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Quantification of motor abnormalities with instrumental tasks among adolescents with first-episode schizophrenia and depressive disorders

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Motor abnormalities, including extrapyramidal symptoms (EPS) induced by antipsychotic medication, are of prognostic value for clinical outcomes for individuals with schizophrenia. Instrumental methods for quantitative assessment of motor abnormalities in schizophrenia are still underdeveloped, with current assessments relying on observations and subjective scales. This study aimed to develop easy-to-implement and reliable instrumental methods to measure motor abnormalities in youth with schizophrenia who started their medication. Three motor tasks, including upper-limb weight holding, quiet standing, and level-ground walking, were instrumentally evaluated to capture essential aspects of motor abnormalities, such as akathisia, dyskinesia, and Parkinsonism. We recruited adolescents with schizophrenia (SZ group), an age-matched healthy control group (NC group), and a group of age-matched patients with depression (DP group). The SZ and DP groups were both newly exposed to antipsychotic drugs, and their comparisons were to determine if motor abnormalities are schizophrenia-specific. SZ patients indeed performed significantly worse with more upper-limb tremors and walking abnormalities. While no group difference was found in standing stability, the SZ group's postural stability measures correlated with clinic scale scores. With motor features from these instrumental methods, a simple linear classifier classified the three participant groups with decent accuracy. Our findings suggest that instrumental motor tasks hold promise for sensitive detection and differentiation of motor abnormalities in adolescents with newly diagnosed schizophrenia and antipsychotic intake. Further developments of these instrumental methods are promising for improving motor assessment and treatment outcomes in clinical practice.

Keywords Schizophrenia, Depression, Extrapyramidal side effect, Instrumental assessment, Antipsychotics medication

Schizophrenia is a major psychiatric disorder that typically develops in late adolescence or early adulthood¹. Individuals with schizophrenia have impaired mental and social functioning² and, often, abnormal movements such as tremors, involuntary movements, abnormal muscle tone, and hypokinesia^{3,4}. These motor symptoms are intricately linked to psychotic disorders with shared neural basis^{5–8}, and are also caused by the use of psychiatric drugs^{6,9–11}. Besides intrinsic psychopathology-related motor deficits, antipsychotics often cause extrapyramidal side effects (EPS), which is an umbrella term for an array of drug-induced movement disorders¹². Children and adolescents have shown more severe EPS symptoms than adults^{13,14}.

Motor abnormalities predict functional outcomes in schizophrenia^{15,16}. Researchers also found motor abnormalities have predictive power for schizophrenia onset: motor-first patterns occur in 60% of cases,

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with motor abnormalities emerging 12–36 months before positive symptoms, while 25% show simultaneous emergence and 15% develop motor signs after initial symptoms¹⁷. Adolescence represents the peak predictive window, with larger effect sizes than early childhood and young adulthood¹⁸. On the other hand, reducing the adverse effects of EPS is a common consideration for clinicians when adjusting the dose of antipsychotics for better therapeutic efficacy¹⁹. Notably, EPS ratings, such as Parkinsonism, akathisia, and dyskinesia, were negatively correlated with the efficacy of antipsychotic drugs, meaning worse motor abnormalities were associated with poorer drug responses²⁰. Especially, the EPS signs in first-break schizophrenia patients have been shown to predict the efficacy of antipsychotics^{21–23}. Current strategies for managing EPS, including prophylactic use of anticholinergic medication, dose reduction, or medication switch²⁴, also demand an accurate assessment of EPS. Thus, quantification of motor abnormalities is essential to maximizing treatment outcomes, improving medication adherence, and reducing re-hospitalization²⁵.

Clinic assessment of motor abnormalities mainly relies on scales with subjective observations, popular scales including Neurological Evaluation Scale (NES;²⁶), Cambridge Neurological Inventory (CNI;²⁷), Bush-Francis Catatonia Rating Scale (BFCRS;²⁸), the Extrapyramidal Symptom Rating Scale (ESRS;²⁹), Abnormal Involuntary Movement Scale (AIMS;³⁰), Simpson-Angus Extrapyramidal Symptoms Scale (SAS;³¹). However, certain scale items are considered over-representative in the scales, e.g., rigidity measures in the SAS scale³². Some items have unsatisfactory interrater reliability³³. Researchers and clinicians have suggested that the application of these scales is hindered by their insufficient internal reliability, potential subjective bias, and the need for extensive training in scale use^{34–36}.

Instrumental methods are promising for objective and reliable quantification by using detailed movement analyses on dedicated tasks. For example, Caligiuri and his colleagues have developed methods to quantify the severity of EPS by analyzing the handwriting movement measured by a digital tablet^{25,37–39}. Kinematic features of writing strokes were found to correlate with antipsychotic dose and clinical scale scores among schizophrenia patients. This method has also been used in early screening or diagnosis of schizophrenia with decent accuracy⁴⁰. Another approach is to target Parkinsonian gait by measuring people's footprints during tandem gait⁴¹. Notably, many prominent EPS signs, such as static tremor, muscle rigidity, and postural instability, are not measured by these two methods. Furthermore, these methods were predominantly developed by testing adults over 40 years old, leaving young patients, who are more affected by EPS, unexamined.

We aimed to develop a set of motor tasks to comprehensively assess motor abnormalities with portable devices and evaluate their utility in adolescents with first-episode psychosis and first antipsychotic use. We included a group of adolescents with schizophrenia (SZ group), an age-matched healthy control group (NC group), and a group of age-matched patients with depression (DP group). The anti-depressants used by DP patients are substantially less likely to cause motor abnormalities, but occasionally, Parkinsonism and dyskinesia, which are also typical EPS symptoms, are reported. Furthermore, depression and Parkinsonism share some common motor abnormalities, including bradykinesia⁴². Thus, the group comparison between SZ and DP groups would inform whether the motor abnormalities observed in our tasks are schizophrenia-specific. To measure postural tremors commonly seen in Parkinsonism, we asked participants to hold a weight with an extended arm to elicit tremorous movements, which are continuously recorded by an inertial sensor. As this task also requires an isometric force production against gravity, it might also capture dyskinesia, which is often manifested as increased force variability⁴³. To measure postural stability that has been recently associated with EPS^{44,45}, we asked participants to stand still for 30 s with their foot pressure recorded by a high-resolution pressure mat. To measure Parkinsonism and dystonia's effect on walking, we asked participants to walk straight on the level ground for 8 m and measured their dynamic foot-ground contact pressure. The goal of the current research is to examine (1) whether instrumental assessments can sensitively detect motor abnormality in adolescents with newly diagnosed schizophrenia and antipsychotic intake and (2) whether motor abnormalities among SZ and DP groups are distinguishable, especially when both groups are new to antipsychotic intake. This study is our first endeavor to use objective movement measures to quantify motor abnormalities and their possible association with antipsychotic efficacy in longitudinal terms.

