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Handwriting movement kinematics for quantifying extrapyramidal side effects in patients treated with atypical antipsychotics

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ABSTRACT

Ongoing monitoring of neuroleptic-induced extrapyramidal side effects (EPS) is important to maximize treatment outcome, improve medication adherence and reduce re-hospitalization. Traditional approaches for assessing EPS such as Parkinsonism, tardive akathisia, or dyskinesia rely upon clinical ratings. However, these observer-based EPS severity ratings can be unreliable and are subject to examiner bias. In contrast, quantitative instrumental methods are less subject to bias. Most instrumental methods have only limited clinical utility because of their complexity and costs. This paper describes an easy-to-use instrumental approach based on handwriting movements for quantifying EPS. Here, we present findings from psychiatric patients treated with atypical (second generation) antipsychotics. The handwriting task consisted of a sentence written several times within a 2 cm vertical boundary at a comfortable speed using an inkless pen and digitizing tablet. Kinematic variables including movement duration, peak vertical velocity and the number of acceleration peaks, and average normalized jerk (a measure of smoothness) for each up or down stroke and their submovements were analyzed. Results from 59 psychosis patients and 46 healthy comparison subjects revealed significant slowing and dysfluency in patients compared to controls. We observed differences across medications and daily dose. These findings support the ecological validity of handwriting movement analysis as an objective behavioral biomarker for quantifying the effects of antipsychotic medication and dose on the motor system.

1. Introduction

Neuroleptic medications have been the mainstay for treating psychotic illness for over 50 years. While neuroleptics improve the lives of schizophrenic patients, the occurrence of neuroleptic-induced extrapyramidal side effects (EPS) with increasing dosage often imposes limits on the dosage actually required to treat the disease. Even after the emergence of second generation antipsychotics, EPS continue to cause concern (Miller et al., 2008), particularly in vulnerable populations, such as the elderly (Caligiuri et al., 2000).

Ongoing monitoring of EPS is important to maximize treatment outcome, improve medication adherence and reduce re-hospitalization. Effective management of EPS begins with early detection, and eventually, prevention. Early detection of EPS requires sensitive and reliable measurement. Traditional means of assessing EPS rely upon observer judgments of severity, but these subjective ratings suffer from low reliability, even after the required extensive training, and are insensitive to mild subclinical abnormalities (Lohr and Caligiuri, 1992; Caligiuri, 1997). Different examiners show different average judgments of the same patients, resulting in examiner bias. To overcome these limitations, investigators have developed instruments for quantifying EPS (e.g., load cells, strain gauges, accelerometers, and electromyograms). While these instruments enjoyed appeal in research settings, they have not been adopted for routine clinical or bedside use. The main reason is because these procedures require levels of technical expertise not always available in clinical settings. Currently, no techniques for the quantitative and objective measurement of EPS severity are available that can be easily used by neurologists, psychiatrists, and other practitioners in the clinical setting.

One such approach to quantifying drug-induced motor side effects involves the analysis of handwriting movements. Haase (1961) was the first to demonstrate a relationship between the clinical effectiveness of neuroleptic mediation and EPS using handwriting analysis. Haase noted that as neuroleptic dosage increased, patients showed Parkinsonism; their handwriting slowed (bradykinesia) and decreased in size, resembling the micrographia observed in Parkinson's disease. The use of handwriting movements to assess EPS has been a focus of research primarily in Europe (Haase, 1978; Gerken

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et al., 1991; Künstler et al., 1999, 2000). However, the results have been mixed. For example, Gerken et al. (1991) used movement size (expressed by the area encompassed by handwriting) in schizophrenic patients for predicting treatment response. In their small sample of patients, they observed reductions in handwriting size in three of the nine treatment responders and in nine of the 12 treatment non-responders, suggesting that the handwriting movement size was unable to predict treatment response. Künstler et al. (2000) used single photon emission tomography to examine the relationship between the handwriting area and the dopamine D_2 receptor occupancy in schizophrenic patients before and after treatment with haloperidol, clozapine, or risperidone. They reported a highly significant linear relationship between the D_2 receptor occupancy and the reduction in handwriting area. In a second study of 10 schizophrenic patients who received medication for the first time, Regenthal et al. (2005) reported positive correlations between the D_2 receptor occupancy, the plasma level of risperidone and its active metabolite 9-hydroxyrisperidone and the reduction in handwriting area. While none of the patients exhibited clinically observed EPS, the authors concluded that the analysis of handwriting movements might be well suited for evaluating the neurological side effects of neuroleptic medications because of their sensitivity to D_2 receptor occupancy.

