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Short communication

Parkinson's disease patients experiencing peak-dose dyskinesia redistribute involuntary movements throughout their body to improve motor control

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ABSTRACT

Introduction: In Parkinson's disease (PD), dyskinesia is considered a major side effect of dopamine replacement therapy. Nevertheless, many patients with dyskinesia function adequately.
Objective: To study objectively dyskinesia phenomenology in order to understand why or how patients with dyskinesia are still able to perform motor tasks.
Methods: Patients with and without dyskinesia, as well as healthy older adults, performed a geostationary task during which they attempted to stabilize a glass of water at eye level. Dyskinesia amplitude displayed by each body segment was extracted from accelerometers, and its distribution among the segments, analyzed.
Results: Patients experiencing dyskinesia initially distributed most of their dyskinesia away from the segments directly involved in the task. With time, this distribution shifts back towards the hand.
Conclusion: Our results suggest that patients developed a strategy of involuntary movement's redistribution to attenuate their functional impact on voluntary movements. However, this strategy can only be maintained for a certain period before "re-emerging" dyskinesia occurs.

1. Introduction

In Parkinson's disease (PD), occurrence of drug-induced dyskinesia (DID) is considered one major side effect of long-term use of oral levodopa replacement therapy [1]. As a result, clinicians tend to delay or limit its use in the treatment of PD [2], despite its proven higher efficacy to counteract most symptoms [3]. It has also been noted that only a minority of patients report DID as a major problem in their everyday life [2]. Working towards providing objective data on the dyskinesia phenomenology during functional tasks to shed the light on this important aspect, we recently demonstrated that DID are not associated with the worsening of the functional performance of the patients, as assessed using a series of activities of daily living (ADL) [4]. These results suggest the presence of on-line motor strategies that limit the functional impact of dyskinesia. We also reported that voluntary movements generate increased DID amplitude in limbs not directly involved in a task [5]. Thus, we hypothesized that there may be a redistribution of DID in other limbs when performing a voluntary movement. Accordingly, the objective of this study was to investigate if dyskinesia amplitude redistribution occurs during a geostationary motor task.

2. Methods

This study was embedded within a larger research project which aims at better understanding the impact of dyskinesia on ADL [4,6]. As such, a total of 121 patients diagnosed with Parkinson's disease, were recruited in collaboration with the Quebec Parkinson Network and the Movement Disorders Clinic of the University of Calgary on the premises that they were all dyskinetic (i.e. they all reported experiencing choreic-type drug-induced dyskinesia in the 6 months preceding the experiment). Patients with an orthopedic condition that could hinder the performance of the tasks, a significant psychotic illness such as hallucination or delusion, and patients requiring assistance to walk were excluded. A group of 69 age- and gender-matched healthy controls were also recruited from the community with the help of the Centre de Recherche de l'Institut universitaire de gériatrie de Montréal

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(CRIUGM). However, to meet the current study objective, the subset of patients experiencing the most dyskinesia who did not display any remaining tremor during the experiment, according to Refs. [4,6], was selected (45 PD_D: 51.1% male, mean age of 65.4 ± 9.8 years old, living with PD for 10.6 ± 5.4 years, mean LEDD = 1226 ± 591.7 mg, H&Y score distribution: 1–28.9%, 2–46.7%, 3–20.0% and 4–4.4%). Furthermore, 14 patients did not display any choreiform of dyskinesia during the experiment, which consequently provided a baseline comparison for patients living with PD (14 PD_{ND}: 69.2% male, mean age of 69.2 ± 9.4 years old, living with PD for 12.7 ± 7.8 years, mean LEDD = 723.9 ± 425.3 mg, H&Y score distribution: 1–7.7%, 2–61.5%, 3–7.7%, 4–23.1%). Finally, a subset of the control group composed of 59 older adults (OA: 49.2% male, mean age of 67.4 ± 7.9 years old) was also considered for comparison purposes. Participants were asked to perform a series of ADL while equipped with a suit (IGS-180, Synertial Ltd, UK) holding 17 inertial modules (OS3D, Inertial Labs, USA) that enable full-body kinematics assessment. Details on the protocol is available elsewhere [6]. Briefly, visits were planned to coincide with the patients' medication schedule. Participants were instructed to take their medication upon arrival to the laboratory. They were then equipped with the suit, and activity testing began as soon as the evaluators could visually detect any signs of choreiform dyskinesia. The study was composed of repeated blocks of ADL (e.g. reading, eating soup, walking, etc.), between which a clinical evaluation of the cardinal symptoms as well as a geostationary task were performed. For each ADL, the amplitude of dyskinesia and the presence of other cardinal symptoms were assessed using the 17 sensors positioned on each body limb [6]. The block of ADL containing the maximum number of activities displaying dyskinesia, per patient, was considered at peak-dose and was therefore further investigated. The study was approved by the CRIUGM ethics board and the Conjoint Health Research Ethics Board. All participants provided written informed consent.

