# Increased response to visual feedback of drug-induced dyskinetic movements in advanced Parkinson's disease

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## Abstract

To investigate the response to visual feedback of involuntary movements which have a frequency composition similar to cerebellar tremor but are not caused by cerebellar damage, we have tested six advanced Parkinson's disease (PD) patients with drug-induced dyskinetic movements using visually guided wrist tracking tasks. Tracking performance was assessed under three visual conditions: (1) both guiding target and movement cursor were displayed continuously; (2) the target display was turned off for the second half of each trial; or (3) the cursor display, but not the target, was turned off for the second half of each trial. The response to visual feedback of drug-induced dyskinetic movements at 1–5 Hz in these advanced PD patients were significantly increased than in normal controls. This suggests that increased response to visual feedback might be a common feature of low frequency involuntary movements and not directly caused by cerebellar damages. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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We have been investigating how visual feedback affects action tremors caused by multiple sclerosis (MS) with cerebellar involvement [6] and Parkinson's disease (PD) [7] using simple manual tracking paradigms. We have shown that increases in tracking error after suppression of visual feedback are significantly larger in MS but not in PD patients than those in normal controls. Furthermore, the amount of action tremor significantly decreases if visual feedback is withdrawn in MS but not in PD patients. Two possible explanations have been proposed: (1) The cerebellar circuit may be more concerned with sensory information processing and sensorimotor integration, whereas the basal ganglia may be more concerned with the selection of the appropriate movements/muscles; and (2) the frequency of action tremor in PD is usually higher (6–8 Hz) than that (3–5 Hz) in MS. Given an internal conduction delay of 200 ms or more in the visuomotor processes, PD patients would therefore be unable to react fast enough to visual feedback of their high frequency tremor in order to correct it [7]. If this were so, would patients with low frequency involuntary

movements caused by damage outside the cerebellar circuit react excessively to the visual display of their involuntary movements during visually guided manual tracking?

Two major types of involuntary movements in PD, action tremor and drug-induced dyskinesia [4,8], had clearly separated frequency ranges and could be quantitatively differentiated by frequency analysis of patient's wrist movements during visually guided smooth tracking [12]. Action tremor has a frequency range of 6–8 Hz, whereas drug-induced dyskinesias have lower frequencies (1–5 Hz). Thus the frequency of drug-induced dyskinesia in PD patients is similar to the frequency of MS action tremor but there is no evidence that the cerebellum is directly involved in PD, whereas it is in MS. This provides a unique pathological model for studying how visual feedback affects low frequency involuntary movements caused by basal ganglia rather than cerebellar lesions. In this paper therefore, we have compared magnitude of drug-induced dyskinetic movements in advanced Parkinson's disease during manual tracking with and without visual feedback.

Six inpatients at the Department of Neurosurgery, Radcliffe Infirmary, Oxford, four females and two males, aged 56–70 years (63 in average), were studied. All had been diagnosed as having clinically definite PD for 10–35

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(mean 20) years with on-medication UPDRS scores of 64–98 (average 86). These patients had clear dyskinesias induced by medication (Sinemed plus, 750–1750 mg daily) and were selected for possible surgical treatment. Tracking performance was assessed in eight hands of these six patients while they were 1.5 h (on) and 12 h (off) after taking medication, and matched number of hands from five healthy subjects without neurological deficits were also tested as controls. Ethical approval and informed consent were obtained for this study.

Our wrist tracking task was previously described in detail [6] and is summarized as follows: A target of $12 \times 12$ pixel moved horizontally across a computer screen at four velocities of 13.64, 9.23, 7.50 and 5.50°/s over 16 trials. The subject sat in front of the screen with his or her forearm held by a plastic splint fixed onto the chair when allowed comfortable wrist flexion and extension over a range of 60° ($\pm 30°$ around the neutral position) in the horizontal plane. The subject was instructed to track the moving target by controlling a hand-held joystick with a wrist flexion movement. The subject movements were also displayed on the screen as a $6 \times 6$ pixel cursor. After completing each trial, the subject moved the cursor back to the starting point. Pursuit tracking was recorded under three visual conditions: (1) both target and cursor were displayed continuously for the first half of each trial, so that feedback of visual comparison of target and cursor was available; (2) the target, but not the cursor, display was turned off for the second half of each trial. The subject was instructed to keep tracking the estimated position of target, and had visual feedback of his or her own movement from the cursor throughout; and (3) the cursor, but not the target, display was turned off for the second half of each trial. The subject was instructed to track the continuously displayed target without visual feedback of movement position. Each subject was allowed a few practice trials on each visual condition before recording began. The wrist position signals were digitally filtered using a zero phase, four-pole Butterworth filter at 5 Hz and differentiated. A computer algorithm then selected the

tracking segment beginning 1 s after the target started moving in order to avoid the subject's initial reaction delay and acceleration phases until the end of the first half. The second half of each trial was selected for visual conditions 2 and 3. The mean movement velocity, and the standard deviation of movement velocity (SD-MV) were separately determined for two segments in each trial. Means and standard deviations over 16 trials were then calculated for each hand tested.