Methods

Participants

We recruited twenty-five adolescents with schizophrenia (14 females, age 14.17 ± 2.60 years) and twenty-four age-matched adolescents with depression (17 females, age 13.48 ± 1.34 years) at Peking University Sixth Hospital (Table 1). Motor abnormalities are typically salient among SZ patients³⁹; our power analysis indicated that a minimum of 22 participants is sufficient to achieve a power of 0.9. The participants of the SZ group and DP group were recruited if they (a) were diagnosed by two qualified psychiatrists based on International Classification of Diseases-10 (ICD-10) criteria, (b) aged 10–18 years old, (c) had first-episode psychosis, (d) used atypical antipsychotic medicine over seven days. Note that they were naïve to antipsychotic medicine. Their medication was prescribed according to clinical choice, including Olanzapine, Quetiapine, Risperidone, etc. The average daily dose of antipsychotic medication was transformed into Chlorpromazine equivalents⁴⁶. We also recruited 23 adolescents without any psychiatric problems as a control group (NC group; 9 females, age 13.95 ± 2.27 years). The average duration of antipsychotic treatment is 113.5 days (SD = 172.1 days). The 25th and 75th percentile are 20 and 100 days, respectively. All participants were right-handed, with normal or corrected vision, and naïve to the experimental tasks. The participants in the SZ group and the DP group were diagnosed according to the International Classification of Diseases-10 (ICD-10) criteria. Their bibliographical information is shown in Table 1. The exclusion criteria included clinically significant physical and neurological disorders such as vision problems, history of developmental disability, neuropathy, and substance or alcohol abuse or dependence. The NC group was required to be free of a previous or family history of mental disorders.

	Schizophrenia	Depression	Control	T value	p
N	25	24	23	N/A	N/A
Female (Male)	14 (11)	17 (7)	9 (14)	N/A	N/A
Age	14.17 (2.60)	13.48 (1.34)	13.95 (2.27)	1.13	0.26
Brief psychiatric rating scale (BPRS)	31.71 (10.25)	35.00 (10.00)	N/A	−0.59	0.57
Clinical global impression (CGI)	4.33 (1.24)	4.44 (0.88)	N/A	−0.29	0.77
Barnes akathisia rating scale (BARS)	1.75 (2.54)	1.26 (1.68)	N/A	0.77	0.44
Abnormal involuntary movement scale (AIMS)	0.36 (1.05)	0.55 (1.18)	N/A	−0.54	0.59
Simpson-angus EPS (SAS)	5.58(3.16)	2.52 (2.21)	N/A	3.86	<0.001
Chlorpromazine equivalents (mg/day)	669.85 (469.21)	248.74 (159.82)	N/A	2.58	0.015
Fluoxetine equivalents (mg/day)	N/A	46.61 (26.38)	N/A	N/A	N/A

Table 1. Participants Characteristics. For scale scores, Chlorpromazine equivalents, and Fluoxetine equivalents, the mean and standard error are shown. Antipsychotics used in the SZ group include Aripiprazole, Olanzapine, Paliperidone, and Haloperidol.

All procedures were approved by the Ethics Committee of Peking University Sixth Hospital. All participants or their legal representatives gave written informed consent for their participation.

Clinical assessment

Clinic symptoms were assessed by using the Brief Psychiatric Rating Scale (BPRS⁴⁷) and Clinical Global Impression Scale (CGI⁴⁸). For both scales, higher scores indicate more severe psychopathology. EPS signs, including akathisia, tardive dyskinesia, and Parkinsonism, were assessed by the Barnes Akathisia Rating Scale (BARS⁴⁹), AIMS³⁰, and SAS³¹. Each participant took about an hour to complete these assessments.

The BARS contains four items: subjective items (awareness of restlessness and distress related to restlessness), objective criteria, and global items⁴⁹. We used the global item of BARS for correlation analysis. The AIMS contains seven items that assess abnormal movements in various anatomical locations, including facial and oral, extremity, and truncal movements. It also includes a global judgment of three items, i.e., the severity of abnormal movements overall, incapacitation due to abnormal movements, and the patient’s awareness of abnormal movements^{30,48}. We used the global judgment for correlation analysis. The SAS consists of ten items, including one item measuring gait (hypokinesia), six items measuring rigidity, and three items measuring glabella tap, tremor, and salivation, respectively. For each item, the severity of symptoms is rated from 0 (none) to 4 (severe). Scale scores for the SZ and DP groups were summarized (Table 1).

Instrumental tasks

Weight holding

To evaluate postural tremor, we asked the participants to extend and raise their right arm at shoulder level while holding a 150-g bottle-shaped object. Weight holding would require antagonist muscles to co-contract to maintain a stable posture against gravity; the resulting miniature movements depend on the tremor type and amplitude^{50,51}. The instructions were “Hold the bottle while extending your arm straight at the shoulder level, and keep it as steady as possible for 30.” We attached an inertial sensor on the flat top of the object (9-axis Wireless Motion Sensor, Senbodi Inc.). The inertial sensor was tethered to a cell phone via Bluetooth, and the acceleration of the object was measured at a sampling rate of 50 Hz. Similar to a wrist-worn device for detecting tremors among people with Parkinson’s disease⁵², the movements registered by the inertial sensor can reflect Parkinsonism in schizophrenia. The measurement was stored for offline analysis (Fig. 1A).

Quiet standing

We evaluated participants’ postural stability by asking them to stand still for 30 s with their eyes open (Fig. 1B). Previous studies have identified impaired standing stability among people with schizophrenia⁵³ and depression⁵⁴. Some researchers also proposed a possible link between postural instability with EPS^{44,45}. Participants stood on a 578 × 418 × 12 mm pressure mat (0.5 m Entry Level footscan system, RsScan Inc.), which had 64 × 64 pressure-sensitive sensors with a sampling frequency of 100 Hz. The instruction was “Face the wall with eyes open and maintain a steady, shoulder-wide stance on the mat for 30 s.” The foot pressure data was saved for offline analysis to derive the displacement of the center of pressure (COP).

Ground walking

We measured people’s ground-level walking as a test of their motor coordination (Fig. 1C). Previous studies have identified impaired gait among people with schizophrenia and depression⁵⁵. Though standard scales (except SAS) did not include a dedicated test of gait, we postulate that walking might show EPS-specific abnormality, especially due to acute dystonia and parkinsonism⁵⁶. Participants were instructed to walk barefoot in an unobstructed, straight walkway in the corridor of the ward at their preferred pace. The walkway was 8 m long, with a fixation cross printed on an A4 paper hung at the far end of the corridor. The participants were instructed to fixate on the cross during walking. A 1068 × 418 × 12 mm pressure mat (1 m Entry Level footscan system, RsScan Inc.) was placed at 5 m in the walkway; the mat was form-padded on the floor to make it level with the ground. The pressure mat had 128 × 64 pressure-sensitive sensors with a sampling frequency of 100 Hz. The