The purposes of the present study were to test whether handwriting kinematic measures show greater impairments for some atypical antipsychotic medication than for others and whether the severity of impairment is related to the daily dose. Additionally, we aimed to compare the medication and dose effects on handwriting kinematics with those for traditional observer-based EPS severity ratings.

2. Methods

2.1. Subjects

This study involved a multi-site parallel group design. Subjects were recruited and tested at the three sites including: San Diego, CA; Minneapolis, MN; and Indianapolis, IN. The study was carried out in accordance with the 1964 Declaration of Helsinki and all subjects signed institution-approved informed consent prior to participating. Subjects from each site received the same clinical evaluation and a computer-controlled handwriting motor test in the same order, using the same procedures. The original cohort consisted of 113 psychosis patients and 46 healthy comparison subjects. Patients were excluded for the following reasons: treatment with multiple antipsychotics including conventional agents ($n=17$); treatment with an anticholinergic medication ($n=18$); off antipsychotic at the time of testing ($n=11$); insufficient clinical or medication data ($n=8$). Thus, the final group consisted of 59 psychosis patients with active psychotic illness.

The mean (S.D.) age of the patient group was 50.55 years (8.72), which was higher than the mean for the healthy comparison subjects of 42.21 years (9.30) ($t=4.70$; $P<0.01$). We do not assume that the group difference we found could be explained as an aging effect. For example, Teeken et al. (1996) found that most age-related slowing is observed in discrete aiming movement tasks, while rapid, reciprocal arm movement tasks, comparable to continuous handwriting, show no significant slowing across this age range. The patient group consisted of 43 males and 16 females, whereas the healthy comparison group comprised 14 males and 32 females. The male: female ratio for the two subject groups was different ($\chi^2=18.77$; $P<0.001$). Similar to the aging effect, gender shows mainly an effect on the discrete movements but no effect on the reciprocal movements, which is comparable to the continuous handwriting (Teeken et al., 1996). In spite of this evidence that the age and gender differences between groups is expected to have little effect, additional statistical tests were performed to examine any effects of these demographic variables on the handwriting movements.

2.2. Clinical characteristics of study patients

Patients met the DSM-IV criteria for either schizophrenia ($n=45$) or schizoaffective disorder ($n=14$). The study patients underwent clinical movement disorder assessment using the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976) for tardive dyskinesia, the Simpson–Angus EPS scale (SAEPS; Simpson and Angus, 1970) for drug-induced Parkinsonism, and the Barnes Akathisia Scale (BAS; Barnes, 1989) for akathisia. The severity of the positive and the negative symptoms of psychosis was rated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987).

Fifty-one of the 59 patients were treated with a single atypical antipsychotic: aripiprazole ($n=10$); risperidone ($n=17$), quetiapine ($n=9$), olanzapine ($n=10$), ziprasidone ($n=3$) or clozapine ($n=2$). The remaining eight patients were on two atypical antipsychotics (risperidone in seven of the eight patients plus another atypical antipsychotic). The antipsychotic dose for each of these medications was converted to the risperidone equivalent dose based on the conversion table published in a consensus report (Kane et al., 2003). For cases treated with more than a single antipsychotic, the equivalent doses for all antipsychotics were summed to yield the net equivalent dosage. Table 1 shows the statistics of the examiner assessments and the equivalent dosage for the group of the 59 patients.

Table 1
Patient characteristics ($n=59$).

