Title

The nature of bradykinesia in schizophrenia treated with antipsychotics

Authors

Caligiuri, Michael P
Teulings, Hans-Leo
Dean, Charles E
et al.

Publication Date

2019-03-01

DOI

10.1016/j.psychres.2019.01.058

Peer reviewed

HHS Public Access

Author manuscript

Psychiatry Res. Author manuscript; available in PMC 2020 March 01.

Published in final edited form as:

Psychiatry Res. 2019 March ; 273: 537–543. doi:10.1016/j.psychres.2019.01.058.

The Nature of Bradykinesia in Schizophrenia Treated with Antipsychotics

Michael P. Caligiuri, Ph.D.[1], **Hans-Leo Teulings, Ph.D.**[2], **Charles E. Dean, M.D.**[3], and **James B. Lohr, M.D.**[1,4]

[1]University of California, San Diego, CA

[2]NeuroScript LLC, Tempe AZ

[3]Minneapolis VA, Minneapolis MN.

[4]VA San Diego, Center of Excellence for Stress and Mental Health

Abstract

Recognizing drug-induced parkinsonian bradykinesia in psychosis patients can be challenging due to overlapping presentation with psychomotor slowing associated with depression, negative symptoms, or cognitive disturbances. In this study, we apply prior findings on the pathophysiology of bradykinesia in Parkinson's disease to gain an understanding of motor slowing in psychosis patients. Handwriting movements from 57 healthy participants and 70 psychosis patients were recorded on a digitizing tablet. Temporal and kinematic features were extracted from handwritten loops and circles. An independent objective measure based on peak velocity for circles written at maximum speed was used to classify patients as bradykinetic. Using a statistical cut-point derived from normative data, 64% of the patients met criterion for bradykinesia compared with 46% using a conventional observer-based severity rating scale. Bradykinetic patients produced handwriting movements with longer stroke durations, smaller amplitudes and lower peak velocities compared with non-bradykinetic patients. Thirty-six percent of the pen strokes produced by the bradykinetic patients were non-ballistic compare with 20% for the non-bradykinetic patients. The proportion of nonballistic movements observed in handwriting was unrelated to current antipsychotic dose, severity of negative psychosis or depression. The ease-of-use and standardization of a tablet-based approach to quantifying parkinsonian bradykinesia can aid in diagnosing parkinsonian bradykinesia in patients treated with antipsychotics.

Address Editorial Correspondence to: Michael P. Caligiuri, Ph.D., University of California, Department of Psychiatry (0603), 9500 Gilman Drive, La Jolla, CA 92093, mcaligiuri@ucsd.edu.

Conflict of Interest

Drs. Caligiuri, Dean and Lohr disclose no financial conflicts of interest with commercial entities involved in this research. Dr. Teulings is founder and owner of Neuroscript, LLC, a privately held company that developed and markets Movalyzer® software used in this research.

1. Introduction

Humans use their upper extremities in a variety of ballistic movements including sports such as tennis and golf, waving, striking, reactions to avoid injury, and handwriting. The term ballistic movement was initially proposed by Lashley (1917) and Stetson and McDill (1923) referring to movements that are so short in duration that the initial electromyographic (EMG) agonist burst dampens before the end of the movement. Motor control theorists use the term “open-loop movement” and ballistic movement interchangeably to refer to movements performed without feedback or the possibility of correction (Flowers, 1976).

In their pivotal paper on the physiological mechanism of bradykinesia in Parkinson’s disease (PD), Hallett and Koshbin (1980) found that the normal reciprocal agonist-antagonist-agonist EMG burst pattern associated with rapid ballistic elbow movements was replaced by asynchronous prolonged EMG co-contraction. This led the authors to hypothesize that bradykinesia “must reflect itself in an abnormality of ballistic movements…” (p 301). Others consider motor slowness to stem from an inability of the basal ganglia to sufficiently energize the motor cortex to reach the threshold required to execute movement at a desired speed (Berardelli et al., 2001; Hallett, 2011). The result is prolonged movement time and slow movement speed.

The motor signs associated with drug-induced parkinsonism are thought to be indistinguishable from idiopathic PD (Hassin-Baer et al., 2001; Shin and Chung, 2012; Blanchet and Kivenko, 2016), in that the hallmark signs of rigidity, tremor, and bradykinesia of PD are also present in drug-induced parkinsonism. While most antipsychotics disrupt dopamine transmission leading to extrapyramidal side effects (EPS), the motor signs associated with newer antipsychotics tend to be attenuated and more subtle than with conventional antipsychotics. Unlike idiopathic PD, differentiating parkinsonian motor slowing from psychomotor slowing can be difficult in psychosis patients with comorbid mood disorders. Recognizing parkinsonian bradykinesia is an ongoing challenge due to overlapping presentation of psychomotor and neuromotor slowing in a psychiatric population with comorbid depression, negative symptoms, and cognitive disturbances (Prosser et al., 1987; Weiden et al., 1987; Rummel-Kluge et al., 2012; Geerts et al., 2012). The best pharmacologic treatment decisions aimed at managing medication side effects in such a population depend on a reliable differential diagnosis. We reasoned that gaining a deeper understanding of the nature of motor slowing in patients exposed to antipsychotics may help elucidate the nature of parkinsonian bradykinesia.