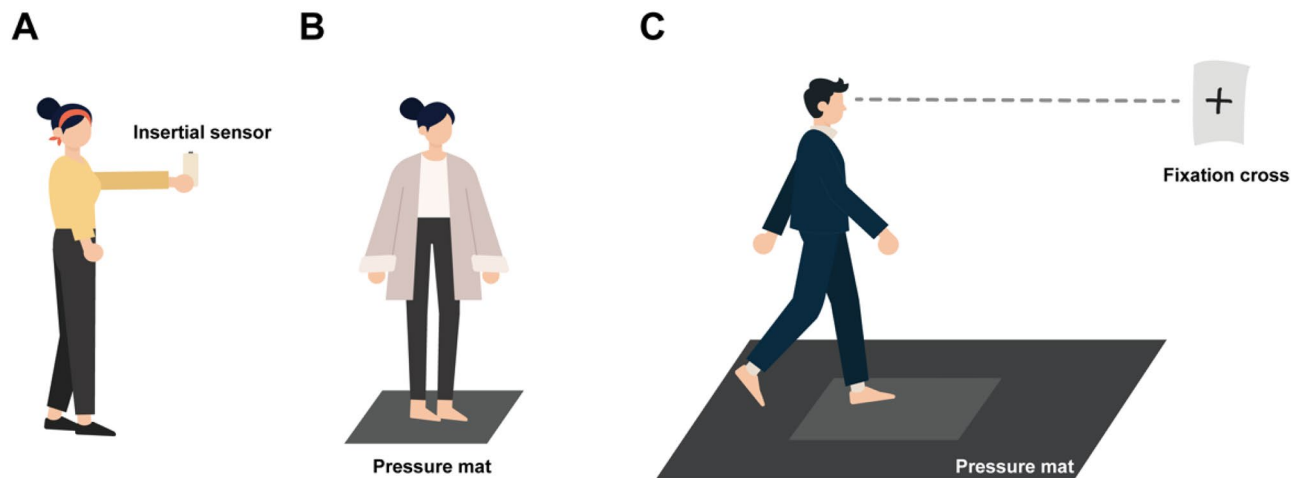


Fig. 1. The illustrations of the weight-holding task (A), the quiet standing task (B), and the straight walking task (C). The weight-holding task required the participant to stabilize their loaded and extended arm for 30 s, with an inertial sensor mounted on the hand-held object. The quiet standing task required the participant to maintain a steady standing posture for 30 s on a plantar pressure mat. The ground walking task required the participant to walk straight on the level ground equipped with an embedded plantar pressure mat that measured the dynamic foot pressure during walking.

instruction was “Fixate on the cross, walk normally with your preferred pace, and without looking down to aim your feet at the pressure mat.” The starting position was slightly adjusted for each participant to make sure at least one of their feet would land on the mat. The participants walked 5 m before stepping on the pressure mat and were asked to keep their normal walking pace for an additional 2 m. Each participant walked more than 20 times to ensure that each foot could be registered by the pressure mat at least 10 times. Note that we urged participants to rest whenever they felt any fatigue. The foot pressure data was saved for offline analysis.

Data analysis

Data processing for the three motor tasks and subsequent statistical tests were conducted offline using Matlab (R2020a, Mathworks Inc., USA). For the weight-holding task, we computed the overall acceleration as the square root of the sum of the squares of acceleration data in each spatial dimension after removing the gravitational acceleration (Fig. 2A⁵⁷). The tremor intensity is computed as the standard deviation of the overall acceleration across time. We also computed the power spectral density of the acceleration using the Welch periodogram⁵⁸ with an average at every 3 s segment of signal with 50% overlapping of the Hanning windows. Previous studies have related the area under the curve of the power spectrum between 4 and 7 Hz to Parkinsonian tremor and between 5 and 15 Hz to essential tremor^{59,60}. Thus, we computed the integral for these two frequency bands to quantify Parkinsonian tremor and essential tremor, respectively.

For the quiet standing task, we first obtained the time series of COP displacement. The first two seconds of data were excluded for further analysis to remove the transient changes at the beginning of a trial. A Butterworth low-pass filter filtered the data at a cutoff frequency of 15 Hz. To assess the postural sway, we computed the root mean square (RMS), total length, and the area of COP displacement for each participant. The area was quantified by fitting an ellipse to contain 95% of the COP trajectory, thereby excluding extreme deviations (Fig. 2B). The power spectrum density of COP displacement was also computed using the same Welch periodogram as for the acceleration data from the weight holding task, except that a Hanning window of 12 s was applied. Then, the body sway was characterized by the area under the curve of the power spectrum density function between 0 and 3 Hz for the anteroposterior and mediolateral directions separately⁶¹.

For the ground walking task, we calculated the contact duration of each foot on the ground, which characterized their preferred walking speed. For analyzing the spatial distribution of foot pressure, we first spatially aligned the principal axis of each footprint with the direction of straight ahead. To remove the difference in contact duration across trials and across participants, we interpolated the time series of foot pressure data to 101 frames. Thus, the data from each trial ranged from time 0 to their respective 100% contact duration. As previous studies reported clumsy gait among people with schizophrenia⁵⁵, we expect that they would exhibit abnormal foot movements that can be manifested in COP progression underneath the foot. The COP travel distance from initial foot contact to foot takeoff, relative to the foot length, is an indicator of how complete the foot roll-off is⁶². We thus computed the anteroposterior displacement of COP, normalized by dividing each participant's foot length. We also analyzed how the foot pressure developed underneath the foot during a step. As the foot pressure is affected both by body weight and walking speed, we normalized the pressure data by dividing each participant's body weight and contact duration. The total foot pressure resembles the vertical ground reaction force (Fz), showing a typical bimodal curve (called “M curve” or “butterfly diagram”). The first peak corresponds to heel contact (FzHC), and the second peak corresponds to the push-off (FzPO), with a downfall in between these two peaks (FzDF). The difference between the average of the first and second peaks

