Research report

Movement patterns of peak-dose levodopa-induced dyskinesias in patients with Parkinson’s disease

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Received 30 January 2007; received in revised form 10 April 2007; accepted 9 May 2007
Available online 4 June 2007

Abstract

The present study characterized involuntary movements associated with levodopa-induced dyskinesias (LID) in patients with Parkinson’s disease. We used amplitude, proportional energy, frequency dispersion and sample entropy to determine whether LID movement patterns are truly random, as clinical description seems to suggest, or possess some underlying pattern that is not visible to the naked eye. LID was captured using a magnetic tracker system, which provided 3D rendering of whole-body LID. Patients were instructed to maintain a standing position, with arms extended in front of them. We compared the measurements of the dyskinetic PD group (DPD) with 10 patients without dyskinesias (NDPD) and 10 control subjects. In comparison to the other two groups, movement patterns from the DPD group had significantly higher amplitude, confirming the presence of dyskinesias. In addition, higher frequency components in the power spectrum of velocity were detected, suggestive of higher velocity in LID movement. Furthermore, there was a concentration in narrow frequency bands, which suggested stable oscillatory activity. Finally, sample entropy revealed more regularity in the DPD group. Although not statistically significant, we found that the amplitude from the NDPD group had a tendency to be smaller than those of controls. As well, the spectra were often more dispersed for the NDPD group. In conclusion, the present results suggest that LID cannot be considered as purely random movement since they possess some deterministic pattern of motion. This may provide a way for patients to adapt to these involuntary movements while performing voluntary motor acts.

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Keywords: Levodopa-induced dyskinesias; Idiopathic Parkinson’s disease; Amplitude; Proportional energy; Frequency dispersion; Sample entropy motor pattern

1. Introduction

Idiopathic Parkinson’s disease (PD) is a neurodegenerative disease characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain. To date, the most effective treatment for symptoms of PD remains L-D-3,4-dihydroxyphenylalanine (levodopa), a precursor which is metabolized to dopamine in the brain. Disease management with levodopa remains effective for several years without substantial fluctuations in the clinical response. As the disease progresses however, the pool of surviving dopaminergic neurons has difficulty managing the exogenous levodopa, of which the consequence is irregular neurotransmitter release. This results in motor fluctuations, bringing the patients from an “OFF” stage (where symptoms are prominent) to an “ON” stage (where the patients should demonstrate improved motor function) in an uncontrolled fashion. In addition, the ON phase will eventually be accompanied by excessive abnormal movements termed levodopa-induced dyskinesias (LID).

The most common type of LID are choreic peak-dose dyskinesias which are random in appearance, involuntary, purposeless, non-rhythmic, abrupt, rapid, irregular, and unsustained [9]. As such, LID represents a challenge to patients, as they have to “fight” against these involuntary movements while
attempting to perform everyday motor acts. To date, there is little understanding of the exact nature of LID movement patterns, which is a crucial step towards a better understanding of their impact on voluntary motor behaviours. For instance, no studies have yet determined whether LID are truly random, or possess some deterministic pattern. This is especially relevant for patients since it is possible that random involuntary movements may be more difficult to counteract than predictable ones. The quantification of kinematic characteristics beyond amplitude may also provide some clues about the central mechanism producing these movements, as demonstrated for tremor [5–8], and, greatly help in the assessment of treatment regimes by enabling comparisons between them.

Therefore, the main goal of the present study was to accurately quantify the amplitude of whole-body involuntary movements in patients with PD having LID, assess the spectral characteristics of LID and determine whether LID possess some structured movement pattern. In order to do so, we quantified characteristics of LID kinematics—amplitude, frequency content and power dispersion, as well as the ‘regularity’ or degree of organization of the movement. We applied this analysis to whole-body involuntary movement recordings on 10 dyskinetic patients. For the purpose of comparison, we also examined whole-body movement in 10 non-dyskinetic PD patients and 10 control subjects.

