Motor learning in Parkinson's disease: limitations and potential for rehabilitation

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ARTICLE INFO

SUMMARY

The striatum is very much involved in learning motor sequences particularly in the consolidation phase, predicting that motor learning is affected in Parkinson's disease (PD). We conducted a literature review on this question and showed that behavioural studies indicate a relatively preserved acquisition as well as retention of motor learning in PD. Persons with PD did demonstrate slower learning-rates than controls. Brain imaging studies highlighted that much more brain activity is needed and different neural networks are recruited in PD, suggesting a reduced efficiency of learning.

Using additional sensory information may optimize motor learning in PD. There is abundant evidence that cueing helps to achieve better movement performance and that these effects are retained immediately after withdrawal, possibly indicating the first signs of consolidation. Also, automatization of cued learning was demonstrated, as cues not only enhanced dual-task performance but these increments were retained after cue withdrawal. However, the effect of longer periods of cued training on retention of cued and uncued performance is not well established and some studies suggest that learning effects may be cue-dependent. The results of this review support the notion that adopting motor learning principles could benefit rehabilitation in PD. Even so, the limitations of reduced flexibility, efficiency and increased context-specificity of motor learning in PD need to be taken into account.

1. Introduction

The question of whether motor learning is possible in Parkinson's disease (PD) is pertinent in the context of a neurodegenerative disease affecting the basal ganglia. However, animal models of PD suggest that there is a dynamic interplay between degenerative and regenerative mechanisms of these structures, which are mediated by exercise and learning [1]. Focused physical activity may tap into a variety of molecular repair mechanisms which not only appear to restore motor function but also promote neuroprotection at least in PD animal models [2]. These findings coincide with an increasing number of studies showing benefits of rehabilitation in PD [3–5]. The reported benefits are supported by level II evidence, but so far effect sizes are small to moderate and tend to fade with time [3]. Systematic reviews [4,5] of physical therapy suffer from clinical and statistical heterogeneity. This may reflect clinical practice as being too multi-focused and offering too low intensities of training.

Motor learning is classically defined [6] as a set of processes associated with practice or experience, leading to relatively permanent changes in the capability for movement. Fitts and Posner [7] proposed that motor learning involves three stages. During the first or cognitive stage of learning, the performer engages in receiving instructions and feedback from the instructor, figuring out what to do and how to do it. This is an error-prone stage with a high degree of variability in performance. The second or associative stage of learning is marked by associating specific environmental cues with the movements required to achieve the goal or the skill. This is a refining stage, in which the person makes fewer errors and shows increases in task consistency. In the third or autonomous stage, automaticity is reached. Performers no longer think about the specific movement characteristics and can often do another task at the same time, for example carrying on a conversation while driving a car.

Augmented feedback is often used in normal motor learning [8] and can include goal-directed information about performance (knowledge of results) or information about the movement itself (knowledge of performance) [9], such as additional visual information displayed on screen or virtual reality applications. Its drawback may be that it creates specificity of learning, which implies deterioration of performance when the sensory information is withdrawn [9]. This suggests that the augmented sources of information have become part of the central representation of the movement.

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Table 1
Motor learning studies in PD – single tasks