Our approach to this problem is to leverage findings from prior research on the pathophysiology of bradykinesia in PD (Hallett and Koshbin, 1980; Berardelli et al., 2001). These showed a fundamental deficit in the ability to execute ballistic movements in PD. Whereas ballistic movements are rapid, executed in the absence of on-line feedback, and have single peak velocity profiles, non-ballistic movements are generally slower, executed within a time period that allows adjustments in trajectory or endpoint based on peripheral feedback, and have velocity profiles containing multiple peaks. Guided movements where accuracy is important are considered non-ballistic due to the reliance upon peripheral feedback to achieve accuracy. Given the range of human motor behaviors wherein endpoint

accuracy is replaced by speed as a performance priority, assessment of handwriting offers advantages over other motor behaviors. First, kinematic analyses of individual pen strokes during natural handwriting reveal velocity profiles consistent with ballistic movements (Plamondon, 1983). Second, handwriting is a well-learned motor behavior requiring minimal attention or cognitive processing making it suitable for studies of psychiatric populations with potential cognitive disorders.

The goal of the present study was to examine whether impairments on objective measures of motor slowing schizophrenia patients share the same features as those observed in idiopathic PD. We hypothesized that patients with unambiguously defined motor slowing based on an independent quantitative measure will exhibit a greater prevalence of non-ballistic pen strokes during handwriting than patients without motor slowing.

2. Methods

2.1 Subjects

Fifty-seven right-handed healthy participants (20 males and 37 females) and 70 right-handed psychiatric patients (48 males and 22 females) meeting DSM-IV criteria for schizophrenia were enrolled into this study. The mean ages of the healthy subjects (42.47± 9.36) and patients (47.40 ± 8.89) were not significantly different. The proportion of male subjects in the patient sample was significantly greater than in the healthy sample (Chi-square = 14.16; $p<0.001$). Subjects were recruited from two sites: San Diego, CA and Minneapolis, MN. Each participant read and signed institutionally approved informed consent prior to participating.

2.2 Clinical Characteristics

All participants underwent a brief medication and psychiatric history, administration of the Abnormal Involuntary Movement Scale (AIMS, Guy, 1976) a modified version of the Simpson-Angus Extrapyramidal Signs Scale (SAEPS, Simpson and Angus, 1970), the Barnes Akathisia Scale (BAS, Barnes, 1989), the Positive and Negative Symptom Scale (PANSS, Kay et al., 1987) to assess the presence and severity of psychosis, and the Calgary Depression Scale (CDS, Addington et al., 1990) to assess severity of depression. Negative symptoms were also rated using the Marder-5 negative symptom factor (Marder et al., 2011) from the PANSS. The modified SAEPS consisted of the standard eight items with the addition of an item to rate bradykinesia by asking the subject to rapidly and repeatedly pronate and supinate each hand separately. The items from the SAEPS (gait, arm drop, four items for rigidity (neck, shoulder, elbow, and wrist) rapid alternating hand movements, tremor, and salivation) were each scored by trained raters using a 4-point ordinal scale with “0” representing absent or normal, “1” mild, “2” moderate, and “3” severe. None of the healthy subjects demonstrated impairment on any of the examiner-rated motor or psychiatric assessments.

Of the 70 patients enrolled in the study, 57 were treated with second generation antipsychotic monotherapy including 13 with aripiprazole, 24 with risperidone, 11 with quetiapine, 7 with olanzapine, and 2 with ziprasidone. Five patients were treated with low

potency conventional agents and eight were off antipsychotics at the time of the study. Daily antipsychotic dose was standardized for statistical purposes across the different antipsychotics by converting to mg/day risperidone equivalents (Kane et al., 2003). Table 1 shows the demographic and clinical characteristics of the study subjects.

2.3 Handwriting Procedures

Upon completion of the clinical assessments, subjects completed the procedure for quantifying handwriting movements. Pen movements were recorded using a non-inking pen and Wacom[1] Intuos UD 9 × 12 digitizing tablet (30 cm × 22.5 cm, sampling rate = 100 samples/second, RMS accuracy 0.01 cm) attached to a notebook computer running MovAlyzeR® software[2]. Our prior studies of handwriting movement in psychiatric patient samples involved a battery of 15 tasks (Caligiuri et al., 2009; 2010). For the purpose of this study with its focus on bradykinesia, we report a reanalysis of handwriting kinematics from five of the original tasks: writing complex loops (“lleellee”), writing simple loops written from left to right (“llllllll”), drawing overlay circles with the dominant and non-dominant hands at a comfortable speed, and drawing overlay circles written with the dominant hand at maximum speed. Subjects were instructed to write the loops and circles within a 4 cm vertical boundary marked on the tablet surface. The rapid overlay circles were produced with 2 cm vertical boundary markers. The tasks were administered in random order with a fixed block of 5 trials for each condition. Minimal training is required to administer the handwriting assessment as the procedures involve no decision-making on the part of the examiner and stimulus delivery is automatic.

