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Motor facilitation during real-time movement imitation in Parkinson's disease: A virtual reality study

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A B S T R A C T

Background: Impaired temporal stability and poor motor unit recruitment are key impairments in Parkinsonian motor control during a whole spectrum of rhythmic movements, from simple finger tapping to gait. Therapies based on imitation can be designed for patients with motor impairments and virtual-reality (VR) offers a new perspective. Motor actions are known to depend upon the dopaminergic system, whose involvement in imitation is unknown. We sought to understand this role and the underlying possibilities for motor rehabilitation, by observing the execution of different motor-patterns during imitation in a VR environment in subjects with and without dopaminergic deficits.
Methods: 10 OFF-dose idiopathic Parkinson's Disease patients (PD), 9 age-matched and 9 young-subjects participated. Subjects performed finger-tapping at their "comfort" and "slow-comfort" rates, while immersed in VR presenting their "avatar" in 1st person perspective. Imitation was evaluated by asking subjects to replicate finger-tapping patterns different to their natural one. The finger-pattern presented matched their comfort and comfort-slow rates, but without a pause on the table (continuously moving).
Results: Patients were able to adapt their finger-tapping correctly, showing that in comparison with the control groups, the dopaminergic deficiency of PD did not impair imitation. During imitation the magnitude of EMG increased and the temporal variability of movement decreased.
Conclusions: PD-patients have unaltered ability to imitate instructed motor-patterns, suggesting that a fully-functional dopaminergic system is not essential for such imitation. It should be further investigated if imitation training over a period of time induces positive off-line motor adaptations with transfer to non-imitation tasks.

Keywords: Movement, Imitative behavior, Parkinson's disease, Virtual environment

1. Introduction

The human ability to imitate is a key developmental element, with profound influences on motor skills acquisition and social interaction. Recently, imitation has gained interest in the clinical domain [1] as it seems possible to establish rehabilitation programs based on imitation by the learning of new, imitated actions to replace or repair motor patterns altered by diseases like PD [2]. Impairment is known to be greater during performing automatic movements (gait, repetitive hand movements, etc) even though the motor program is available as demonstrated by "paradoxical kinesia" [3], or auditory cueing in PD with freezing of gait [4]. Although neural networks ruling imitation have been fairly well characterized [5,6], recent evidence has suggested a role for the basal ganglia (BG) in such networks [7].

In PD imitation of movement may not be impaired, perhaps if performed at the same time as observation, given that the motor programs are available, though not properly implemented [8]. Thus, storing and subsequent retrieval (a characteristic of impaired working memory in PD [9]), may be by-passed.

We propose to evaluate dopaminergic involvement in motor imitation and the real-time effect of motor imitation on impaired movement features in PD. This is a preliminary step taken to devise a

rehabilitation protocol based on imitation in PD. PD patients are greatly impaired in carrying out over-learned motor programs [10] and also in performing repetitive movements [11], so we focused on a simple intransitive task: finger tapping (FT). This movement is usually imitated by the newborn [12] (therefore over-learned and stored early in motor repertoire), which is easily controllable but clearly altered in PD [11]. In line with other work in healthy subjects [5,13], this simple task allows control of the level of experience on the kind of task to be imitated [14], and clinical studies support the view that ideomotor apraxia involving intransitive movements is not present in PD [15].We therefore focused on imitation not in the classic sense of learning a new behavior, but trying to improve an impaired pattern already stored in the motor repertoire.

The classic form of FT test is repetitive flexion-extension movements of the metacarpo-phalangeal joint; the test can detect arrhythmokinetic/hypokinetic alterations of movements in PD and aging [11]. Regulation of the tapping cycle during the FT is balanced between the time the finger is moving and the time the finger rests on the table. A whole set of different cyclic (motor) patterns are therefore available for a fixed tapping frequency, which includes the natural pattern. Here we investigated dopaminergic involvement in imitation of movement by evaluating PD's ability to imitate customized finger tapping patterns and compare their ability with appropriate control subjects. Also we would like to obtain evidence for an effect of real-time movement imitation on motor execution in PD, by evaluating if some specific movement impairments in the disease can be modified during imitation, and therefore gaining grounds for devising a training protocol with the objective of inducing lasting improvements in motor execution after an imitation program.