References	Groups	Task paradigm	Intensity	Acquisition in PD	Retention in PD
Verschueren et al. 1997 [15]	7 PD (H&Y I–III); 7 CTR	Out-of-phase bimanual circle drawing with and without visual feedback	40×; 1 Day	Learning increment PD=CTR; Performance PD<CTR	No transfer to no-feedback task
Swinnen et al. 2000 [16]	13 PD (H&Y I–III) 13 CTR	Bimanual figure drawing normal and blindfolded. Both conditions were paced by auditory cues	500–600×; 2 Days	Learning increment PD=CTR; Performance PD < CTR	Not tested
Behrman et al. 2000 [17]	15 PD (H&Y II–III) 15 CTR	Simple and complex arm reaching	120× 2 Days	Learning increment PD≥CTR	Retention after 2 days
Ghilardi et al. 2003 [18]	15 PD 19 CTR	Predictable and unpredictable arm reaching towards targets	– 2 Days	Learning increments PD=CTR; Learning was slower in PD	Not tested
Flament et al. 2003 [19]	11 PD (H&Y II–III)	Targeted arm flexion towards visual target	400×; 1 Day	Significant performance increments	Not tested No transfer to EMG-signals
Jöbges et al. 2004 [20]	14 PD (H&YII.5–IV)	Reactive compensatory stepping	180–230×; Daily for 2 weeks	Significant performance increments	Retention after 2 months and transfer to gait
Smiley-Oyen et al. 2006 [21]	7 PD 7 CTR	Postural sequence Buttoning task	288 or 144; 3 Weeks	Learning increments PD=CTR; Learning was slower in PD	Retention after 3 weeks
Jessop et al. 2006 [22]	10 PD (H&Y II–III) 10 CTR	Visually guided balance task	45× 1 Day	Learning increment PD=CTR; Performance PD < CTR	Retention after 1 week
Mak and Hui-Chan 2008 [14]	20 PD 21 PD 21 PD (H&Y I–III)	No training Strengthening Cued sit-stand	4 Weeks; 3 Times a week	Learning increment cued training > strength and no training	Retention after 2 weeks
Onla-or and Winstein 2008 [23]	20 PD (H&Y I.5–III) 20CTR	Goal-directed elbow movement in high- and low-demand learning conditions	270×; 2 Days	Learning increment PD=CTR in both conditions	Retention after 3 days. No transfer to different context
Michel et al. 2009 [24]	17 PD (H&Y I.5–III) 15 CTR	Bilateral obstacle stepping with some acoustic feedback	120× 1 Day	Learning occurred in PD but was slower; Performance PD < CTR	Not tested

CTR: controls; PD: Parkinson's disease; ×: number of repetitions; H&Y: Hoehn & Yahr stage

A recent brain imaging study [10] throughout the learning phases in healthy adults has shown that there is a general reduction of brain activity as a result of learning as well as a shift from cortical to subcortical neural activity. During acquisition, activity gradually decreases in the prefrontal-parietal regions, involved in attention demanding sensory processing. In contrast, brain activity increases in the putamen and cerebellum, which is maintained during automatization. This confirms that not only the cerebellum but also the striatum is involved in motor learning, particularly in the storage of motor representations in motor memory [10]. Doyon et al. (2008) proposed that experience-dependent changes in the brain depend not only on the stage of learning, but also on whether subjects are required to learn a new sequence of movements (motor sequence learning) or learn to adapt to environmental perturbations (motor adaptation) [11]. While the striatum and the cerebellum are both involved in initial consolidation, these structures take on a specific role during later automatization, i.e. the striatum is responsible for learning predictable motor sequences [12] and the cerebellum for motor adaptation tasks. Based on these studies, we can predict that motor learning in PD is affected throughout the learning phases but particularly during the automatization phase.

In this paper, we will study whether motor learning is affected in PD by reviewing those investigations that focus on training paradigms and outcomes relevant to rehabilitation. In analogy with the Fitts and Posner model we will examine the evidence on the *acquisition* of motor learning, the attention-demanding early phase [7]. We will also consider studies that address the *automatization* phase of motor learning, signifying consolidation. Both resilience to dual task interference and *retention* of the learned task after a period without training are conceptualized as signs of consolidation [11,13]. Lastly, we will examine studies on cued motor learning in PD, given the potential impact of augmented sensory information on the learning process [9].

2. Behavioural evidence of motor learning in PD

2.1. Single task learning

The 11 studies that were included for this part of the review involved the learning of well-defined motor tasks, usually in laboratory-based environments all involving patients with PD [14–24]. Most of the studies compared motor learning increments with those of controls. Only one study used a randomised group design with two control conditions in PD patients only [14]. Table 1 shows that a broad variety of tasks were investigated addressing discrete movements of both upper and lower limbs [15–19,23] as well as complex tasks and gross functional movements such as balance manoeuvres [20–22], sit-to-stand [14], postural sequences [21] and obstacle stepping [24]. One study compared the learning of two different tasks: a novel postural sequence and a daily buttoning task [21]. Similar improvements were apparent. Overall, the findings showed that acquisition is preserved in patients with PD across a wide range of tasks. After training, PD patients showed improvements on a number of typical signs and symptoms of the disease such as bradykinesia [15–19], scaling of amplitude [15–18], variability of bimanual coordination [15,16] and postural instability [20,22]. The most striking findings were that even complex balancing tasks were responsive to learning and showed retention effects after 1 week to 2 months [20–22]. However, several studies [18,21,24] showed slower learning-rates in PD than in controls and sustained performance differences between groups [15,16,22,24].