Subjects were seated comfortably at a table with the digitizing tablet positioned to allow natural writing for a given subject. Subjects were free to move the tablet to improve comfort and create a normal writing environment. Prior to the start of data collection, the subject was shown a visual copy of the task, given instructions, and provided with a practice period to ensure familiarity with writing on the tablet using an inkless stylus. Subjects were instructed to begin writing the continuous loops or circles until told by the examiner to stop and lift the pen. Each trial lasted 10 seconds with a 2-second interval between trials. When the five trials were completed, the program paused while the examiner issued a new set of instructions for a new condition. This sequence was repeated for all conditions. Trials with delays in initiating the writing task or trials where the subject stopped before the writing task was completed were re-administered. The handwriting procedures required approximately 10 minutes. Samples of the loop and circle tasks from a healthy subject are shown in Figure 1. The figure shows handwriting traces from single trials for each of three tasks: drawing repetitive overlay circles (top), writing continuous left-to-right loops (middle), and writing complex loops (bottom). Pen movements associated with each up and down stroke for each trial (14–16 strokes in these examples) were subjected to kinematic analyses (see below).

[1] http://wacom.com
[2] http://neuroscript.net

2.4 Data Reduction and Analysis

Handwriting samples were subjected to processing and analysis using Movalyzer software. Handwriting patterns were low-pass filtered at 12 Hz and time derivatives were estimated. Reduction and analysis of the handwriting kinematics involved the automatic extraction of multiple variables from each vertical pen stroke from each trial of each handwriting pattern. The kinematic variables measured for this study included: stroke duration (in milliseconds), vertical stroke amplitude or size (in centimeters), peak vertical velocity (in centimeters/second), and the percentage of non-ballistic strokes. Non-ballistic pen strokes were defined as strokes containing more than a single velocity peak over the movement period from stroke amplitude minima to stroke maxima. The kinematic features were computed for both upstrokes and downstrokes and then averaged across all vertical strokes of the trial and across trials. Figure 2 shows two examples of overlay circles written by a healthy subject (left) and a study patient with suspected parkinsonism (right). Raw data in X and Y coordinate space are depicted in the top traces. Shown below the raw waveforms are the vertical displacement (middle) and its 1st time derivative (bottom). Multiple velocity peaks per stroke are evident in the 1st time derivative for the patient sample (right) compared to the healthy subject. In this example, the proportion of vertical strokes containing multiple peaks in the velocity waveform indicating non-ballistic movement patterns was 17% for the healthy subject and 77% for the patient for the trial shown.

Bradykinesia is traditionally evaluated using observer-based rating scales such as the modified SAEPS. Due to concerns over the reliability, subjectivity, and insensitivity of observer rating scales to detect mild forms of parkinsonian bradykinesia in patients with psychosis, we decided to classify patients as presenting upper extremity bradykinesia using an independent objective quantitative measure derived from the circle drawing task performed at maximum speed. This measure was chosen as simple circles drawn as fast as possible requires minimal information processing, memory, attention, sequencing or set-changing and as such would have little mechanistic overlap with psychomotor slowing. Upper extremity bradykinesia was objectively defined as the average peak velocity across trials and strokes for the maximum speed overlay circle task that were below the 95th percent confidence limit (i.e. 17.43 cm/s) of the healthy age-comparable subject mean. Scores from the heathy control subjects on the rapid overlay circle drawing task were used to establish the 95th percent confidence interval and cut-point for classifying bradykinesia. As the rapid circle drawing task was used to identify patient subgroups, velocity scores on this task were not included among the experimental variables used to test the study's hypothesis.

2.5 Statistical Analyses

We tested the study's hypothesis by performing statistical tests for differences in handwriting kinematics associated with parkinsonian bradykinesia in bradykinetic and nonbradykinetic patients. Group scores were subjected to tests of homogeneity of variance and normal distribution and found not to satisfy these assumptions for using parametric statistics. Thus, for all comparison, we used non-parametric Mann-Whitney tests. Nonparametric Spearman correlation coefficients were used to identify potential associations between the putative bradykinesia variables extracted from handwriting movements and non-motor conditions that could manifest as slow movement such as negative symptoms of

psychosis, depression and other motor side effects such as tardive dyskinesia (TD) and akathisia that could impact performance on the handwriting measures. P-values from statistical difference tests were adjusted for multiple comparisons using the Benjamini-Hochberg (BHp) method for correcting alpha to control the false discovery rate (Benjamini and Hochberg, 1995). BHp values ≤ 0.05 were considered significant. Statistical comparisons between the healthy subjects and psychosis patients were not performed.

3. Results

Forty-five (64%) of the 70 patients produced rapid overlay circles with mean peak velocity below the lower 95th confidence interval of peak velocity scores obtained from healthy comparison subjects and were considered bradykinetic for the purpose of this study. Based on individual item scores of the modified SAEPS, 32 of the 70 patients (46%) were rated as having mild-moderate bradykinesia. Significantly more patients met the instrumental criterion for bradykinesia compared to SAEPS ratings (Chi-Square = 4.88; $p<0.05$). Among the 45 patients considered bradykinetic based on the instrumental measure, 22 (49%) were rated has having at least mild bradykinesia on the clinical measure, indicating that the handwriting measure for classifying bradykinesia (maximum speed circle drawing) and the SAEPS bradykinesia item are independent. Table 2 shows the clinical characteristics of the 50 bradykinetic and 27 nonbradykinetic patients. None of the group differences shown in Table 2 reached statistical significance based on paired t-tests or Chi-Square test (for gender) indicating that the bradykinetic and non-bradykinetic patients are comparable in all other respects.

Table 3 shows the descriptive statistics for two patient groups on variables associated with parkinsonian bradykinesia including movement duration, movement amplitude, peak velocity and the proportion of non-ballistic movements.

