global; DYK ta, Dyskinesia total active; DYK ga, Dyskinesia global active; DYK tp, Dyskinesia total passive; DYK gp, Dyskinesia global passive.

with the SHRS subscores parkinsonism total and parkinsonism global (see [table 3](#)).

#### Longitudinal Stability: PANSS<sub>mot</sub> in OCoPS-P at Week 3

A total of 75 patients of OCoPS-P completed PANSS and motor assessments at week 3. Descriptives are given in [supplementary table S7](#). Analyses at week 3 revealed strong correlations between PANSS<sub>mot</sub> and catatonia, parkinsonism, and psychomotor slowing (Spearman-Rho range 0.31–0.65,  $P \leq .007$ ,  $P_{(FDR)} \leq .009$ ). The correlation between PANSS<sub>mot</sub> and dyskinesia was the weakest (Rho = 0.26,  $P = .023$ ,  $P_{(FDR)} = .023$ ).

#### External Validity: PANSS<sub>mot</sub> and Physical Activity Levels in OCoPS-P

A total of 113 patients of OCoPS-P wore wrist-actigraphs during baseline assessments. Higher PANSS<sub>mot</sub> was associated with lower physical activity levels (Rho =  $-0.44$ ,  $P < .001$ ,  $P_{(FDR)} < .001$ ). Moreover, Mann-Whitney-U-tests indicated that patients with high vs low PANSS<sub>mot</sub> differed in physical activity levels,  $U = 539$ ,  $P = .007$ . Activity levels were inversely correlated with PANSS negative (Rho =  $-0.54$ ,  $P < .001$ ,  $P_{(FDR)} < .001$ ) and PANSS total (Rho =  $-0.31$ ,  $P < .001$ ,  $P_{(FDR)} = .002$ ), but not with PANSS positive or general score omitting the 3 PANSS motor items G5, G7, and G13 (see [supplementary table S8](#)).

#### Sensitivity Analyses: PANSS Hyperkinetic Score and Motor Ratings

Addition of either P04 or G14 to the PANSS<sub>mot</sub> failed to increase the correlation values with motor rating scales or actigraphy (see [supplementary tables S9 and S10](#)) When a separate hyperkinetic PANSS<sub>mot</sub> was computed summing P04 and G14, correlations were low and insignificant, except for the BFCRS ( $r = 0.21$ ) and NCRS affect ( $r = 0.26$ ) (see [supplementary table S11 and figure S6](#)). Including all 5 PANSS items into the motor score had no additional benefit for the correlations with motor rating scales ([supplementary table S12](#)).

## Discussion

With our study, we wish to introduce a new PANSS motor subscore based on the PANSS items G5 mannerisms and posturing, G7 motor retardation, and G13 disturbance of volition as a proxy of expert rating scales for specific motor abnormalities in schizophrenia. Our analysis revealed that the PANSS<sub>mot</sub> correlated with all motor rating scales. Moreover, schizophrenia patients categorized into high and low PANSS<sub>mot</sub> groups differed substantially in all hypokinetic motor rating scales, ie, BFCRS, NCRS, UPDRS, and SRRS. Additionally, PANSS<sub>mot</sub> proved to be an effective predictor of catatonia case definition based on DMS-5 as well as BFCRS with moderate accuracy. Further, we replicated the correlation between PANSS<sub>mot</sub> and parkinsonism in the RESIS dataset. In addition, the associations between PANSS<sub>mot</sub> and motor rating scales remained stable over a period of 3 weeks in the OCoPS-P sample. Finally, PANSS<sub>mot</sub> correlated with instrumental measures of physical activity. Thus, the PANSS<sub>mot</sub> holds promise in capturing broad hypokinetic psychomotor abnormalities with little information from a standard rating scale.

#### Proxy for Motor Abnormalities?

Our analyses suggest that PANSS<sub>mot</sub> does qualify as a proxy for motor abnormalities in schizophrenia spectrum disorders. This is mainly true for hypokinetic motor abnormalities, including catatonia, psychomotor slowing, and parkinsonism.<sup>47</sup> The correlations were especially high between PANSS<sub>mot</sub> and all hypokinetic motor abnormalities, but less so with dyskinesia. This is in line with recent findings from imaging studies demonstrating different neuronal correlates for dyskinesia and parkinsonism, respectively.<sup>48</sup> In addition, the cutoff set at 3 on each PANSS motor item (G5, G7, and G13) identified a group of patients with higher levels of catatonia, psychomotor slowing, and parkinsonism, compared to patients below the cutoff. However, the cutoff was not able to differentiate between patients with more severe vs less severe dyskinesia or neurological soft signs, especially in the subscores sensory integration and motor coordination. The RESIS study used a different rating scale for



motor abnormalities but replicated our initial findings. PANSS<sub>mot</sub> was linked to parkinsonism but not to hyperkinetic motor abnormalities (akathisia, dystonia, and dyskinesia) in this sample. This is slightly different compared to the findings in the Bern samples, where dyskinesia was also correlated with PANSS<sub>mot</sub>. Next to differences in the operationalization of the different motor rating scales we must consider that expert raters for OCoPS-P and BrAGG-SoS were specifically trained to detect motor abnormalities and are probably also more sensitive using the PANSS motor items. Furthermore, RESIS patients demonstrated pronounced negative symptoms at baseline and not all patients had the capacity to complete SHRS assessments.