The magnitude of drug-induced dyskinesia was quantified by calculating the SD-MV: For perfectly smooth tracking, the standard deviation of the movement velocity would be zero. The power spectra of the drug-induced dyskinetic movements were also calculated by Fourier transformation of the velocity records filtered with a bandwidth of 0.5–6 Hz. Averaged values of SD-MV across the tested hands were statistically analyzed between visual conditions in PD and controls using two-way analysis of variance (ANOVA).

Drug-induced dyskinesia was recorded when the patients were on medication. The frequency of the dyskinetic movements was in the range of 1–5 Hz as shown in the power spectra of tracking movements (Fig. 1). When either the guiding target or the movement cursor being turned off, tracking became much smoother. The magnitude of drug-induced dyskinetic movements significantly decreased (Fig. 2).

The averaged standard deviation of movement velocity (SD-MV) during tracking with and without display of either visual cue in PD patients and controls are shown in Table 1. The PD patients had significant larger SD-MV than that of controls due to their drug-induced dyskinesia ($F(1, 42) = 105.8$; $P < 0.000001$). The SD-MV reduced significantly when visual feedback was withdrawn ($F(2, 42) = 4.4$; $P < 0.02$); and the interaction in the ANOVA was also significant ($F(2, 42) = 4.3$; $P < 0.03$) suggesting that decreases in SD-MV after withdrawing visual displays were significantly higher in PD than in controls.
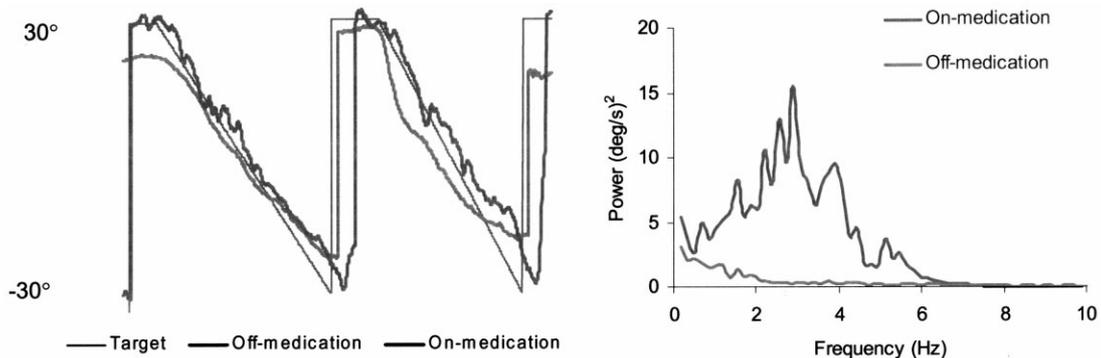


Fig. 1. Left: two consecutive trials of manual tracking recorded from one PD patient with both visual cues being displayed throughout the trials. Tracking when the patient was on-medication (thick black trace) was dyskinetic in comparison with the tracking when she was off-medication (thick grey trace). Right: power spectra show that frequency of the drug-induced dyskinesia (more precisely as the difference between two spectra) ranged from 1 to 5 Hz peaking at 3 Hz.
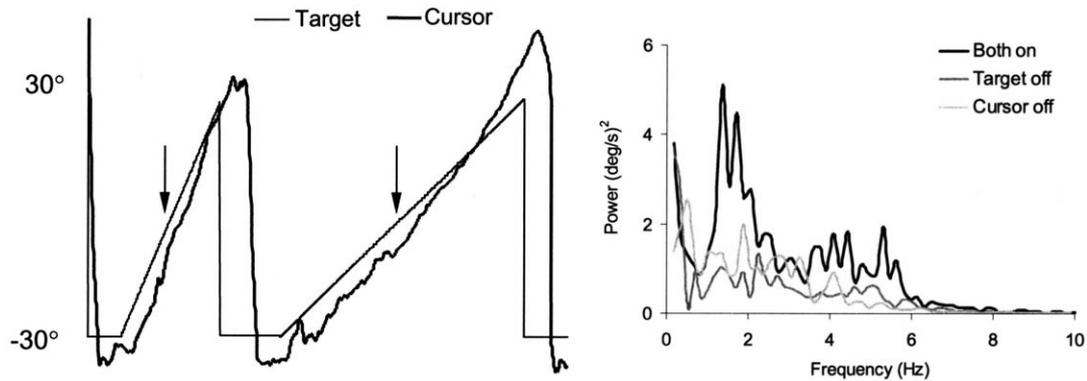
Fig. 2. Left: two consecutive trials of manual tracking recorded from one PD patient at on-medication and with display of both visual cues over the first half of each trial. For the second half of each trial (starting points are indicated by the arrows) the movement cursor but not the guiding target display was selectively turned off and tracking became smoother as the magnitude of drug-induced dyskinesia decreased. Right: power of drug-induced dyskinesia during manual tracking with display of both visual cues (both on) reduced after either the target (target off) or the cursor cue (cursor off) being turned off.