Stroke Duration.

For all tasks, bradykinetic patients produced pen strokes with significantly longer stroke durations than non-bradykinetic patients. Mann-Whitney tests for two independent groups were significant for the complex loop ($Z=2.47$; $p=0.012$; BHp = 0.02); left-to-right loops ($Z=2.92$; $p<0.003$; BHp=0.008); overlay circles with the dominant hand ($Z=3.77$; $p<0.0001$; BHp<0.0005); and overlay circles with the non-dominant hand ($Z=2.34$; $p=0.018$; BHp=0.025).

Vertical Stroke Amplitude.

With the exception of complex loops, bradykinetic patients produced pen strokes with significantly lower stroke amplitudes than non-bradykinetic patients. Mann-Whitney tests for two independent groups were nonsignificant for the complex loop ($Z=-1.84$; $p=0.06$; BHp = 0.06); however, significant for left-to-right loops ($Z=-3.25$; $p=0.0009$; BHp=0.004); overlay circles with the dominant hand ($Z=-2.25$; $p=0.02$; BHp=0.025); and overlay circles with the non-dominant hand ($Z=-2.87$; $p=0.003$; BHp=0.008).

Peak Vertical Velocity.

For all tasks, bradykinetic patients produced pen strokes with significantly lower stroke velocities than non-bradykinetic patients. Mann-Whitney tests for two independent groups were significant for the complex loop ($Z=-3.43$; $p=0.0004$; $BHp=0.009$); left-to-right loops ($Z=-4.40$; $p<0.0001$; $BHp<0.0005$); overlay circles with the dominant hand ($Z=-4.64$; $p<0.0001$; $BHp<0.0005$); and overlay circles with the non-dominant hand ($Z=-2.77$; $p=0.005$; $BHp=0.01$).

%Nonballistic Movements.

With the EXCEPTION of the complex loop task, bradykinetic patients produced handwriting movements with significantly more non-ballistic strokes than nonbradykinetic patients. Mann-Whitney tests for two independent groups were significant for the left-to-right loops ($Z=1.97$; $p<0.05$; $BHp<0.05$); overlay circles with the dominant hand ($Z=3.33$; $p=0.0006$; $BHp=0.002$); and overlay circles with the non-dominant hand ($Z=2.31$; p-0.019; $BHp=0.025$). When averaged across the four tasks, 36% of the pen strokes produced by the bradykinetic patients were non-ballistic compare with 20% for the non-bradykinetic patients.

Correlational tests revealed that scores on the handwriting kinematic variables were unrelated to severity of negative or positive symptoms of psychosis (PANSS), depression (CDS and Marder-5), or TD (AIMS total score). Concern over differences in the gender distribution between patients and healthy subjects prompted an exploratory analysis of gender effects on the kinematic measures. Analyses of variance were performed to test main effects of gender on handwriting stroke duration, stroke size, peak velocity, and % non-ballistic movements and, where appropriate, interactions between gender, bradykinesia group, and handwriting task. None of the main effects of gender reached statistical significance for any of kinematic measures.

Among patients treated with second generation antipsychotic monotherapy (n=57) we found a low but positive relationship between % non-ballistic movements and average daily dose (in RispEq mg/d) for the left-to right loop task ($r=0.27$ $p=0.02$) and overlay circle drawing with non-dominant hand ($r=0.27$; $p=0.02$). With the exception of risperidone-treated patients, sample sizes for patients treated with the same antipsychotic were insufficient for this analysis. Among the 24 risperidone-treated patients, we found significant relationships between increase in % of non-ballistic movements and average daily dose for overlay circle drawing with non-dominant hand ($r=0.45$; $p=0.03$) and complex loops ($r=0.58$; $p=0.004$). No other relationships between kinematic features of motor slowing and antipsychotic dose were observed. There were no differences in the proportion of patients meeting the study's criterion for bradykinesia versus not among patients treated with risperidone (13 vs 11), quetiapine (6 vs 5), olanzapine (5 vs 2), or among the untreated patients (4 vs 4). Only among the aripiprazole-treated patients did more meet criterion for bradykinesia than not (11 vs 2).

4. Discussion

The present study tested the hypothesis that patients with unambiguously defined motor slowing based on an independent quantitative measure will exhibit a greater prevalence of non-ballistic pen strokes during handwriting than patients without motor slowing. Deficits in the execution of ballistic movement during handwriting has been shown in prior research to form the physiologic basis of bradykinesia in PD (Hallett and Koshbin, 1980; Berardelli et al., 2001). The results of the present study show that 36% of the handwritten pen strokes produced by the bradykinetic patients were non-ballistic in contrast to 20% for patients not meeting criteria for bradykinesia.

Our criterion for classifying patients as meeting criteria for bradykinesia based on a statistical cut-point for hand movement velocity is a novel component of the present study. Using a normative sample of 57 healthy individuals, we identified the 95% confidence interval around the mean velocity for rapid circle drawing. Patients producing movement velocities below the 95% cut-point on the same task were defined as having bradykinesia. Based on this objective measure for bradykinesia, 65% of the study patients exhibited bradykinesia compared to 42% based on observer ratings. The lower prevalence of clinically defined bradykinesia compared with an instrumental approach suggests that many patients treated with second generation antipsychotics may exhibit at least mild parkinsonism that can be difficult to assess using traditional rating scales.