We used a Virtual Reality (VR) environment, an advantageous resource for evaluating and treating a number of pathologies [16]. It provides outcomes indistinguishable from real world in evaluating motor patterns [17] and allows presentation of motor patterns to be imitated in controlled and customized ways, not easily achievable in the real world. The VR system [17] presented a virtual avatar seated at a table, executing finger tapping movements in predefined patterns to be imitated by the subjects. Therefore we compared execution during self-paced, natural patterns with the new patterns to imitate. While the system allows presentation in 1st person (egocentric) or 3rd person perspective the 1st person perspective may offer advantages; much like children preferring a "like-me" model during imitation [13].

In basic science terms, our research hypothesis investigated the involvement of the dopaminergic system in motor imitation, by evaluating subjects in which this system is deficient. The initial step characterized natural finger tapping patterns for each subject/patient; PD vs. age-matched or young controls. These patterns were then either directly translated into VR ("Self-Paced$_{VR}$") or modified to be imitated ("Imitation$_{VR}$") by the different sets of subjects. Success in such an imitative action is a necessary small step towards testing VR as an environment suitable for rehabilitativework in motor system disorders. A second hypothesis predicts that during the imitation PD can use the information available (the stimulus presented e a moving hand-) to reduce some of parkinsonian motor impairments, like arrhythmokinesis. This will produce a reduction of the cycle time variability while imitating the avatar's finger tapping movement.

2. Methods

All experimental subjects signed consent forms. The protocol conformed to the declaration of Helsinki and was approved by the Ethics Committee of the University of A Coruña (Spain) (CE-UDC 23/09-2009).

2.1. Participants

28 participants were recruited: 9 healthy young (HY), 9 healthy elderly (HE) and 10 non-demented idiopathic Parkinson's Disease (PD) subjects. Because one objective of the study was to investigate the potential influence of the dopaminergic system on motor imitation, PD were evaluated in absence of dopaminergic drugs; disease severity was rated as in stages II-IV$_{OFF}$ of the Hoehn and Yahr scale. OFF-dose was at least 12 h since their last antiparkinsonian medication intake; 24 h for slow release drugs. All PD had no history of freezing of gait, and were examined using the motor part of UPDRS scale (Supplementary Table 1). Participants were excluded if they presented any neurological disease (other than PD in the case of the patients); musculoskeletal impairment disturbing the execution of the task, not-

correctable visual deficiency, or dementia (MMSE score < 24). PD had a mean age of 67.1 yrs (_2.9, Standard Error of Mean, SEM). HY and HE were 27.3 yrs (± 2.1) and 66.2 yrs (± 2.9), respectively.

All groups were screened for hand dominance through Edinburgh Handedness Inventory [18], PD were also asked about their hand dominance before the first manifestation of the disease.

2.2. Protocol

Self-paced tapping in VR is known to match self-paced tapping in the real world in the groups of interest [17].We performed 3 blocks of tapping: Self-Paced$_{REAL}$, Self-Paced$_{VR}$, and Imitation$_{VR}$; the 3 blocks were performed at comfort, and slow-comfort rates.

Subjects were asked to tap with their index finger of their dominant hand. For self paced conditions each subject was told “tap at your comfortable rate”, and “tap at your comfortable slow rate”, either in Self-Paced$_{REAL}$, and Self-Paced$_{VR}$ while looking at their index finger. For imitation, ImitationVR, they were asked to tap imitating the avatar’s animated finger pattern, “tap imitating the movement of the finger” while looking at the index finger of the avatar.

For Self-Paced$_{REAL}$ subjects executed the movements in the real environment, at both the comfort and slow-comfort rates (for slow-comfort conditions subjects were asked to tap at the most comfortable tapping rate slower than the natural confort pattern). Subsequently, subjects tapped at the same rates but immersed in the virtual world (Self-Paced$_{VR}$). In this condition the VR system tracked real-time the finger tapping executed by the subject and reproduced it by means of the virtual avatar adopting the same posture and position as the subject. Subjects also tapped in VR during the imitation protocol. Here they were asked to imitate the pattern animated by the avatar (Fig. 1). During Imitation$_{VR}$ we used each subject’s own Self-Paced$_{REAL}$ comfort and slow-comfort tapping-rates as the frequencies of movement to be imitated, but modifying the structure of the movement. This was done by reducing contact-time to ≈ 0 and increasing movement-time (Fig. 1c), so that the finger was moving throughout the cycle. In all VR cases, actions were observed through the head mounted display (HMD, Fig. 1).