Clinical variable	Mean (S.D.)
Positive and Negative Syndrome Scale (PANSS), total score	63.98 (17.49)
Positive symptom score from PANSS	15.75 (5.81)
Negative symptom score from PANSS	16.69 (5.77)
Barnes Akathisia Scale (BAS), global score	1.13 (1.16)
Abnormal Involuntary Movement Scale (AIMS), total score	3.19 (2.92)
Simpson-Angus EPS (SAEPS), total score	4.84 (3.74)
Average daily dose, mg/day risperidone equivalents	4.85 (3.26)

2.3. Kinematic variables of handwriting

Handwriting movements were quantified using a commercial digitizing tablet and MovAlyzeR software (NeuroScript, LLC; Tempe, AZ, USA). We used a non-inking pen with a Wacom UD 9×12 digitizing tablet (30 cm×22.5 cm, RMS accuracy 0.01 cm). Sampling rates were either 100 Hz or 200 Hz due to tablet driver updates in some sites during the course of the study. Data processing took individual sampling rates into account so that kinematic features are independent of the sampling rate. The tablet was attached to an MS Windows laptop computer running MovAlyzeR software.

The data reported herein were collected as part of a larger study of the handwriting kinematics in psychosis patients. The complete handwriting battery included 15 different writing patterns varying in vertical size and pattern complexity for both dominant and nondominant hands and normal and high speeds. The full battery of writing patterns included: 1) cursive loops, 2) continuous circles 3) a complex cursive loop sequence, and 4) a sentence, "*Today is a nice day*". All tasks were repeated 3 times[1] each at 1, 2, and 4 cm vertical stroke heights except the sentence and the high-speed circles which were produced only at the 2-cm vertical stroke size. The subjects performed all replications of one task before moving to the next task. The sequence of tasks was random. The duration of the handwriting test was about 20 min. For the purpose of this study, we report only the results from the sentence task. Subjects viewed only the tablet and because we used an inkless pen, the handwriting trace was not visible to the subject. The resultant handwriting traces were visible only to the examiner. Subjects were prevented from viewing the recorded trace to minimize any distracting effects of visual feedback on movement speed and smoothness. Data collection began when the pen tip came in contact with the tablet and ended when the pen was lifted for more than 3 s.

The *X* and *Y* coordinates were low-pass filtered at 8 Hz using a sinusoidal transition band of from 3.5 to 12.5 Hz (Teulings and Maarse, 1984). Movements were then segmented into successive up and down strokes using interpolated vertical velocity zero crossings. The basic unit of movement we are studying is the stroke. Each sentence produced approximately 60 vertical strokes depending upon the writing style. The initial down stroke per trial was discarded. Only the first 14 remaining strokes were adopted in this analysis. These strokes correspond generally to the writing of "Today" until the middle of the "y". Therefore, there were no large between-word movements.

The number of strokes per letter varies per writing styles. While some subjects developed writing styles that require more strokes per letter than others, we do not assume it will affect the group differences due to the moderately large sample size. It is possible that differences between the cursive and the handprint writing style could lead to differences in the kinematic variables such as the stroke duration, the peak velocity or the writing fluency. However, we assume that the hand printers and the cursive writers per group are proportionally spread across all subject groups in our large sample. Therefore, the more frequent pen lifts in handprint and its dysfluencies should not be confounded with groups.

Pen lifts, during writing a word are considered part of the motor program. Pen lifts higher than about 1 cm above the tablet will cause the digitizing tablet to loose samples. This will manifest itself in the raw data as a discontinuity which could jeopardize the filtering and the stroke-feature estimation. Therefore, we applied a discontinuity-detection algorithm which fills in an estimated number of samples based on the average pen speed enabling us to substitute the estimated number of missing samples. These discontinuities appeared to occur rarely, though, as most participants did not introduce discontinuities. Therefore, we do not think these discontinuities will affect the groups differently.

[1] One of the three study sites administered five trials. As with the sites that administered only three trials, trials were averaged. We can assume the mean values were unaffected by the number of trials and that there were no systematic differences between groups on the number of trials administered.