Clinical assessments of extrapyramidal signs in psychiatric patients generally involve observer severity ratings using multi-item scales such as the SAEPS to detect the presence and severity of parkinsonian signs. However, as with all subjective use of such scales in research settings may introduce problems in reliability and sensitivity due to the variability in clinical experience and training of the rater in the use of such scoring systems. This can be particularly problematic in studies of bradykinesia with this patient population where cognitive, affective, and/or neurological factors can contribute to slow movement and blur the distinction between neuromotor and psychomotor slowing.

In the present study, the possibility that psychomotor slowing could manifest as significantly reduced movement velocity during handwriting was examined by comparing bradykinetic with non-bradykinetic patients on several clinical scales. We found no significant differences between bradykinetic and non-bradykinetic patients in terms of severity of psychosis or depression. As such, our classification of patients into bradykinetic or non-bradykinetic subgroups appears to be based on a pure motor criterion uninfluenced by psychosis or mood state. Importantly, the proportion of nonballistic movements in handwriting was unrelated to negative psychosis or depression. In practice, it is difficult to dissociate psychomotor slowing from parkinsonian bradykinesia as both phenomena can co-exist in schizophrenia patients treated with antipsychotics who continue to present negative symptoms or affective psychosis. The present study demonstrated that a disturbance in the execution of ballistic movements reported to underly bradykinesia in PD (Hallet and Koshbin, 1980) is also a feature in drug-induced parkinsonism.

The association between average daily antipsychotic dose for risperidone-treated patients and proportion of nonballistic movements supports the notion that the anti-dopaminergic properties of some antipsychotics may underly the deficits in execution of ballistic handwriting movements and subsequently, parkinsonian bradykinesia. The lack of this relationship among patients treated with agents having minimal dopamine D_2 receptor blocking properties (such as quetiapine or olanzapine) lends further support to this notion. Nonetheless, the question of whether a given antipsychotic agent is associated with more or liability for parkinsonian bradykinesia can best be answered by studying patients before and following their first exposure to an antipsychotic.

This study departed from the convention of diagnosing bradykinesia using an observer rating scale and instead relied upon an instrumental measure of handwriting speed. Performance on this handwriting speed measure was unrelated to severity of psychopathology or other co-morbid movement disorders such as TD and akathisia, supporting the face validity of the handwriting speed measure. More importantly, slowness on this measure coincided with other aspects of movement as predicted by decades of research on the phenomenology of bradykinesia in Parkinson's disease (Hallett and Koshbin,1980; Berardelli et al., 2001; Hallett, 2011). Thus, a cluster of motor signs consisting of reduced movement velocity, increased movement duration, reduced movement amplitude, and greater proportion of non-ballistic movements characterizing bradykinesia in idiopathic PD is also seen in drug–induced parkinsonism. Nonetheless, caution should be exercised in future research aimed at kinematic modelling of parkinsonian bradykinesia due to potential inter-correlations between velocity, duration and amplitude. The proportional relationship between movement speed and distance (velocity scaling or isochrony) has been well established in studies of human motor control (Teulings, 1996) and can be demonstrated in studies of handwriting in PD (Nackaerts et al., 2017) and drug-induced parkinsonism (Caligiuri et al., 2006).

Prior research on quantifying bradykinesia in drug-induced bradykinesia has relied largely upon measures of upper limb or hand movement speed (Caligiuri et al., 2009; Koning et al., 2011; Mentzel et al., 2016). These procedures exhibit greater sensitivity to mild early forms of bradykinesia than observer ratings; however, their specificity in distinguishing psychomotor retardation from parkinsonism has not been established because slowness per se can be a manifestation of several conditions including depression, negative psychosis, motivation, advanced age, and drug-induced parkinsonism. As the present study suggests, with access to minimal technology capable of recording simple unidirectional movements, clinicians can extract important diagnostic information (e.g. the number of velocity peaks present in a single movement) from these recordings to detect pure neuromotor abnormalities. While the present findings were based on handwriting movements, it is possible to extend these observations to other forms of movement. An optimal test battery for distinguishing neuromotor from psychomotor abnormality would include tasks with varying cognitive demands. Efforts are underway to develop applications on mobile devices for recording peak velocities (and the number of velocity peaks) from stylus-based handwriting and drawing.

In conclusion, the inability to execute rapid movements as a single ballistic motion may be a core feature in both antipsychotic-induced bradykinesia and idiopathic Parkinson's disease.

Measures of handwriting kinematics including pen stroke duration, velocity and disruption in formation of ballistic movements can improve objectivity and sensitivity in the clinical assessment of mild antipsychotic-induced bradykinesia. Nevertheless, additional research is needed to confirm that kinematic features of handwriting including disturbances in the execution of ballistic movement are valid indices of parkinsonian bradykinesia and should be relatively spared in neuroleptic-naïve patients with psychomotor retardation secondary to major depressive disorder. The ease-of-use and standardization of a tablet-based approach to quantifying parkinsonian bradykinesia can aid in diagnosing parkinsonian bradykinesia in patients treated with antipsychotics.

Acknowledgments

This research was supported by NIH grant R44 MH073192.

References

Addington D, Addington J, Schizzel B 1990 A depression rating scale for schizophrenics. Schizophrenia Research 3: 247–251. [PubMed: 2278986]

Barnes TR 1989 A rating scale for drug-induced akathisia. British Journal of Psychiatry 154, 672–676. [PubMed: 2574607]

Benjamini Y, Hockberg Y. 1995 Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Royal Statistical Society, Series B 57 (1) 289–300.