Each block of 50 tapping cycles was performed twice at Comfort and Slow-comfort tapping-rates. Imitation abilities were evaluated in VR conditions (Self-Paced$_{VR}$ vs. Imitation$_{VR}$); the order of presentation was randomized. Self-Paced$_{REAL}$, always performed first and was used to set the avatar’s tapping frequencies for Imitation$_{VR}$.

2.3. Material

The tapping cycle was recorded by an event detector comprising a conductive plate and flexible conductive ring attached to each subject’s distal phalange. For PD and HE only, we recorded surface EMG activity on the extensor digitorum (SX230 electrodes, Biometrics Ltd, amplified x1000; filtered: 20-450 Hz; sampling frequency 1 KHz). One of the investigators (blind to the condition) determined the start and end of each burst off-line in MatLab (The Mathworks, Ltd). The signal was amplitude normalized, full-wave rectified and averaged using a 10 ms time window. Normalization involved dividing each point by a maximum obtained during a maximal voluntary contraction (index extension against an un-moveable load).

2.4. Variables

We calculated the tapping cycle frequency (FQ, in Hz); Contact-time (ms, finger in contact with the plate); Movement-time (ms, finger moving); and Coefficient of Variation (CV, %) of tapping cycle duration. EMG power was expressed (mV, RMS (root mean squared)) for each burst, as % of Self-Pace$_{REAL}$ EMG value.

2.5. Statistical analysis

2.5.1. Preliminary analyses

We characterized the tapping profile during Self-Paced$_{REAL}$ at comfort and slowcomfort tapping-rates. For this an ANOVA with repeated measures (2 x 3 ANOVA-RM) was performed for FQ, with factor TAPPING_RATE at two levels (comfort; slow-comfort), and GROUP at three levels (HY, HE, PD).

Another 2 x 2 x 3 ANOVA-RM was performed; with an extra factor, CYCLE_PHASE with two levels (Contact-time and Movement-time, each in ms, as % of tapping cycle).

In the patients group, we also evaluated any potential interaction between the tapping rate and its CV with disease severity (UPDRS$_{motor\ section}$). This was done for both comfort and slow-comfort rates, when not imitating in VR. For this, we calculated Pearson's Correlation Coefficients.