The current study focuses on the analysis of a geostationary task consisting in lifting and stabilizing a glass of water at eye-level. This task was selected on the premises that it requires the person to plan and coordinate adequately the movement to achieve a functional goal, while including a period with limited voluntary movement, thus allowing assessment of involuntary movement in a cleaner fashion. Specifically, a glass nearly full of water was placed on a table in front of the seated participant. Upon a visual signal (a light coming on), the participant would reach for the glass, lift it, and stabilize it at eye-level until the light goes off (the light remained on for a total of 20 s). To reproduce a set-up as close as possible to reality, participants were instructed to use their dominant hand to perform the task. In total, each participant performed the glass stabilization task three times, but only the trial closest to the block of ADL performed at peak-dose was analyzed.

Trials were first segmented to deduce the reaction time (difference between the time at which the light went on and movement initiation), the time spent rising the glass (from motion initiation to first eye-level reach) and the time to stabilize the glass (from first eye-level reach to stable position, determined by comparing the standard deviation in angular displacement captured at the hand, by windows of 2 s, with a noise level threshold determined at 1°). Dyskinesia amplitude displayed during the stable period was then computed for both hands, head, trunk, pelvis, as well as for both thighs and feet. Dyskinesia amplitude was estimated from the energy expended, calculated using the sum of the variance in the 3-axes band pass filtered accelerometer signals of each of these segments [7], per window of 2 s. The process used for dyskinesia amplitude evaluation has been previously validated for various ADL and was shown to strongly correlate with the Unified Dyskinesia Rating Scale (ρ = 0.75 to 0.89 depending on the ADL). Global energy level (E) as well as the distribution of this energy within the segments were then examined. Specifically, differences in timing parameters were assessed using one-way ANOVAs, while dyskinesia amplitude were analyzed using two-factors ANOVAs, followed by Bonferroni post hoc analysis where applicable. Finally, evolution in global energy versus energy distribution was studied through a change point analysis approach. All statistical analyses considered a significance level of 0.05 and were conducted using SPSS (v23.0.0, IBM).

Table 1
Task timing parameters for glass stabilization reported for each group: older healthy adults (OA), patients with dyskinesia (PD_D), patients without dyskinesia during testing (PD_{ND}).

	OA	PD_D	PD_{ND}	P value
N	59	45	14	
Stabilized angle	61.4° ± 9.8°	62.2° ± 11.1°	64.8° ± 10.1°	p = 0.555
Reaction time (s)	0.67 ± 0.15 s	0.80 ± 0.18 s	0.90 ± 0.27 s	p < 0.001*
Time to raise (s)	1.81 ± 0.74 s	1.96 ± 1.45 s	2.29 ± 0.81 s	p = 0.321
Time to stabilize (s)	1.11 ± 0.65 s	1.70 ± 1.24 s	1.04 ± 1.23 s	p = 0.006*
Total time (s)	3.59 ± 0.67 s	4.46 ± 1.41 s	4.23 ± 1.12 s	p < 0.001*

3. Results

All participants succeeded in stabilizing the glass; the timing parameters achieved in doing so are reported in Table 1. Patients with PD had a longer reaction time and were globally slower to achieve final stabilization than controls ($p < 0.001$). The time taken to raise the glass was not statistically significant between the groups ($p = 0.321$), but patients with PD_D took significantly longer than older adults to stabilize the glass ($p_{PDD\text{-}OA} = 0.013$).

The importance of dyskinesia was then studied through the analysis of the total energy expended during the stable period, per window of 2 s (see Fig. 1). During the first 10 s of stabilization, the total energy was shown to be steady ($p = 0.083$). However, mean energy level was different, with a significantly higher level in the PD_D group (mean $E_{OA} = 0.020 \pm 0.009\,m^2/s^4$; mean $E_{PDD} = 0.468 \pm 0.101\,m^2/s^4$, mean $E_{PDND} = 0.106 \pm 0.063\,m^2/s^4$; $p < 0.001$, $p_{PDD\text{-}OA} < 0.001$, $p_{PDND\text{-}OA} = 1.0$, $p_{PDD\text{-}PDND} = 0.099$). The energy distribution during that first 10 s of stabilization revealed that both OA and PD_{ND} had about 60% of their total body energy engaged at hand level (61% in hand for OA, 56% in hand for PD_{ND}), while 44% was allocated to the hand in the PD_D group over that same period ($p < 0.01$). This difference is even more prominent for the third of our patients exhibiting the most significant dyskinesia measured by the inertial sensors (36% of energy allocated to the hand). With time, we observed a switch in energy distribution in dyskinetic patients, with an increased proportion of energy in the hand performing the task, despite the initially relatively stable level of energy, as confirmed by change point analysis (see Fig. 1).