Berardelli A, Rothwell JC, Thompson PD, Hallett M 2001 Pathophysiology of bradykinesia in Parkinson's disease. Brain 124: 2131–2146. [PubMed: 11673316]

Blanchet PJ, Kivenko V 2016 Drug-induced parkinsonism: diagnosis and management. J Parkinsonism and Restless Legs Syndrome. 6: 83–91

Caligiuri MP, Teulings HL, Filoteo JV, Song D, Lohr JB 2006 Quantitative measurement of handwriting in the assessment of drug-induced parkinsonism. Hum Mov Sci. 25(4–5):510–22. [PubMed: 16647772]

Caligiuri MP, Teulings HL, Dean CE, Niculescu AB, Lohr JB 2009 Handwriting movement analyses for monitoring drug-induced motor side effects in schizophrenia patients treated with risperidone. Human Movement Science. 28:633–42. [PubMed: 19692133]

Caligiuri MP, Teulings HL, Dean CE, Niculescu AB, Lohr JB 2010 Handwriting movement kinematics for quantifying EPS in patients treated with atypical antipsychotics. Psychiatry Research 77(1–2): 77–83.

Flowers KA 1976 Visual 'closed loop' and 'open loop' characteristics of voluntary movements in patients with parkinsonism and intention tremor. Brain 99: 269–310. [PubMed: 990899]

Geerts H, Spiros A, Roberts P, Twyman R, Alphs L, Grace A 2012 Blinded prospective evaluation of computer-based mechanistic schizophrenia disease model for predicting drug response. PLoS ONE 7: e49732 Doi:10.1371/journal.pone.0049732 [PubMed: 23251349]

Guy W 1976 Abnormal Involuntary Movement Scale (AIMS) In: ECDEU Assessment Manual for Psychopharmacology, rev. ed. DHEW Pub. No. (ADM. 76–338). National Institute of Mental Health, Rockville, MD, pp. 534–537.

Hallett M 2011 Bradykinesia: Why do Parkinson's patients have it and what does it cause? Movement Disorders 26: 1579–1581. [PubMed: 21547949]

Hallett M and Koshbin S 1980 A physiological mechanism of bradykinesia. Brain 103: 301–314. [PubMed: 7397480]

Hassin-Baer S, Sirota P., Korczyn AD Treves TA Epstein B, Shabtai H et al., 2001 Clinical characteristics of neuroleptic-induced parkinsonism. J Neurol Transm 108: 1299–1308.

Kane JM, Leucht S, Carpenter D, Docherty JP 2003 Expert Consensus Panel for Optimizing Pharmacologic Treatment of Psychotic Disorders. The Expert Consensus Guideline Series.

Optimizing pharmacologic treatment of psychotic disorders: introduction, methods, commentary, and summary. Journal of Clinical Psychiatry 64 (Supplement 12), 5–19.

Kay SR, Fiszbein A, Opler LA 1987 The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin 32, 261–76.

Koning JP Kahn RS Tenback DE van Schelven LJ van Harten PN 2011 Movement disorders in nonpsychotic siblings of patients with nonaffective psychosis. Psychiatry Res. 188: 133–137. [PubMed: 21277026]

Lashley KS 1917 The accuracy of movements in the absence of excitation from the moving organ. American Journal of Physiology 20: 169.

Marder SR, Daniel DG, et al., 2011 Methodological issues in negative symptom trials. Schizophr. Bull 37 (2), 250–254. [PubMed: 21270473]

Mentzel TQ, Lieverse R, Levens A, Mentzel CL Tenback DE, Bakker PB, Daanen HAM, van Harten PN 2016 Reliability and validity of an instrument for the assessment of bradykinesia. Psychiatry Res 238: 189–195. [PubMed: 27086232]

Nackaerts E, Broedeer S, Pereira MP, Vandenberghe W, Nieuwboer A, Hermans E 2017 Handwriting training in Parkinson's disease: A trade-off between size, speed, and fluency. PLoS ONE 12(12): e0190223. [PubMed: 29272301]

Plamondon R 1993 Looking at handwriting generation from a velocity control perspective. Acta Psychologica 82: 89–101. [PubMed: 8475778]

Prosser ES, Csernansky JG, Kaplan J, Thiemann S, Becker TJ, Hollister LE 1987 Depression, parkinsonian symptoms, and negative symptoms in schizophrenics treated with neuroleptics. Journal of Nervous and Mental Disorders175(2):100–5.

Rummel-Kluge C, Komossa K, Schwartz S, Hunger H, Schmid F, Kissling W, Davis JM Leucht S 2012 Second-generation antipsychotic drugs and extrapyramidal side effects: A systematic review and meta-analysis of head-to-head comparisons. Schizophrenia Bulletin 38: 167–177 [PubMed: 20513652]

Shin H-W; Chumg SJ 2012 Drug-induced parkinsonism. J Clin Neurol. 8: 15–21 [PubMed: 22523509]

Simpson GM, Angus JWS 1970 A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica 212 (Suppl 44), 11–19. [PubMed: 4917967]

Stetson RH, McDill JA 1923 Mechanisms of different types of movements. Psychological Monographs. 32: 18–45.