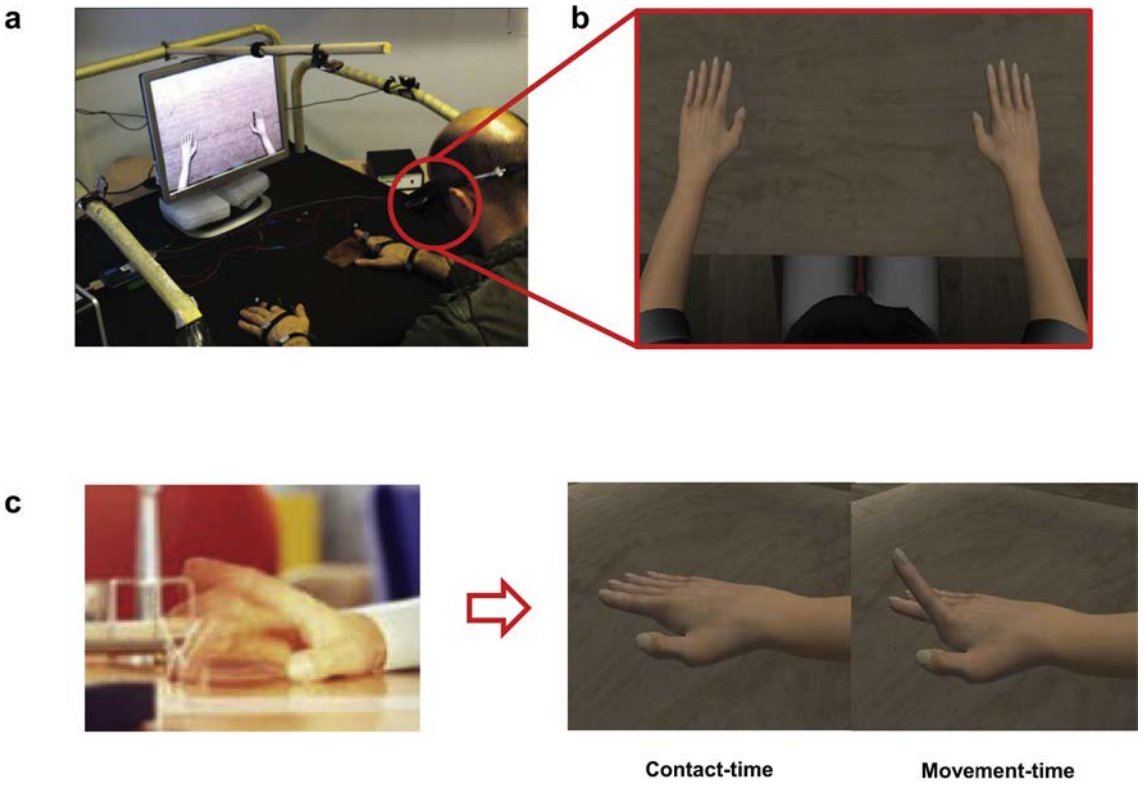

Fig. 1. Virtual Reality System. a) Subjects wore a Head-Mounted Display unit (HMD) and were "immersed" in VR, showing the avatar in 1st person perspective; observing the world only through the HMD, (the PC monitor illustrated was a copy of the display for the experimenter). b) The "field of view" of the immersed subject was arranged such that their own hands were "in register" with those of the avatar. c) Normal tapping was translated from the subjects own recorded movements, left, to the VR avatar, right, showing still-frame illustrations of contact and movement components of the tapping pattern- these could be adjusted while maintaining the required frequency.

2.5.2. Main outcomes: movement imitation and clinical relevance

2.5.2.1. Imitation abilities. The subject's ability to imitate the motor pattern presented in VR was evaluated by a 2 x 2 x 2 x 3 ANOVA-RM; as above but adding the factor CONDITION, with two levels (Self-Paced$_{VR}$; Imitation$_{VR}$). This allowed us to evaluate changes in CYCLE-PHASE (Contact and Movement-times) between GROUPs, when the CONDITION was imitation (compared to self-pace) at confort and slow-comfort TAPPING_RATEs.

2.5.2.2. Clinical relevance: electromyographic and kinematic profile during imitation. Because PD show an impaired execution of FT, we analyzed EMG activity, CV of cycle time, and cycle time (as FQ). This would provide insight on a potential role for imitation in movement rehabilitation in PD. We use the same

3 x 2 x 2 ANOVA-RM model for this analysis, with factors GROUP, CONDITION and TAPPING_RATE.

Normality of distributions was assessed by a one-sample Kolmogórov-Smirnov test. Univariate-ANOVA was used and therefore degrees of freedom were corrected with Greenhouse Coefficients (ε) in the case of sphericity violation, assessed by the Mauchly test. Significance was set at $p < 0.05$. In each figure, values are mean ± SEM.

3. Results

3.1. Characterization: execution in absence of imitation

3.1.1. Self-paced tapping patterns at comfort and slow-comfort rates

Participants significantly reduced their tapping rate at slowcomfort vs. comfort self-paced tapping rates, as expected ($F(1,25) = 25.394$ $p < 0.001$). At both tapping rates, however, PD tapped faster than the other two groups ($F(2,25) = 5.918$ $p = 0.008$, Fig. 2a). Unexpectedly, there was a significant difference in the pattern of slowing seen. All groups increased contact-time as tapping frequency reduced over time (Fig. 2b), but PD and HE slowed their tapping frequency by increasing both Contact and Movementtimes, maintaining the ratio of Contact and Movement time within the cycle (Fig. 2c,d) while HY Movement-timewas unaltered but Contact-time increased (Fig. 2b) a significant difference ($F(2,25) = 4.740$ $p = 0.018$). Supplementary Table 2 shows the correlation between disease severity ($UPDRS_{motor\ section}$) and motor execution (CV and tapping rate), at slow-comfort and comfort selfpaced rates.

3.2. Main outcomes: motor imitation and clinical relevance

3.2.1. Dopaminergic deficiency has no effect on imitating motor patterns

Having defined tapping profiles at self-paced Comfort and Slow-Comfort rates, the subject's ability to imitate was evaluated by examining how they adapt their tapping when asked to imitate the avatar's animated pattern, a pattern showing a continuously moving finger at the appropriate frequencies.