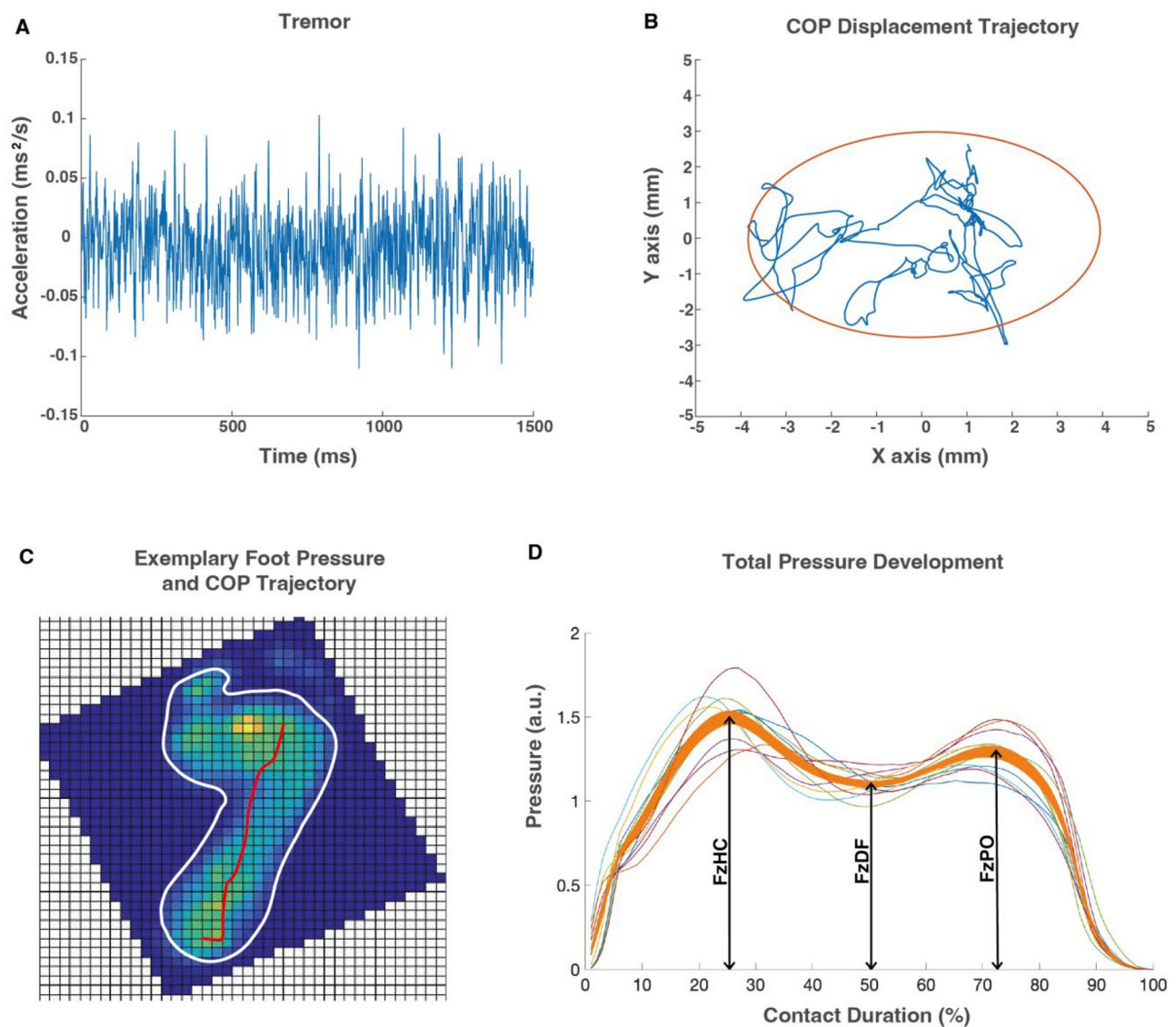


Fig. 2. Typical trials from the three instrumental tasks. **(A)** Acceleration signal in the weight-holding task. **(B)** COP displacement from the quiet standing task (blue) and its fitted ellipse with 95% confidence intervals. **(C)** Foot pressure and COP trajectory during a typical foot contact in the ground walking task. The colored patches denote the maximal pressure registered by all the force sensors. The red line denotes the estimated COP trajectory. **(D)** Time series of normalized total pressure during a foot contact. Individual traces are from a single participant, and the shaded line denotes the mean and SEM across these trials. FzHC denotes the first pressure peak at heel contact, FzPO denotes the second peak at push-off, and FzDF denotes the minimum during the downfall between the two peaks.

and the downfall (i.e., $(FzHC + FzPO)/2 - FzDF$) characterizes the dynamic range of foot–ground interaction force during walking. For ground walking, we excluded the trials that only registered a partial foot on the pressure mat. The participants with less than five valid trials were excluded from the group analysis, leading to the exclusion of five SZ participants.

To test the group differences, we first examined the normality of the data by the Shapiro–Wilk test and Kolmogorov–Smirnov test. If the variable did not follow a normal distribution, its median and IQR were reported, and nonparametric tests were used; otherwise, mean and standard error (SEM) were reported, and parametric tests were used. One-way independent-measures ANOVA was used if the data met the normality assumption. Otherwise, the Kruskal–Wallis test was used. Greenhouse–Geiser tests were used if the equal variance assumption was violated, and post-hoc pairwise comparisons were conducted using Scheffé’s tests. We used Spearman correlation to relate the movement variables from the three tasks to the EPS ratings (SAS, BARS, and AIMS), psychopathology scores (BPRS and CGI), and the antipsychotic dosage. Note that the three groups are unbalanced concerning gender, but the exact binomial tests failed to detect any gender effect ($p=0.655$, 0.094 , and 0.429 for the SZ, DP, and NC groups, respectively), nor any gender effect between groups ($\chi^2 = 4.78$,

$p=0.091$). Thus, we did not further analyze a potential gender effect in subsequent statistical tests. The α level was set at 0.05.

We also tested whether we could classify participant groups solely based on individual participants' motor measures from the three instrumental tests. All the performance measures were used as features for automatic classification with a simple decision tree algorithm. The probability of Type I error was capped by removing a priori selection of features. The group label was used as the response variable. We used the leave-one-out cross-validation to quantify the classification performance. The accuracy, specificity, and sensitivity were computed for two-group (NC and two patient groups) and three-group (NC, DP, and SZ) classifications separately.

Results

We first compared their characteristic movement measures across groups for each motor task. Then, correlation analyses were performed to examine whether these measures correlated with EPS and psychopathology scale scores. Lastly, we used all the movement variables, without a prior selection, to automatically classify individual participants with cross-validation.

Weight holding

Our participants held weight with their extended right arm for 30 s, and the inertial sensor measured their postural tremor. SZ participants exhibited more tremors than the other two groups as indexed by larger variability (standard deviation) and higher spectral power between 4 and 7 Hz (Parkinsonian tremor) and between 5 and 15 Hz (essential tremor; Fig. 3). For the variability of acceleration, the group effect was significant ($H(2,65)=9.94$, $p<0.01$), with posthoc tests showing that SZ and DP participants had significantly larger variability than NC participants (both $ps<0.05$). The standard deviation of acceleration (median and IQR) were 0.033 (0.019), 0.054 (0.031), and 0.051 (0.022) mm/s^2 for NC, DP, and SZ groups, respectively (Fig. 3A). For Parkinsonian tremor, the group difference was also significant ($H(2,65)=10.25$, $p<0.01$), and the posthoc tests only identified a significant difference between SZ and NC participants ($p<0.05$). The Parkinsonian tremor spectral power (median and IQR) were 0.00054 (0.0014), 0.0012 (0.0022), and 0.0017 (0.0022) $(\text{ms}^{-2})^2 \times 10^{-2}$ for NC, DP, and SZ groups, respectively (Fig. 3B). For essential tremor, the group difference was significant ($H(2,65)=8.91$, $p<0.05$), and post-hoc tests found that the SZ participants showed more power than the NC participants ($p<0.05$). The essential tremor spectral power (median and IQR) were 0.0013 (0.0020), 0.0022 (0.0019), and 0.0029 (0.0024) $(\text{ms}^{-2})^2 \times 10^{-2}$ for NC, DP, and SZ groups, respectively (Fig. 3C).

However, all three tremor variables did not correlate with any clinical scales, i.e., BPRS, CGI, BARS, AIMS, and SAS, across participants from two patient groups. We singled out the score of the tremor item in the SAS scale and correlated it with the movement variables, but still failed to find any correlation. We noticed that 20 of the 47 SZ participants scored 0, and others scored 1 in this item, indicating that tremors were not pronounced among our participants. We nevertheless calculated the point serial correlation of all the movement variables over the tremor scores 0 and 1, but still failed to detect any significant difference.