We have investigated in six advanced PD patients how their drug-induced dyskinetic movements were affected by visual feedback using pursuit manual tracking tasks. Visual display of either the guiding target or the movement cursor was selectively withdrawn. The involuntary movements induced by L-DOPA was concentrated in the frequency range of 1–5 Hz. Compared with the normal controls, the PD patients with dyskinesia had greatly increased variation in tracking velocity. This variation was considerably reduced on withdrawing visual feedback.

Even in normal subjects, pursuit tracking movements are usually intermittent rather than perfectly smooth [10]. This intermittency is reduced if the visual display of the guiding target or the movement cursor is switched off. This is because the intermittency is largely due to voluntary error corrections in response to visual feedback. In PD patients with dyskinesia, the positional mismatches between the guiding target and movement cursor were much larger because of their dyskinetic movements. The patients react to feedback of the visual errors with voluntary error-correcting movements, so that their dyskinesia and error corrections sum together. The reason for the increase in visual dependence of responding to the positional errors in PD patients than that in normal controls is not yet clear. We propose several possible explanations. Firstly, it may simply come from the fact that frequency of drug-induced dyskinesia in PD was in the range of 1–5 Hz. Given the average

conduction delay approximate 200 ms in the visuomotor processes, one would be able to make on-line correction of any 'unintentional' movement with frequency lower than 5 Hz [10]. Under the instruction for the present tasks of 'tracking the target as accurately as possible', the patients would 'intentionally' correct any 'unintentional' movements caused by dyskinesia of lower than 5 Hz. This has also be observed in patients with intention tremor of similar frequency range but caused by cerebellar damages [3,5,6] but not seen in PD patients with action tremor of higher frequency [7]. Secondly, one might assume that these PD patients somehow rely more on feedback control for their pursuit tracking rather than the predictive control being usually adapted by the normal controls [1,2,9]. This kind of shift in motor control strategy is often seen in the patients with cerebellar dysfunction [11]. Perhaps, the cerebellar function in this group of PD patients might be compromised secondarily to their long term and advanced dysfunction in the basal ganglia. However, results of our previous study [7] in a group of PD patients with similar severity and period of disease suggested that the visual dependence of controlling manual tracking in the advanced PD patients was not significantly increased since there was no significant increases in their tracking error while the visual feedback of either the guidance or the movement representation being withdrawn. Thus it is unlikely that shift in motor control strategy due to cerebellar dysfunction is being responsible for the increased

Table 1
Magnitude of drug-induced dyskinesia (SD-MV, °/s) during manual tracking with and without display of visual cues in PD patients in comparison to errors made by controls

| Subjects ($n = 8$) | Magnitude of drug-induced dyskinesia in three visual conditions (deg/s, mean (SEM)) | | | |
| --- | --- | --- | --- | --- |
| | Both on | Target off | Cursor off | ANOVA |
| PD | 274.1 ± 43.5 | 156.3 ± 29.5 | 160.4 ± 18.4 | $F_{(1,42)} = 105.8$; $P < 0.000001$ |
| Controls | 6.4 ± 0.3 | 5.8 ± 0.4 | 5.9 ± 0.4 | |
| ANOVA | | $F_{(2,42)} = 4.4$; $P < 0.02$ | | $F_{(2,42)} = 4.3$; $P < 0.03$ |

responses to visual feedback of their dyskinetic movements in these PD patients. Thirdly, PD patients may have significantly higher tendency of reacting to their larger tracking errors caused by dyskinesia than normal subjects do because that the tendency of reacting to the error signal seems to relate to the size of the error. However, one may argue that error may be corrected once its size becomes larger beyond a threshold of detection [13], and may not depend on its final size.

In conclusion, responses to visual feedback of low frequency drug-induced dyskinetic movements in PD patients were significantly increased. This increase may be a common feature in various neurological conditions via the feedback control mechanism and may not be directly caused by cerebellar lesions.

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