2. Methods

2.1. Participants

Whole-body movements were quantified in thirty patients at the Brock University motor disorders lab. Ten patients diagnosed with idiopathic PD (aged 56–76 years old, mean 67.5 ± 6.3 years) who demonstrated mild to moderate peak-dose choreic dyskinasias (named the DPD group) following their levodopa treatment were recruited from the Movement Disorder Clinic at the London Health Science Centre, Ontario, Canada. Participants were excluded from the study if they suffered from dementia or psychiatric disorders, used neuroleptic drugs, presented with dystonia as their predominant form of dyskinesia, were tremor predominant, or had undergone surgical procedures related to their Parkinson’s disease. Characteristics of patients, such as age, disease duration, medication, etc., are described in detail in previous studies performed the same day [11,17]. Ten age/gender-matched non-dyskinetic patients with PD (NDPD) who also met the above basic criteria but had not yet experienced LID in their lifetime (aged 47–78 years old, mean 67.9 ± 9.3 years), and 10 age/gender-matched healthy control subjects (aged 47–79 years old, mean 66.5 ± 10.9 years) were also tested. DPD patients were tested during their peak-dose period ON condition where LID were most prominent (see [11,17] for details on methods for determining the best ON period). Testing took place in the afternoon, since LID were most prominent (see [11,17] for details on methods for determining the best ON period). Subjects were positioned (within the middle of the working space) approximately 1 m away from the transmitter. For each subject, after setting up the sensors, body segments were digitized (using a stylus) based on predetermined anatomical landmarks, in order to automatically assign each sensor the center of mass of local segment axes. The software calculated these anatomical landmarks based on the manual entry of subjects’ height and weight, in combination with an automated algorithm using predetermined anthropometric tables. The sampling rate was set at 100 Hz for each sensor.

2.3. Experimental procedure

Subjects were asked to stand with arms stretched horizontally in front of them for 60 s, and to look at a blank projector screen in front of them. They were instructed to remain in that position and to abstain from making any voluntary movements, but not to suppress any involuntary movements. During recording, they were asked to count backwards from 100 to zero by seven in order to maintain a constant cognitive load. The sampling rate was set at 100 Hz for each sensor. Three trials were performed for each subject, with a 1 min rest between trials during which they were allowed to sit.

2.4. Movement analysis

The first and last 2 s were removed from every time series to allow for starting and finishing effects (e.g. hands dropping too soon). To remove noise arising from the data collection process, all time series were filtered to remove frequencies above 15 Hz. In order to calculate certain velocity characteristics (see below), a velocity time series was derived from each recorded position time series by numerical differentiation. Velocity has proven to be a useful compromise between displacement and acceleration time series in spectral analysis of physiological time series [5,23]. Very slow drift was then eliminated from the position time series by a ramp filter from 0.1 to 0.2 Hz (so that all components below 0.1 Hz were removed completely). Measures taken are described as follows:

Amplitude is the ‘amount’ of three-dimensional (3D) movement, or the RMS distance from the center point of the position trajectory.

Proportional energy measures the power (or energy) in the velocity power spectrum occurring between 1.0 and 1.5 Hz as a proportion of total power between 0 and 7 Hz. Non-dyskinetic movement appears to be dominated by lower frequency components (below 1 Hz) and higher frequencies reflect other components of movement, such as tremor. Since dyskinetic movement is mainly visible in increased power in a range above 1 Hz, a range of 1.0–1.5 Hz was selected in an attempt to isolate distinctively dyskinetic components of movement.

Frequency dispersion measures the extent to which power is dispersed across the velocity power spectrum. Regular oscillatory movement at a particular frequency will have power concentrated at one (or several) narrow frequency bands and therefore have low dispersion. Noisy, irregular movement will have a more dispersed power spectrum. ‘Dispersion’ is obtained by sorting the power spectrum into bins of decreasing amplitude and calculating the centre of mass of the result [2].

We used sample entropy to approximate the amount of ‘determinism’ or ‘temporal structure’ in our kinematic time series. Sample entropy measures the regularity or predictability of a variable over time—in our case, velocity of body movement. A time series that contains many repeated patterns has relatively small entropy, whereas a less predictable time series has higher entropy. More precisely, sample entropy is calculated as the negative natural logarithm of the conditional probability that two sequences similar (within a specified radius of tolerance) for m points remain similar at the next point (excluding self-matches) [30]. This is an improvement on ‘approximate entropy’, which was an earlier attempt to characterize the entropy of a time series in a simple way. Sample entropy requires an embedding dimension and a radius of tolerance for repeated
sequences. The embedding dimension should reflect the dimension of the under-
lying deterministic process if there is one, and a common way to estimate this is
by means of false nearest neighbour (FNN) analysis. If the embedding dimension
is too low, many sequences of points that appear close in the embedded space do
not appear close if the dimension is increased, suggesting that the appearance of
proximity was false. The embedding dimension is thus the lowest dimension that
precludes most of these false neighbours [15]. The FNN algorithm was applied
to each of our times series and the resulting minimum dimensions ranged from
4 to 7 but the majority were near 5. We selected as an average value a common
embedding dimension of 5.

We also used a common choice for the radius of tolerance, namely 20% of
the standard deviation of the time series [16,30]. There is some indication that
this type of criterion may not always be appropriate, depending on the ratio of the
standard deviation of the underlying deterministic process and the standard devi-
ation of the superimposed ‘noise’ [31]. However, for a given physiological signal
it is difficult to determine this ratio, so we have elected to use the standard 20%.