Quiet standing

Our participants stood still for 30 s with their eyes open on the pressure mat to evaluate their postural stability. The displacement of COP during this period was used to quantify the postural sway. Despite an increasing tendency (Fig. 4), all the body sway variables did not show significant group difference (RMS: $H(2,64)=1.83$, $p=0.40$; LNG: $H(2,64)=5.40$, $p=0.07$; area: $H(2,64)=2.86$, $p=0.24$; spectral power: $H(2,62)=5.23$, $p=0.07$). The RMS (median and IQR) was 0.430(0.422), 0.487(0.503), and 0.594(0.465) mm for NC, DP, and SZ groups,

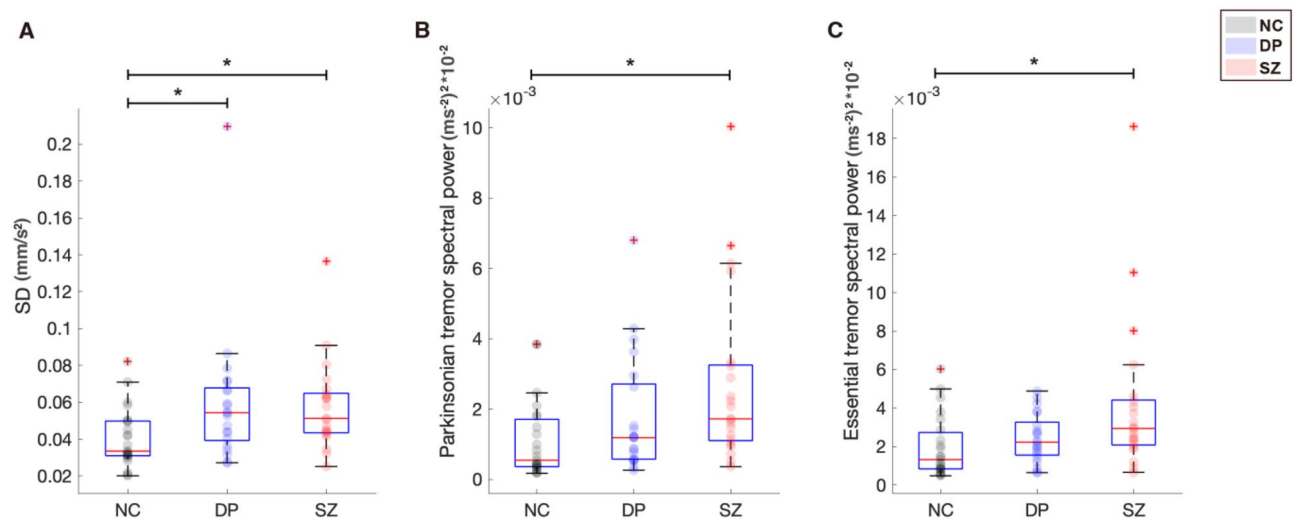


Fig. 3. The amplitude of tremor during weight holding as a function of group. (A) Standard deviation (SD) of acceleration. (B) Parkinsonian tremor spectral power. (C) Essential tremor spectral power. Box plots denote the median and interquartile interval for each group. * $p<0.01$.

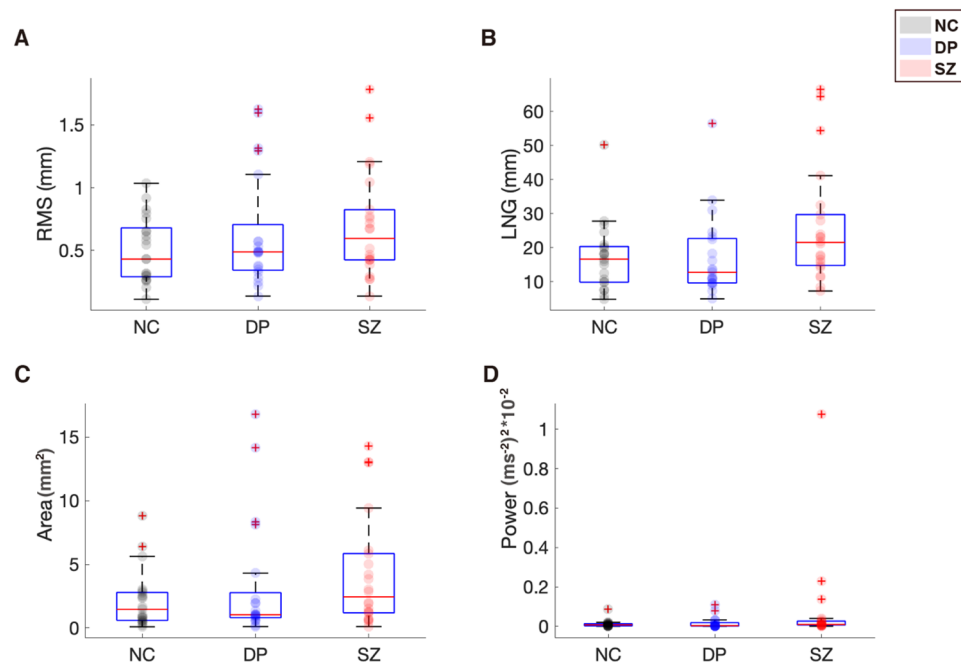


Fig. 4. The performance from the quiet standing task. Root mean square (RMS; **A**), total length (LNG; **B**), the area (Area; **C**), and the power spectrum between 0 and 3 Hz (Power; **D**) of COP displacement are shown. Despite an increasing tendency, no significant group difference was found. The boxplot indicates the median and IQR for each group.

respectively (Fig. 4A). The LNG (median and IQR) were 16.664(10.658), 12.779(13.225), and 21.562(15.747) mm for NC, DP, and SZ groups, respectively (Fig. 4B). The area of COP excursions (median and IQR) was 1.471(2.244), 1.048(2.510), and 2.453(4.838) mm² for NC, DP, and SZ groups, respectively (Fig. 4C). The power spectrum (median and IQR) was 0.0077(0.0111), 0.0097(0.0218), and 0.0036(0.0208) (ms⁻²)² * 10⁻² for NC, DP, and SZ groups, respectively (Fig. 4D). We calculated the correlation between these four sway variables and the clinical scales in the SZ group. We found a significant negative correlation between two COP variables and the SAS score (RMS: $r = -0.430$, $p < 0.05$; area: $r = -0.475$, $p < 0.05$). SZ participants who had worse SAS scores showed *less* postural sway. Since most SAS items reflect rigidity, this negative correlation implies that the reduced body sway during quiet standing might reflect postural rigidity. This was corroborated by the fact that the sum of the seven items of rigidity significantly correlated with the area ($r = -0.450$, $p < 0.05$) and marginally significantly correlated with RMS ($r = -0.408$, $p = 0.059$).