Teulings H-L 1996 Handwriting movement control In: Keele SW and Heuer H (Eds.), Handbook of Perception and Action. 2: Motor Skills: 561–613. London: Academic Press.

Weiden PJ, Mann JJ, Haas GL, Mattson M, Frances A1987 Clinical nonrecognition of neuroleptic-induced movement disorders: A cautionary study. American Journal of Psychiatry 144:1148–53. [PubMed: 2888321]

Highlights

- An objective measure based on speed of handwritten circles was used to classify patients as bradykinetic. Using a norm-based statistical cut-point, 64% of the patients met criterion for bradykinesia vs 42% using an observer-based severity rating scale.
- Thirty-six percent of the pen strokes produced by the bradykinetic patients were non-ballistic compare with 20% for the non-bradykinetic patients.
- Bradykinetic patients produced handwriting movements with longer stroke durations, smaller amplitudes and lower peak velocities compared with nonbradykinetic patients.
- A tablet-based approach to measuring a core feature of parkinsonian bradykinesia can aid in the diagnosis of neuromotor deficits in patients with schizophrenia treated with antipsychotics.

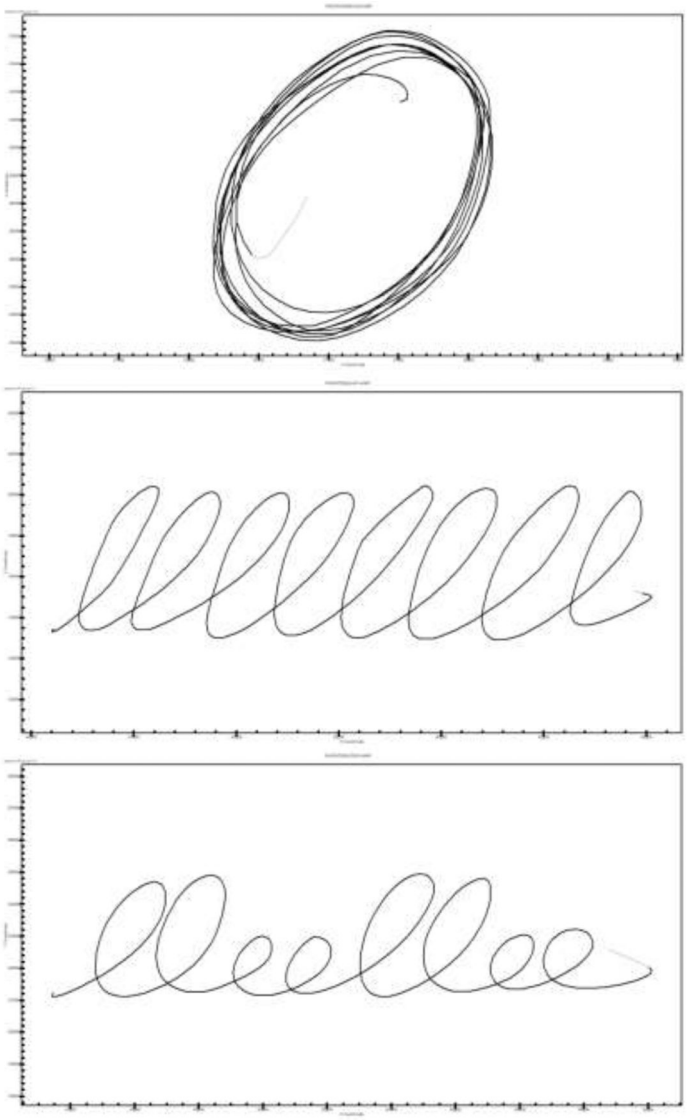

Figure 1.
Sample raw waveforms from a single subject writing repetitive overlay circles (top), continuous left-to-right loops (middle), and complex loops (bottom).