The main finding is that PD were clearly able to imitate this change in finger tapping pattern successfully, at both tapping rates. The way they adapted their execution to the finger movement to be imitated was not significantly different to HE or HY subjects ($F(2,25) = 1.954$ $p = 0.163$). All groups successfully modified their tapping pattern when imitating by reducing contact-time and increasing movement-time ($F(1,25) = 9.658$ $p = 0.005$); the effect was significantly greater, however, at the Slow-Comfort rate ($F(1,25) = 5.246$ $p = 0.031$; Fig. 3ab, Fig. 4a).

When the tapping frequency was analyzed, unsurprisingly, all groups tapped slower during the slow condition ($F(1,25) = 36.235$ $p < 0.001$), regardless of whether this was during $Selfpaced_{VR}$ or $Imitation_{VR}$ ($F(1,25) = 0.820$ $p = 0.374$). Interestingly, the tapping frequency during $Self\text{-}paced_{VR}$ and $Imitation_{VR}$ was not significantly different at each rate, Comfort or Slow-comfort ($F(1,25) = 1.932$ $p = 0.177$; see Figs. 3c and 4b). This means that the change in tapping pattern observed during imitation was not influenced by a change in tapping frequency.

3.2.2. Clinical relevance: inter-tap variability and EMG power during imitation

As expected, variability was different between groups ($F(2,25) = 5.731$ $p = 0.009$), and PD was larger than HE or HY ($p = 0.033$ and $p = 0.003$ respectively). However, $Imitation_{VR}$ induced a change in CV which depended upon the tapping-rate. Slow-Comfort rate CV was significantly reduced during $Imitation_{VR}$ ($F(1,25) = 6.131$ $p = 0.020$, see Fig. 4c). This reduction in CV when imitating at slow rates was observed in all groups ($F(2,25) = 1.461$ $p = 0.251$).

Further, comparing PD with HE, the power of the EMG was increased during $Imitation_{VR}$ ($F(1,17) = 28.870$ $p< 0.001$), though to a different extent in both groups ($F(1,17) = 5.443$ $p = 0.032$). At Slow both PD and HE increased their myoelectric activity ($p = 0.007$); such effect was only significant at Comfort for theHE ($p<0.001$; Fig. 4d-f).