Ground walking

Our participants walked barefoot on a straight walkway, and their foot-ground interaction was measured by the pressure mat. Contact duration, variability of contact duration, COP excursion, and ground reaction force were used to evaluate the foot-ground interaction during walking. The SZ participants walked slower, more variably, and with a stiffer gait. Contact duration differed significantly between groups ($H(2,59) = 8.11$, $p < 0.05$; Fig. 5A), with post-hoc comparisons showing SZ participants placed their feet on the ground significantly longer than NC participants. The contact duration (median and IQR) was 725.00(74.468), 799.587(87.248), and 837.945(145.054) ms for the three groups, respectively (Fig. 5A). The variability of contact duration also differed between groups ($H(2,59) = 12.37$, $p < 0.05$), and the SZ and DP groups both showed larger variability than the NC group (Fig. 5B). The standard deviation of contact duration (median and IQR) was 9.258(3.819), 13.784(8.408), and 14.976(27.295) ms for the three groups, respectively. The dynamic range of pressure also yielded a significant group difference ($H(2,59) = 6.57$, $p < 0.05$; Fig. 5C). However, post hoc comparisons only detected marginally significant group differences: the SZ and the DP groups showed less range than the NC participants ($p = 0.067$ and 0.077 , respectively). The range (median and IQR) was 0.110(0.103), 0.0571(0.0988), and 0.0557(0.0971) for NC, DP, and SZ groups, respectively. This reduction in the range of foot pressure suggests a tendency for these two patient groups to walk more rigidly. Examining the COP excursion in the progression direction (Fig. 5E), we found that both SZ and DP participants terminated their foot contact relatively early, resulting in a significant group difference in the maximum COP excursion in the progression (anteroposterior) direction after normalizing individual foot size (Fig. 5D; $H(2,59) = 10.45$, $p < 0.01$; $p < 0.05$ and $p = 0.067$ for SZ and DP compared to NC, respectively). COP excursion (median and IQR) were 86.6%(3.7%), 78.4%(10.6%), and 82.2%(15.7%) of the foot length for NC, DP, and SZ groups, respectively. We confirmed that no changes were observed between the first 10 and last 10 walking trials in the four walking variables we examined here, suggesting that fatigue did not play a role. Hence, the feet of the two groups left the ground prematurely without

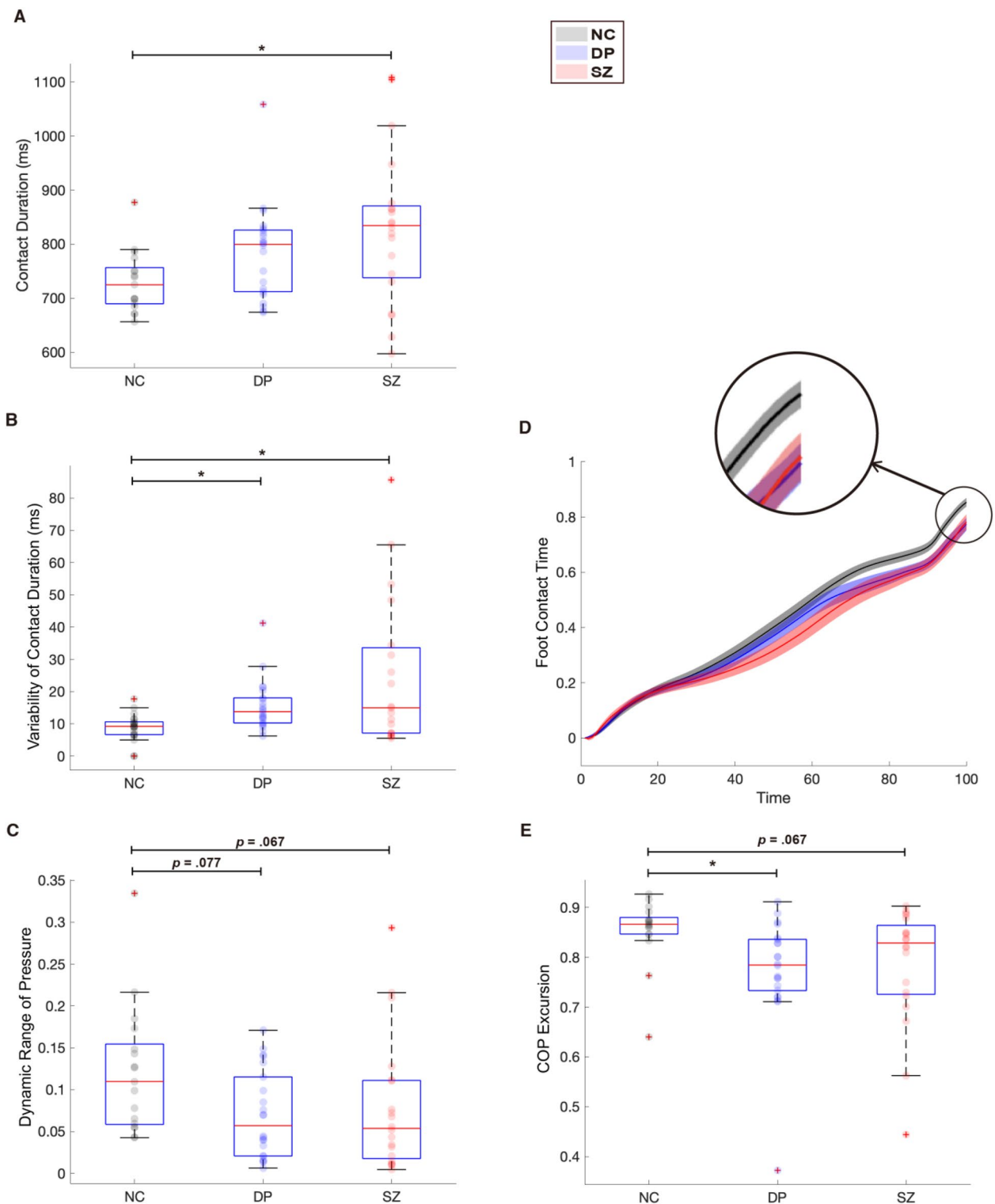


Fig. 5. The performance of the ground walking task. **(A)** Contact duration. **(B)** Variability of contact duration. **(C)** The dynamic range of pressure. **(D)** The displacement of COP in the progression direction, normalized by foot size, as a function of foot contact time. The inset highlights the group difference near the foot takeoff. **(E)** The COP travel distance in the progression direction is divided by foot size. The boxplot indicates the median and IQR for each group.

a complete foot roll-off. Since they also contacted the ground longer with a less dynamic range of loading force, these two groups appeared to walk rigidly at a slow speed.

However, none of the walking variables correlated with clinical scales for DP and SZ group participants. We did not find them to correlate with the gait item score on the SAS scale. We calculated the point serial correlation of all the gait variables with the gait score and still failed to detect any significant correlation. We noticed that 24 of the 47 patient participants scored 0, 20 scored 1, and 3 scored 2 for the gait item. Thus, the fact that our participants were not severely impaired in gait by the clinic assessment might be the reason behind the null correlation effect.

Overall correlation and classification

Correlational tests found that all the movement measures from the three tasks were uncorrelated with the severity of psychosis (BPRS and CGI) and antipsychotic dose (Chlorpromazine equivalents).