4. Discussion

This study aimed at investigating the presence of strategies to alleviate the functional impact of dyskinesia on voluntary movements. It used a global approach to investigate a potential strategy in involuntary movement redistribution. We observed that patients with dyskinesia seemed to concentrate their involuntary movements in limbs not directly involved in the requested movement. These findings lead us to believe that patients may be able to harness the variability in amplitude and in body location associated with dyskinesia [8] and integrate it into their voluntary motor stream during on-line motor control, this by transferring dyskinesia energy to other limbs. However, this redistribution strategy seemed to have some limits. Indeed, we observed that after a while, a switch in dyskinesia amplitude distribution lead to 're-emerging' dyskinesia in the performing hand. The consequence was more unstable glass holding, in some cases. The fact that patients experiencing more severe dyskinesia were more efficient in transferring energy points to an implicit strategy in their part. Conversely, this phenomenon could also be analogous to re-emerging tremor previously described by others [9] where the command of the intended movement (signal) overcomes the command generating the involuntary movement

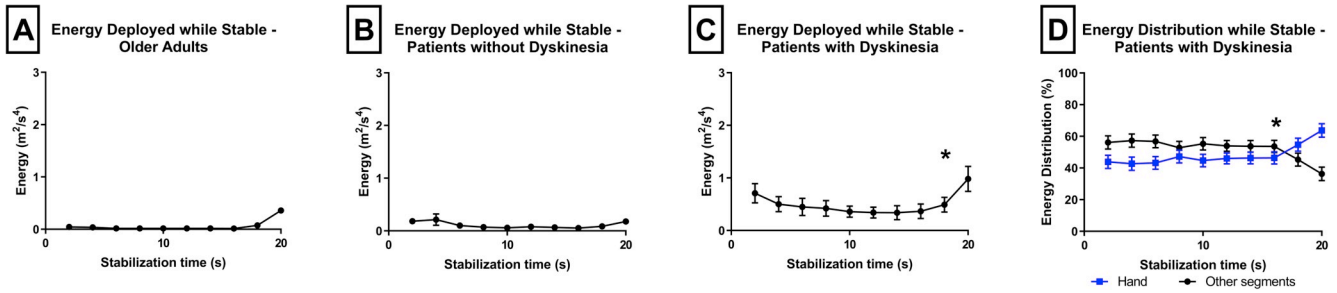

Fig. 1. Energy level and distribution during the stabilized portion of the task. (A to C) Variation in energy expended during the stable period of the task by older adults (A), patients with PD without dyskinesia (B), and patients with PD experiencing dyskinesia (C). (D) Energy distribution during the stable portion of the task in patients with PD experiencing dyskinesia. *Note that change point analysis revealed that at 16 s, an apparent re-emergence of dyskinesia in the limb performing the task is observed, followed by an increase in global energy at about 18s. Error bars represent standard error of measurement.

(noise), hence increasing temporarily the signal-to-noise ratio [10]. However, our data tend to demonstrate that the switch in dyskinesia amplitude distribution occurs prior to the global increase in energy, which makes it less likely that re-emerging dyskinesia shares neurophysiological bases with re-emerging tremor. Nevertheless, this needs to be investigated further, as the length of our task (20 s) was designed to avoid fatigue, which in turn prevented us to expose in a clearer manner this tendency towards instability.

In accordance with the literature and aetiology of the disease [11], our patients had a longer reaction time and took longer to complete the overall task. However, the segmented performance revealed that patients with dyskinesia tended to take less time than patients without dyskinesia to raise the glass, but longer to stabilize it. The shorter rising time and longer stabilization time associated to dyskinetic patients compared to non-dyskinetic patients are consistent with the findings of Stevenson, Talebifard, Ty, Oishi and McKeown [12] who have shown that the motor control system of dyskinetic patients has a significantly lower damping ratio, corresponding to an increased oscillatory system, compared to non-dyskinetic patients. Indeed, in our study, the longer stabilization time was often related to oscillations in the arm movement during stabilization. The timing parameters for non-dyskinetic patients are also consistent with a previous study reporting higher damping coefficient, analogue to a system preventing oscillations, for non-dyskinetic patients compared to controls, leading to an overall increased time to reach a target compared to an optimal motor system [13]. From a clinical point of view, the shorter rising time observed in dyskinetic patients could be associated to a more reactive system with lower *inertia* level in patients with dyskinesia, promoting faster movement onset. The strategy of dyskinesia redistribution and lower inertia may have contributed to the lack of effect of dyskinesia on the performance of ADL seen in our previous study [4].

In conclusion, this study has shown that patients with PD experiencing peak-dose DID may develop a strategy of redistribution of dyskinesia in other parts of the body to limit the functional impact of their involuntary movements before “re-emerging” dyskinesia occurs.

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Conflict of interest

No conflict to declare.

Authors’ roles

KL developed the algorithm, designed the analysis and drafted the manuscript. EG and SB collected the data and provided significant feedback on the study analysis and the paper. CD conceived the experiment, helped in data interpretation and reviewed the paper. PB was involved in the interpretation of the data and the review of the manuscript.

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