2.5. Statistical analysis

Aside from amplitude, which was calculated as a 3D quantity, each char-
acteristic was calculated separately on the X, Y and Z recordings for the three
separate trials, and then averaged over the trials. Transformations were applied to
the resulting values for amplitude (log(x)) and sample entropy (arctanh(2x − 1))
to normalize their distributions. Finally, the transformed values were averaged
over the three dimensions: X, Y and Z.

Differences (unequal means) among the three groups were tested using one-
way ANOVA for each body segment and for each characteristic separately.
Significance was declared at p < 0.05. Post-hoc analysis was performed using
Tukey’s honestly significant difference (HSD) test to indicate which group
comparisons yielded statistical significance. Note that multiple (60) tests were
performed here at a significance level of 0.05. It is of course likely that 1 in 20
such tests would produce the appearance of a significant result by chance. We
are mainly interested in the overall trends, not isolated tests, so a small num-
ber of false positives are not serious. However, to allow us to identify possibly
overoptimistic results we also applied the Holm adjustment, which accounts for
the multiple tests in a conservative way [12].

3. Results

Example recordings and power spectra for three particular
subjects are shown in Fig. 1.

The results of the statistical comparisons are indicated in
Fig. 2a–d. The p-values for significant differences between
means from the analysis of variance (ANOVA) tests for each
characteristic and each body part are given in Table 1. Four
out of the 48 significant tests lose significance after the Holm
adjustment, three of them only marginally.

Table 1
The p-values for ANOVA

<table>
<thead>
<tr>
<th>Body part</th>
<th>Amplitude</th>
<th>Proportional energy</th>
<th>Frequency dispersion</th>
<th>Sample entropy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0031</td>
<td>0.0005</td>
</tr>
<tr>
<td>Left foot</td>
<td>0.0011</td>
<td>0.0016</td>
<td>0.8105</td>
<td>0.8497</td>
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<tr>
<td>Left forearm</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.7337</td>
<td>0.0012</td>
</tr>
<tr>
<td>Left hand</td>
<td>&lt;0.0001</td>
<td>0.0051</td>
<td>0.9539</td>
<td>0.1101</td>
</tr>
<tr>
<td>Left scapula</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0008</td>
<td>0.0002</td>
</tr>
<tr>
<td>Left shank</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0036</td>
<td>0.2790</td>
</tr>
<tr>
<td>Left upper arm</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0170</td>
<td>0.0002</td>
</tr>
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<td>Right foot</td>
<td>0.0012</td>
<td>0.0009</td>
<td>0.4309</td>
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<tr>
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<td>0.5910</td>
<td>0.0002</td>
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<tr>
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<td>&lt;0.0001</td>
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<tr>
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<td>&lt;0.0001</td>
<td>0.1245</td>
</tr>
<tr>
<td>Right upper arm</td>
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<td>&lt;0.0001</td>
<td>0.0036</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sacrum</td>
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<td>&lt;0.0001</td>
<td>0.0003</td>
<td>0.2068</td>
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<tr>
<td>Thorax</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

Significant differences indicated between DPD and other groups are indicated in bold.

a Not significant after the Holm adjustment.
Fig. 2. The Graphs are presented as follows: (a) log (amplitude); (b) proportional energy of the 1–1.5 Hz band (range: 0–1); (c) frequency dispersion (Hz); (d) arctanh (2*sample entropy – 1). The ‘boxplots’ above are a visual representation of basic statistical information about each distribution. The small boxes show the Inter-quartile range (IQR), from the first to the third quartile. The median is shown by a black line within the IQR and the ‘whiskers’ are drawn at the minimum and maximum values or at 1.5*IQR, whichever is smaller. In the latter case, outliers are shown by a single line. In these graphs the three boxes represent the Control, NDPD and DPD groups, from left to right. A light grey DPD box shows a significant difference from both the Control and NDPD groups, whereas a dark grey DPD box shows a significant difference only from the NDPD group.
Fig. 2. (Continued)
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The higher amplitude of movement in the DPD group is clearly seen in all body segments. NDPD amplitudes tended to be smaller than those of controls (possibly reflecting hypokinesia), though this difference was not significant. One particular control subject moved more than any of the other controls and appears as an amplitude outlier in most body segments. Playback of his recording showed that these movements seemed purposeless. The head movement amplitude on this subject was 1.61 cm where the rest of the control group ranged from 0.22 to 0.76 cm. All but one of the DPD group had over 1.0 cm of movement in the head. Interestingly, this control subject appears normal (within the inter-quartile range) with respect to other measures, so large amplitude in itself does not indicate dyskinesia. Fig. 2b confirms the notion that dyskinetic movement has higher frequency components than non-dyskinetic movements, as measured by proportional energy in the 1–1.5 Hz range. Again this appears in all body segments. Fig. 2c shows that in some body segments (especially those in the central axis of the body), the dyskinetic movement was significantly more concentrated in narrow frequency bands than the movement of controls or NDPD patients. This is an indication of ‘regularity’ in dyskinetic movement in the sense of oscillation, compared to the less oscillatory movement of controls. NDPD subjects show signs of having more dispersed spectra than controls, though again this is below the significance threshold.