Next, we used all the movement measures, irrespective of whether they differed among groups, as features for the automatic classification of the groups. Based on these features alone, we tested whether individual participants could be classified into one of the three group categories. With leave-one-out cross-validation, the decision tree model yielded an overall classification accuracy of 71.1%, substantially higher than the chance level of 33.3%. Scrutinizing the confusion matrix (Table 2), we observed that the most common classification error was mislabeling NC and DP participants as SZ participants, yielding the lowest specificity for the SZ group compared to the other two groups. At the same time, the SZ group also had the lowest sensitivity of 60% since 40% of this group was mislabeled as the other two groups. The NC group had the highest sensitivity of 90.3% and specificity of 76.9%. To further evaluate the classifier’s performance, we derived a receiver operating characteristic curve (ROC) for each group and calculated its area under the curve (AUC). The AUC was 0.81, 0.62, and 0.75 for the NC, SZ, and DP groups, respectively (Fig. 6A).

We also examined whether the movement features can be used to classify the drug and no-drug groups accurately. We pooled the SZ and DP groups as a single drug group and performed the same automatic classification (Table 3 and Fig. 6B). The overall accuracy and the AUC increased to 82.2% and 0.75, respectively. A binary classification could achieve much better overall performance with our instrumental movement data.

Discussion

The present study targeted the wide spectrum of motor symptoms in adolescents with schizophrenia who have first-episode psychosis and atypical antipsychotic use. As our first endeavor to quantitatively investigate the changes in psychosis and accompanying motor signs, our cross-sectional study also compared the adolescents with SZ to a group of adolescents with depressive disorders who took antipsychotics and potentially had EPS signs. Indeed, compared to the NC group, the SZ group exhibited larger postural tremors and a more rigid gait. The DP group showed similar effects, though less pronounced. We did not detect group differences in body sway during 30 s quiet standing, but interestingly, the body sway negatively correlated with the EPS scale scores for the SZ group. Furthermore, none of the motor measures was correlated with the antipsychotic dose. With the motor features from these instrumental methods, a simple decision tree classifier could categorize the three participant groups with an overall accuracy of 71.1% and classify the medication-free NC group and the combined medication group of NC and SZ participants with an accuracy of 82.2%.

Few studies have attempted to develop instrumental motor tests for quantification of EPS; one notable exception is the series of work on handwriting movements by Caligiuri and colleagues^{25,38}. They found that medicated SZ participants exhibited abnormal kinematic features of handwriting²⁵, and one specific feature in handwriting was also correlated with SAS scores³⁹. The impairments in writing were correlated with the daily dose of antipsychotic drugs³⁸. Despite its simplicity and success, we note that the handwriting is limited to quantifying bradykinesia and dyskinesia in the upper arm. Apparently, other motor deficits in SZ, including tremors, rigidity, postural instability, and dyskinesia in the lower limb, have not been targeted. This lack of previous research might be related to the fact that tremors and postural instability are less pronounced in drug-induced Parkinsonism than in Parkinson’s disease⁶³.

Clinic assessments use scales such as SAS to evaluate tremors, though only one item exists in SAS for this purpose. We opted to evaluate the postural tremor of an extended arm with weight loading since people with Parkinson’s disease, whose motor symptoms resemble EPS⁶⁴, typically show tremors in the outstretched arm⁵⁰.

	Predicted groups			Actual totals	Actual error%
	NC	SZ	DP		
Actual groups					
NC	10	2	1	13	23.1%
SZ	3	9	3	15	40.0%
DP	1	3	13	17	23.5%
Predicted totals	14	14	17	45	–
Prediction error (%)	28.6%	35.7%	23.5%	–	–

Table 2. The confusion matrix of the three-group classification. NC: Sensitivity = 76.9%, Specificity = 90.3% SZ: Sensitivity = 60.0%, Specificity = 80.6% DP: Sensitivity = 76.5%, Specificity = 85.7% NC = normal control; SZ = schizophrenia; DP = depression.

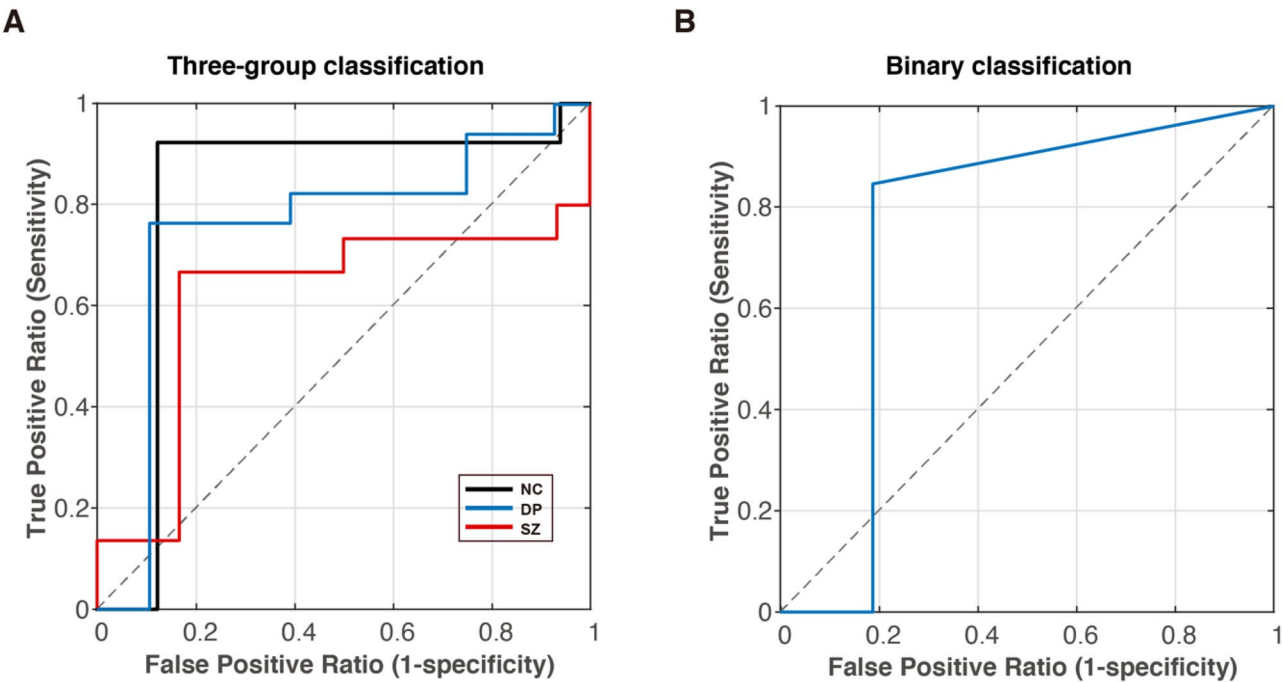


Fig. 6. Receiver operating characteristic (ROC) curves from the classification analysis. **(A)** The ROC curves for the three-group classification. The ROC curves are plotted separately for the NC group versus the two remaining groups, the SZ group versus the two remaining groups, and the DP group versus the two remaining groups. **(B)** The ROC curve for the two-group classification between the drug group (collapsing data from both SZ and DP groups) and the NC group.