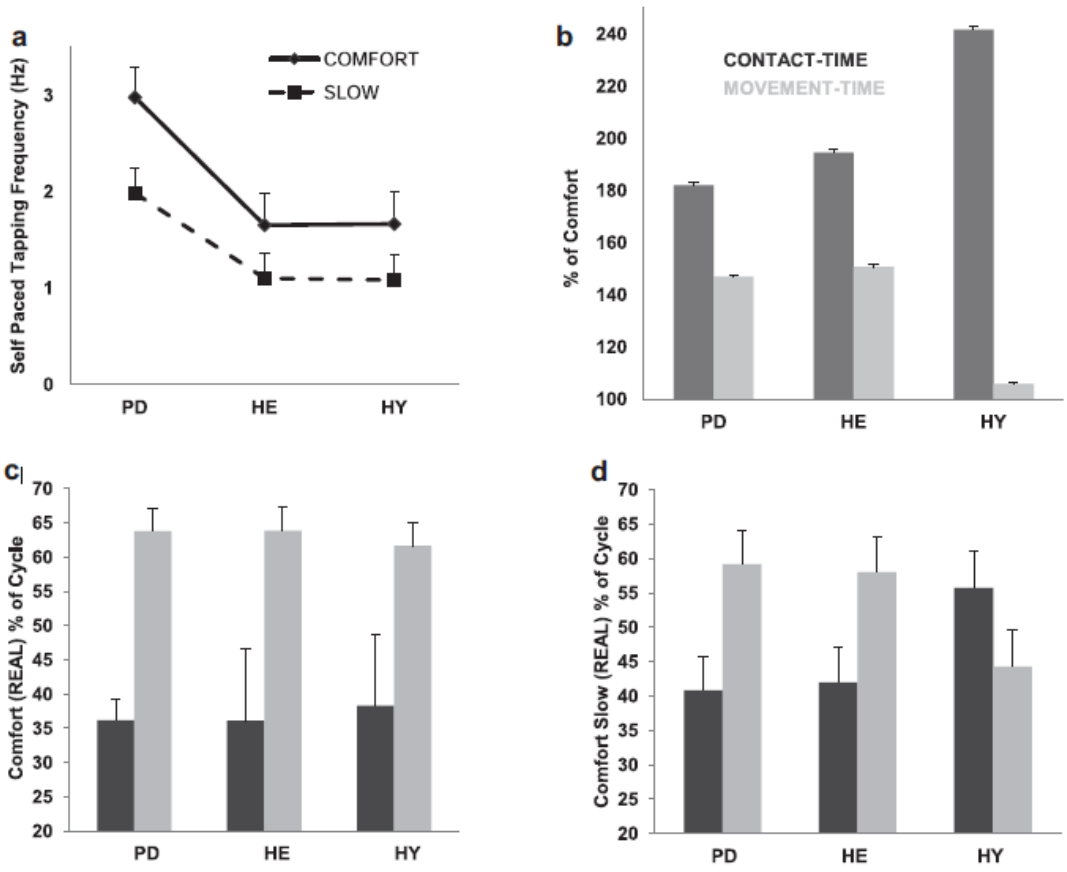

Fig. 2. Tapping pattern characterization. a) Tapping rates were significantly reduced when subjects were instructed to use slow comfort tapping-rate e slow-comfort vs. Confort ($F(1,25) = 25.394$ $p < 0.001$), though PD tapped significantly faster than the other groups ($F(2,25) = 5.918$ $p = 0.008$). b) In relation to Comfort (100%), this reduction in the tapping rate was due to increased contact time ($p = 0.001$ PD & HE; $p = 0.018$ HY). Movement time was unchanged by HY; PD & HE's movement times significantly increased ($p = 0.007$). c,d) The proportion of movement and contact times within the cycles was similar in all groups at Comfort and Slow (~40% contact and ~60% movement time), except for HY at Slow.

4. Discussion

We present two main results. Firstly, successful imitation by our PD suggests that dopaminergic systems known to be damaged are not involved in imitation of simple motor patterns within the subject's motor repertoire. Secondly, despite the fact that a high temporal variability of movements and lower recruitment efficiency are well known features of PD and aging, these subjects increased the power of their myoelectric activity during imitation, and reduced variability in imitated movements at slower tapping rates.

4.1. Imitation and dopaminergic system

Since one objective of the studywas to understand the role of the DAergic system in imitation in the task proposed, we evaluated PD OFF-dose. It can be approached by comparing subjects with pathologic vs. physiologic DAergic systems (HE and HY). This way the DAergic role in imitation is better understood if comparing PD OFFdose to healthy subjects rather than to PD ON-dose, because ONdose PD do not actually have a normal, functional DAergic system, despite the DA replacement, which sometimes leads to motor manifestations like dyskinesias. However, considering the reduction in the CV observed in our healthy subjects, it is likely than a putative therapeutic effect of imitation might be also present in ON-dose PD.