Sample entropy (Fig. 2d) also shows significant differences between the DPD group and the other two groups. There is a distinct tendency for dyskinetic movement to show more organization and structure than non-dyskinetic movements, in the upper body at least. There is a trend, though not significant, for NDPD subjects to have less organized movement than controls.

4. Discussion

To summarize our results: levodopa-induced dyskinesias are characterized by increased amplitude as expected, proportionally more higher frequency components (>1 Hz), and more ‘regularity’ both in the sense of regularity of oscillatory frequency and organized structure, making the movement more predictable than random. Accordingly, LID cannot be considered as purely random movements, but rather have some degree of deterministic pattern. It might be expected that some of this arises simply from the fact that movement of body parts has some inertia, so that once movement in a particular direction is initiated it will tend to continue and cannot immediately be stopped or redirected. However, this is unlikely to account for all of the structure seen in the time series. The fortuitous occurrence of a larger-amplitude movement by one of the control subjects supports this assertion, since even in that case, the regularity measures were entirely within the normal range (determined as two standard deviations from the mean of the remaining nine control subjects). We also quantified amplitude, power spectral and deterministic characteristics in non-dyskinetic patients and healthy controls in order to provide a baseline for comparison, even though the latter groups had no overt involuntary movements. Interestingly, there is some indication (though not significant in our analyses) for the movement of NDPD patients to have opposite characteristics, i.e., expected lower amplitude, and unexpectedly, less regularity. The lower regularity could simply be a consequence of the lower whole-body movements amplitude. Nonetheless, one key finding of the present study is that appropriate measures of regularity of kinematic recordings do capture aspects of movement that are distinctive of LID, but apparently not of arbitrary large-amplitude movements, and thus can be useful in evaluation and comparison of alternate treatment regimes for PD.

4.1. Clinical implications of the present findings

Patients with PD are able to perform voluntary movements while experiencing LID. For instance, patients are known to be able to use corrective strategies and adapt to LID while performing manual tracking tasks [17,19]. It is reasonable to suggest that involuntary movements associated with LID do possess some deterministic pattern, patients could adapt more easily by incorporating the involuntary movements into their strategy during motor planning. This is especially relevant in a context where patients are facing a choice between being either OFF, where initiation and execution of voluntary movement is almost impossible, or, LID in which motor activity is still possible, albeit difficult [11,17,19].

4.2. Neural model implications of the present findings

The presence of regularity may also be a good indication that there may be some structured pattern to the neural circuits that produces dyskinetic movement, and that it does not simply consist of random neural firing. This raises the question of what neural substrate, localized or distributed, is responsible for LID. Here, we believe it may be appropriate to use tremor oscillations in PD for comparison purposes, which are known to be much more deterministic than LID. Currently, the prevailing view is that changes resulting from PD in basal ganglia activity such as increased pallidal inhibition in addition to changes in pallidal neural firing patterns [3,10,22,28] will modify thalamic cell activity [28], which will begin to oscillate at a frequency around 4–6 Hz [13,18]. Accordingly, the result would be some sort of transformation of cell firing within the basal ganglia into a highly synchronized firing pattern within the thalamus that is transmitted to the cortex. The importance of the thalamus in this process is demonstrated by the high efficacy of its lesioning in blocking specifically parkinsonian tremor oscillations [6–8]. In fact, lesions in the thalamus seem to remove central oscillations, leading to a more dispersed power spectrum [6,8], implying that the tremor becomes less organized following the lesion. There are also changes in firing pattern within the basal ganglia associated with LID [1,32]. This altered firing pattern could also be transmitted though the thalamo-cortical pathway. Although less used as a treatment option, it has been shown that thalamic lesions are also effective in stopping LID [25–27]. Similar to tremor, the thalamus may then play an important role in the consolidation of LID movement pattern. A lesion in the thalamus may simply block the transmission of somewhat organized neural firing, which would in turn lead...
to reduced LID. Whereas tremor may represent an involuntary release of part of a motor programs associated with rapid alternating movements [4, 29, 33], LID may simply represent the involuntary release of part of a motor program (or programs) associated with more complex motor behaviours.

In conclusion, we have found that LID are not purely random, but possess some deterministic movement pattern. Determining the neural substrates responsible for the generation and "integration" of LID movements, and how they interact with voluntary movements, will aide in the improvement of pharmacological and neurosurgical treatments.

Acknowledgement

The authors would like to thank the subjects who graciously accepted to participate in the study. This study was primarily funded by Parkinson Society Canada. Partial funding was also provided by the Natural Sciences and Engineering Research Council of Canada, the Canadian Foundation for Innovation and Ontario Innovation Trust.

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