	Predicted groups		Actual totals	Actual error%
	NC	Drug		
Actual groups				
NC	11	2	13	15.4%
Drug	6	26	32	18.8%
Predicted totals	17	28	45	–
Prediction error (%)	35.3%	7.1%	–	–

Table 3. The confusion matrix from the two-group classification. NC: Sensitivity = 84.6%, Specificity = 92.9% Drug: Sensitivity = 81.2%, Specificity = 64.7%

Furthermore, extra weight on the extremities increases the tremor amplitude⁵⁰. Indeed, we found significantly more tremors in SZ than in NC and PD. The PD participants showed the same increasing trend, though less pronounced. As expected, both SZ and PD groups showed larger tremors in the frequency range of Parkinson’s tremor, given the common neural underpinnings of the EPS and Parkinsonism. Interestingly, we also found an increase in tremor in the frequency range of essential tremor among the SZ participants, possibly owing to a partially overlapping frequency band of these two types of tremor (5–15 and 4–7 Hz for essential and Parkinson’s tremor, respectively).

Most previous studies have reported reduced postural stability among people with schizophrenia, both with^{65–67} and without medication⁶⁸ when compared to healthy controls. However, we did not find a group difference between the NC group and the SZ group. We postulate that our task might be relatively easy, as our participants stood with their eyes open and feet shoulder-width apart. Some previous studies, instead, instructed the participants to close their eyes and put their feet together during quiet standing, yielding group differences in postural sway^{65–67}. Standing without visual input (eyes open vs. closed) and with a narrow support area (feet together vs. shoulder-width apart) indeed induces less postural stability, thus challenging postural control (e.g.⁶⁹,). Thus, the methodology differences potentially lead to the lack of group differences in our experiment. The DP participants also did not show reduced postural stability, in keeping with previous studies on simple, quiet standing in this population⁷⁰. Surprisingly, within-group correlational analyses revealed that the SZ participants, but not the DP participants, showed less body sway with more severe EPS symptoms indexed by

SAS. We postulate that rigidity induced by antipsychotic use might reduce postural sway, as the rigidity score in the SAS scale also negatively correlated with the body sway within the SZ group.

When examining walking among people with schizophrenia, most previous quantitative studies focused on walking speed and stride length for the sign of ataxic gait (e.g.^{71,72}). Slower walking, shorter steps, and more variability across strides have been widely perceived as the predominant gait abnormalities in schizophrenia^{41,72–76}. We also found that the SZ participants showed significantly longer contact duration and increased variability of contact duration when compared to the controls, consistent with previous studies^{72,75,76}. More importantly, besides the difference in gait speed, our plantar pressure analyses reveal that both SZ and DP participants have abnormal gait coordination at the ankle: they tend to lift their foot off the ground prematurely with a less dynamic range of vertical foot loading. This less-bouncy walking pattern appears clumsy since walking usually features smooth foot roll-off and adequate vertical body movement. Their rigid walking pattern cannot be explained away by slower walking speed, which should lead to delayed instead of premature foot takeoff. It might be attributed to ataxic gait in schizophrenia, drug-induced Parkinsonism, or both. We postulate that drug-induced Parkinsonism plays a significant role here since even the DP participants, who have no ataxic gait but also take antipsychotic medicine, showed similar walking abnormalities. Furthermore, it has been reported that the reduction in gait speed and stride length among schizophrenia patients was more pronounced in patients taking conventional neuroleptics than in drug-naïve patients or patients taking atypical neuroleptics, highlighting the role of drug-induced Parkinsonism in gait disturbance⁷⁴. On a side note, our depression patients' rigid walking is also consistent with their reduction in vertical head movements during walking⁷⁷. Another new insight from our data is that previous studies have examined adults, and our study, instead, shows that adolescents with first-episode schizophrenia already have this abnormal walking pattern. Since foot contact with the ground depends on inter-limb coordination, we propose that instrumental gait measures may serve as indicators of drug-induced Parkinson's syndrome when assessing EPS among people with schizophrenia.

For improving diagnosis, researchers have investigated the use of machine learning algorithms in distinguishing healthy controls and individuals with schizophrenia^{78,79}. Neurophysiological data, e.g., fMRI and EEG^{80–82}, and behavioral data, e.g., language characteristics or facial expression^{83,84}, have been used as discriminant features with varying levels of success. Movement features have seldom been explored. One rare example used daily activity tracking for 489 days to discriminate schizophrenia sub-populations, i.e., people with passive signs and with positive signs, with an accuracy of 80%⁸⁵. One aim of our study is to design comprehensive motor tasks for quantifying motor abnormalities, not for the automatic classification of patient groups. However, our discriminant analysis results suggest that motor abnormalities are able to distinguish different psychiatric populations (i.e., SZ vs. DP). The fact that our motor tasks can be completed in a total of 5 min while yielding a decent discriminant accuracy suggests the potential of instrumental motor tests in the realm of screening and diagnosis of psychosis.

Future studies on the instrumental quantification of motor abnormalities can be improved based on our initial endeavors. First, we should make the movement tasks challenging to highlight patients' motor abnormalities. For example, standing stability can be examined in a tandem stance with eyes closed to induce large body sway. Second, the well-established handwriting task (cite) should be included to have comparative assessments of instrumented motor tasks. Third, a large sample of participants is needed, both for covering a wide spectrum of motor abnormality severity (e.g., indexed by SAS scores) and for detecting possible associations between objective measures and clinical assessment. Our sample of participants was biased to low or mild EPS severity, thus might have prevented us from detecting associations that are really there. Furthermore, more samples would allow better cross-validation for automatic classification. Fourth, our study was conducted on first-episode patients with a cross-sectional design; we plan to follow the participants longitudinally to probe whether and how the progression of motor abnormalities is associated with the changes in core psychiatric symptoms and how these correlates can be captivated for better clinical decisions such as medication adjustment.

As our first endeavor to quantitatively investigate the changes in psychosis and accompanying motor signs, the present study reveals that adolescents with schizophrenia have distinct motor abnormalities when compared to adolescents with depressive disorders and age-matched controls. The two patient groups are first-episode and new to atypical antipsychotic use, suggesting that schizophrenia-specific motor abnormalities (e.g., increased tremor, rigid walking, and less body sway) hold promises for associating motor measures to the efficacy of antipsychotics and the progression of psychosis.

Data availability

The datasets generated and/or analysed during the current study are available in the [figshare] repository, [<https://doi.org/10.6084/m9.figshare.27119754>].

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Author contributions

All authors contributed significantly to the conception, design, execution, and interpretation of the study. K.W. and X.L. contributed to the conception and design of the study. H.D., H.W., W.J., G.H., and Q.L. were responsible for data acquisition. H.D. and W.J. contributed to data analysis and statistical analysis. K.W. and X.L. contributed to interpretation of the data. K.W., H.D., and H.W. were responsible for drafting and finalizing the manuscript. H.D. and H.W. contributed equally to this work. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Declarations

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Additional information

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