The longitudinal data of OCoPS-P suggests that the associations between PANSS<sub>mot</sub> and ratings of motor abnormalities were stable over 3 weeks. In that regard, PANSS<sub>mot</sub> was linked to expert ratings of hypokinetic motor abnormalities in 2 samples from the baseline values of 3 different clinical trials as well as in the longitudinal follow-up of 1 trial. However, the quality of the ratings depends on the attention paid to motor signs during assessments. In situations where raters are less familiar with the assessment of psychomotor behavior, PANSS<sub>mot</sub> may also fail to detect individuals with motor abnormalities. Finally, PANSS<sub>mot</sub> alone will not allow distinguishing the type of hypokinetic motor abnormality, given the substantial covariance or conceptual overlap between catatonia, parkinsonism, or psychomotor slowing.<sup>24,47,49</sup> Thus, the score will indicate the severity of hypokinetic psychomotor behaviors, but not allow disentangling parkinsonism from catatonia.

We have also considered including 2 PANSS items potentially describing hyperkinetic motor abnormalities, such as agitation, akathisia, or dyskinesia. However, neither the addition of item P04, G14, nor the combination of both did increase the correlation coefficients between the PANSS<sub>mot</sub> and the expert rating scales. Thus, hyperkinetic movement disorders were less likely to be captured by PANSS ratings. Groups of subjects with high vs low scores on the hyperkinetic motor score failed to differ on any motor rating scale. Besides issues with the operationalization of hyperkinetic motor abnormalities in the PANSS one of the most likely reasons for the weak associations observed are probably the sample characteristics. The available datasets included mainly patients with prominent negative symptoms and hypokinetic motor abnormalities.

Instrumental measures of behavior such as wrist-actigraphy are considered the gold standard to capture motor abnormalities, especially hypokinetic motor abnormalities including catatonia, parkinsonism, and psychomotor slowing.<sup>12,30,31,47</sup> In schizophrenia, actigraphically assessed physical activity is related to altered white matter integrity,<sup>50,51</sup> resting-state functional connectivity,<sup>52</sup> negative symptoms,<sup>53,54</sup> positive

symptoms,<sup>55</sup> and the course of schizophrenia episodes.<sup>56</sup> Similarly, higher PANSS<sub>mot</sub> also correlated with lower physical activity levels, corroborating its external validity. Interestingly, in a previous report, no associations were found between each of the single items G5, G7, and G13 and actigraphically determined activity levels in schizophrenia.<sup>22</sup> In contrast, the current study demonstrated associations when these single PANSS items are combined to the PANSS<sub>mot</sub> score.

According to sensitivity analyses, PANSS<sub>mot</sub> was not related to current daily dose and types of antipsychotic medication. Abnormal psychomotor behavior is associated with more severe symptoms of psychosis. Indeed, PANSS<sub>mot</sub> demonstrated strong correlations with negative symptoms or general symptoms of psychosis, less so with positive symptoms. Still, PANSS<sub>mot</sub> has stronger associations to the motor rating scales than PANSS general or PANSS total.

Recognition and assessment of motor abnormalities are critical because of their association with social and community functioning.<sup>10,11</sup> Antipsychotic drug trials involving hundreds of patients diagnosed with schizophrenia spectrum disorders typically assess symptom severity using the PANSS. The PANSS<sub>mot</sub> might prove helpful in detecting motor abnormalities in study participants but would also allow testing for secondary effects on hypokinetic motor abnormalities in these trials. The PANSS<sub>mot</sub> therefore holds promise in secondary analyses of large-scale existing datasets from randomized controlled trials. The utility may even extend to individual-patient meta-analyses. However, in prospective studies addressing abnormal psychomotor behavior specifically, we recommend using validated motor rating scales as well as instrumental measures such as actigraphy or gait analyses instead.<sup>25,31</sup> The choice of instrument will depend on the motor abnormality in question.

### Limitations

Some limitations of these analyses should be considered. First, we combined datasets of clinical trials with heterogeneous patient groups, introducing some selection bias limiting generalizability. For OCoPS-P, patients with severe motor symptoms were recruited, whereas for RESIS, patients with predominantly negative symptoms prevailed. In BrAGG-SoS participants were stabilized outpatients with substantial chronicity. However, the main findings regarding hypokinetic motor abnormalities were similar across samples. We would expect similar associations in clinical trials with schizophrenia patients. Additionally, only few patients presented with severe dyskinesia. This may explain the lack of a group difference in AIMS scores due to low variability. Furthermore, data was mostly acquired in patients with chronic schizophrenia and long-term exposure to antipsychotics.



Thus, we cannot completely rule out medication effect, although PANSS<sub>mot</sub> was unrelated to the current daily dose and type of antipsychotics. Similarly, the PANSS<sub>mot</sub> should also be tested in the early course of psychosis. Finally, the current analyses should be replicated in larger datasets.

### Conclusion

A novel sum score of 3 PANSS motor items correlated with expert ratings of hypokinetic psychomotor abnormalities and instrumental measures of physical activity. Effects were replicable in different datasets and proved reliable over 3 weeks. Thus, the PANSS<sub>mot</sub> may qualify as a proxy measure of hypokinetic psychomotor abnormalities in psychosis in large trials that lack specific motor assessments.

### Supplementary Material

Supplementary material is available at <https://academic.oup.com/schizophreniabulletin/>.

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