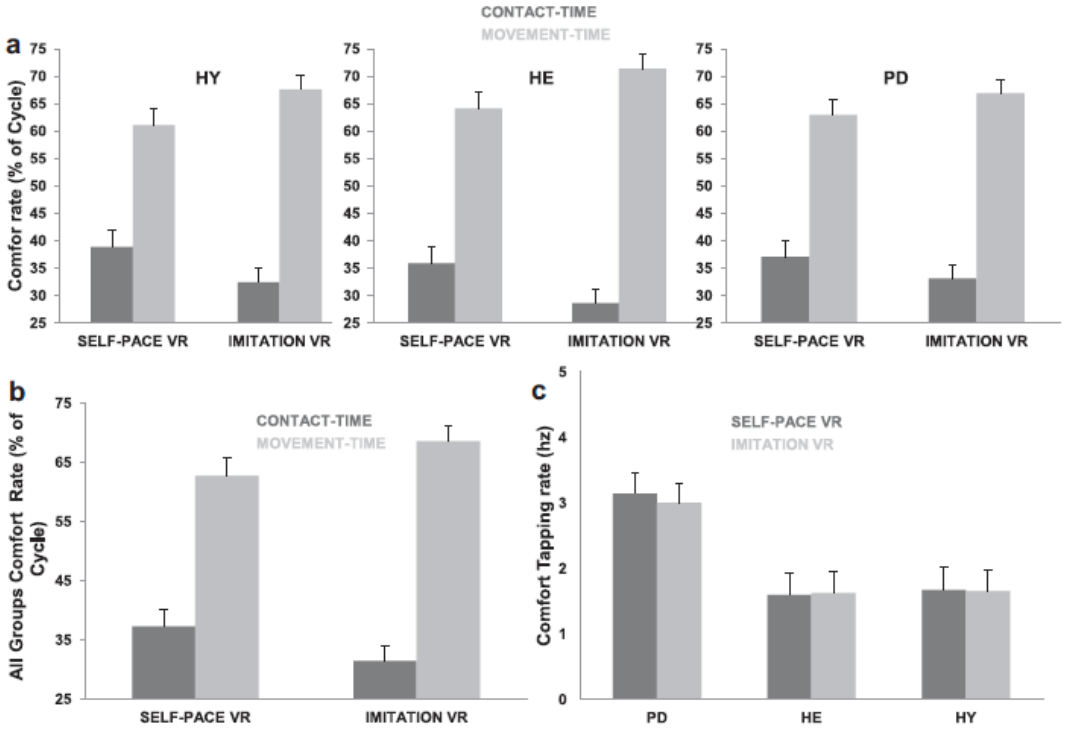

Fig. 3. Imitation at Comfort rate. a) There was no significant difference between groups' behavior when imitating ($F(2,25) = 1.561$ $p = 0.230$). b) All groups reduced the proportion of the cycle in contact time while imitating (pooling the three groups; $p = 0.004$). c) Tapping frequency during Self-paced$_{VR}$ and Imitation$_{VR}$ was not significantly different at each rate.

4.2. Mechanism for improving motor control

Instability in finger tapping frequency is a known feature in both PD and aging [11], associated with disruption to stride and gait patterns [19] and falling [20]. Sensory cueing is a well-studied strategy used in order to induce sensorimotor synchronization, leading to movement facilitation, chiefly in PD [4,21]. Its physiological basis seems to be an apparently decreased involvement of the BG-SMA loop, which is known to be altered in the disease, if movements are executed in presence of rhythms [22,23]. However, while reduction in the variability of the movements has been reported using auditory sensorimotor integration [21], this seems to be less effective if temporal visual cues are presented [21]. The difference here is that by using imitation of an observed moving hand, rather than an abstract "temporal pattern stimulus", PD might become less dependent on the BG-AMS loop or learn to compensate for the deficit by means of the involvement of the mirror neuron system (MNS) [24]. These neurons respond both during observation and execution of appropriate motor actions, including digit movements [5], and studies involving imitation of simple finger extension presented in 3rd person perspective also show the involvement of mirror structures [5].

Our study utilized a 1st person perspective, instead of the 3rd person perspective [5]. While "natural" imitation, by definition, uses a 3rd person perspective, it is known than imitation of a 1st person perspective shares networks involved in the 3rd person perspective, though with a larger involvement of the somatosensory cortex [13]. This might involve the sense of "agency" [25], and was the reason for our choice in this study. Also, a "like-me" model of imitation seems to be preferred during childhood development [26] e a common example is learning to dance, where a teacher adopts a 1st person "role model" position.

It is not then surprising that the reduction in the temporal variability of the pattern during imitation was observed at comfort-slow rate, since comfort rate is likely to be more "locked" within the motor repertoire and therefore less adaptable. Interestingly, the pattern we presented might be not the better to reduce variability in finger tapping (for that purpose a pattern with a stable and similar contact-time and movement-time to the natural tapping pattern would be required), though it allowed a proper characterization of imitation capabilities. Remarkably, the tapping frequency was not changed by the

process of imitating (Imitating$_{RV}$ vs. Selfpace$_{RV}$; either at comfort or slow-comfort rates) ruling out an effect of tapping-rate drift on outcomes. From a clinical point of view increased EMG power in the extensor digitorum muscle when imitating is important, since impairment in the pattern of muscle activation is a reported feature in PD [2]. Therefore, this suggests that a rehabilitation program based on imitation might be useful to induce central adaptations leading to lessening of symptoms of the disease.