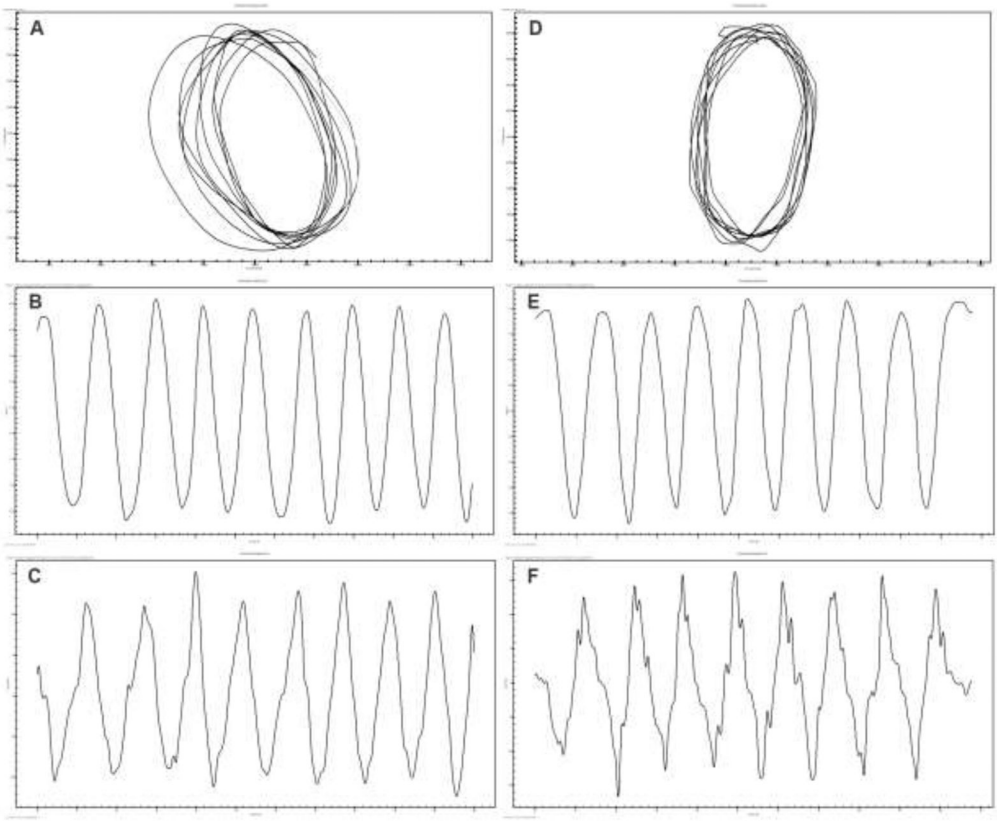

Figure 2.

Handwriting waveforms for overlay circles written with the non-dominant hand by a healthy subject (A, B and C) and an patient with bradykinesia (D, E, and F). Shown are the raw vertical (Y-axis) and horizontal (X-axis) amplitude waveforms (A and D), vertical displacement over time (B and E) and the 1st time derivative of the vertical displacement over time (C and F). Panel F shows multiple peaks in the 1st time derivative indicating non-ballistic pen strokes for the bradykinetic subject not present for the healthy subject (Panel C).

Table 1.

Clinical Characteristics* of the study patients (n=70)

	Mean	SD	range
Age	47.40	8.89	26–59
AIMS	3.66	2.85	0–13
SAEPS	4.71	3.56	0–16
BAS-Global	1.26	1.18	0–3
PANSS Total	66.04	16.74	30–109
Marder-5	12.67	4.47	5–23
CDS-Total	4.25	4.16	0–15
APD daily dose	4.35	3.00	0–10

*AIMS = Abnormal Involuntary Movement Scale; SAEPS = Simpson-Angus EPS Scale; BAS-G = Barnes Akathisia Scale, Global Rating; PANSS = Positive and Negative Symptom Scale; Marder-5 = 5-item negative symptom factor from PANSS; CDS= Calgary Depression Scale; APD=Antip sychotic Drug dose in mg risperidone equivalents/day.

Table 2.

Clinical and demographic characteristics* of the bradykinetic and non-bradykinetic patients. Shown are mean (sd) scores.

Variable	Bradykinetic Patients (n=45)	Non-Bradykinetic Patients (n=25)
Age	47.89 (8.12)	46.52 (10.25)
Gender (M:F)	29:16	19:6
AIMS	3.53 (2.65)	3.88 (3.23)
SAEPS	5.02 (3.79)	4.16 (3.10)
BAS-Global	1.31 (1.24)	1.16 (1.10)
PANSS-Total	64.56 (17.40)	68.72 (15.45)
PANSS-Positive	16.04 (5.41)	18.08 (6.51)
PANNS-Negative	17.47 (5.31)	13.42 (3.36)
Marder-5	12.61 (4.38)	12.79(4.71)
CDS-Total	4.16 (4.57)	4.42 (3.36)
APD Daily Dose	4.36 (2.84)	4.33 (3.12)

* AIMS = Abnormal Involuntary Movement Scale; SAEPS = Simpson-Angus EPS Scale; BAS-G = Barnes Akathisia Scale, Global Rating; PANSS = Positive and Negative Symptom Scale; Marder-5 = 5-item negative symptom factor from PANSS; CDS= Calgary Depression Scale; APD=Antipsychotic Drug dose in mg isperidone equivalents/day

Table 3.

Mean scores (standard deviations) for four handwriting kinematic variables extracted from four handwriting patterns associated with parkinsonian bradykinesia including movement duration, vertical movement size, peak velocity and the proportion of non-ballistic movements (NBM) for bradykinetic (B) and non-bradykinetic (N) patients (see text for statistical significance).

Pattern	Group	N	Duration (seconds)	Size (cm)	Peak Velocity (cm/s)	%NBM
Complex Loops	N	24*	0.40 (0.16)	2.71 (0.36)	13.96 (4.50)	19.26 (19.45)
	B	44*	0.54 (0.25)	2.53 (0.41)	10.03 (3.00)	31.59 (29.93)
Left-to-Right Loops	N	25	0.44 (0.16)	3.82 (0.35)	17.85 (5.07)	18.18 (18.37)
	B	45	0.60 (0.25)	3.43 (0.55)	12.15 (3.31)	32.62 (29.48)
Overlay Circles with Dominant Hand	N	25	0.34 (0.17)	3.64 (0.40)	21.86 (7.32)	10.43 (16.80)
	B	45	0.57 (0.31)	3.33 (0.55)	12.82 (4.75)	30.46 (30.28)
Overlay Circles with Non-Dominant Hand	N	25	0.53 (0.21)	3.87 (0.34)	15.45 (6.31)	32.52 (28.41)
	B	45	0.66 (0.24)	3.52 (0.54)	11.24 (3.42)	48.89 (27.54)

*Complete data not collected from two patients.