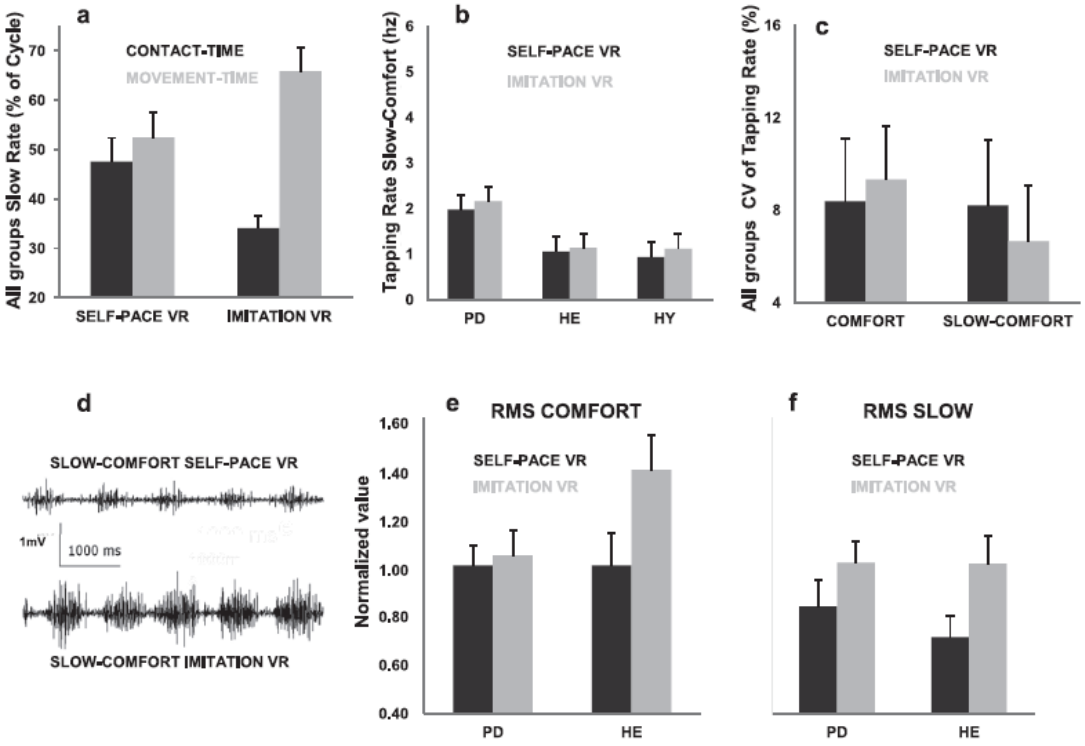

Fig. 4. Imitation at Slow rate (a,b), and effect of imitation on stability of movement (c), and on motor recruitment (d-f). a) Group responses while imitating at slow-comfort rate were not significantly different ($F(2,25) = 2.200$ $p = 0.132$), suggesting that Parkinsonian-induced dopaminergic deficiency did not affect performance in the task. All subjects adapted their finger movement in response to observing the continuously moving finger pattern by significantly reducing their contact times ($p = 0.004$). b) Imitation did not induce significant changes in the slow tapping rates of the different groups. c) At Comfort rate none of the groups significantly changed the temporal stability of the movement when imitating. However, at slow rate imitation lead to a significant reduction in the variability of movement ($F(1,25) = 6.131$ $p = 0.020$), an effect which was also not different for the Groups ($F(2,25) = 1.461$ $p = 0.251$). d) shows a representative EMG-recording in a subject (PD) tapping at Slow comfort either during Self-pace$_{VR}$ (upper trace), or Imitation$_{VR}$ (lower trace). e) The EMG power (expressed in relation to RMS-Self-Paced$_{REAL}$) was increased during imitating in the HE ($p = 0.001$) at comfort rate; f) at slow rates, however, imitation induced also greater EMG power ($p = 0.007$) in both PD and HE.

4.3. Motor control adaptation underlying slowing finger tappingrate in different groups

At both rates PD had faster tapping rates than the healthy groups, reflecting the PD tendency to hasten their rhythmic movements [19]. We have also described how different subjects slowed their self-paced tapping-rate. HE and PD increased both movement and contact-times, on the other hand HY kept constant movement time, but increased contact-time. PD and aging are associated with impairment in rhythm formation [11], thus increasing movement-time might be a compensatory mechanism mediated by a greater involvement of cerebellum [27] (considered a comparator of current movement vs. movement intent), to be less dependent on the BG, and allowing better rhythm maintenance.

5. Conclusion

The dopaminergic system seems not to have a key role during imitation of motor patterns available in PD subject's motor repertoire. Improvement in motor control observed in subjects suggests a possible use for imitation protocols oriented to rehabilitate motor patterns impaired in aging and PD. Further research is needed in order to know if imitation training for several days leads to off-line motor adaptation in patients' motor control.

Conflict of interest

The authors assent that there are no conflicts of interest.

Acknowledgment

No specific regulations. These may be published on line at the discretion of the editor.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2013.08.005.

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