These positive results on acquisition may be partly ascribed to the fact that various methods of external pacing [16,18,24], visual

Table 2
Motor learning studies in PD – dual tasks

Reference	Groups	Task paradigm	Intensity	Automatization in PD	Retention
Soliveri et al. 1992 [35]	21 PD (H&Y I–III) 23 CTR	Buttoning with and without foot tapping	18× 1 Day	Interference decrease PD=CTR; Learning is slower	Not tested
Kelly et al. 2004 [36]	12 PD (H&Y I–III) 9 CTR	Serial reaction time (SRT) tasks with and without tone counting	200 trials 1 Day	Dual task learning PD=CTR for easy SRT task. No learning of difficult STR task in both groups; Performance in PD < CTR	Not tested
Canning et al. 2008 [37]	5 PD (H&Y I–III)	Dual and multi- task walking using cognitive and manual tasks	30 min. 3 Weeks		Retention after 3 weeks

CTR: controls; PD: Parkinson's disease; ×: number of repetitions; H&Y: Hoehn & Yahr stage

targets [14,18,19,22], visual feedback [15,16,22], and providing knowledge of results [14,23] were adopted during the learning process. A recent systematic review on serial reaction time tasks supports the notion that implicit acquisition is specifically affected in PD, although not always consistently [25]. Implicit learning refers to reinforcement or habit learning [26,27], involving no verbalisation or meta-cognitive processing of the learned material. The basal ganglia are suggested to be highly implicated in implicit sequence learning [11,27,28]. Explicit learning on the contrary refers to using a high degree of awareness and ability to verbalise the learning process and outcomes. It is, however, also acknowledged that in practice the distinction between these learning modes is often difficult to make [28]. Using auditory pacing, visual targets, visual feedback and knowledge of results shift the learning mode towards the explicit end of the implicit–explicit continuum [29] and therefore have positively influenced acquisition in the above reviewed studies.

Most of the investigations included patients from the early to mid disease stages, with the exception of one study [20]. Cognitive impairments are likely to limit learning especially with disease progression. Muslimovic and colleagues [30] showed that learning of serial reaction time tasks was correlated with disease progression but not with cognitive functions. However, two recent studies found a negative correlation between serial sequence learning and cognitive impairment [31] and more specifically with cognitive flexibility and executive function [32].

As for retention of learning, overall short term retention effects were reported, pertaining to 1–3 days without training. In 3 out of the 11 studies retention periods of longer than 1 week were examined and in all these cases retention was confirmed. Some specific problems with retention were also reported. Verschueren and colleagues [15] demonstrated that learning a novel coordination task was greatly enhanced by providing augmented visual feedback in both controls and PD-patients. Subsequently, performance increments completely regressed when the extra sensory information was withheld in PD only. Onla-or and colleagues [23] showed that patients and controls benefited equally from different practice order and feedback frequency conditions during acquisition of an upper limb task. Conversely, group differences became pronounced during the retention test when patients but not controls were unable to demonstrate comparable motor learning during dissimilar conditions from the practice conditions. This context-specificity of learning was interpreted as related to the cognitive deficits of impaired shifting ability and task-switching inherent to PD.

2.2. Dual-task learning

Several studies have highlighted that dual- and multi-task performance is substantially compromised in PD compared to controls [33,34], a deficit which is attributed to the executive dysfunction inherent to the hypoactive striatofrontal connections.

This raises the question whether patients with PD are able to learn to perform dual-tasks. Moreover, the ability to withstand dual task interference (induced by a secondary task) is considered a measure of automatization of motor learning of the primary task [7].

Table 2 summarises 3 studies which addressed motor learning of dual task paradigms. Soliveri and colleagues [35] studied the learning of a skilled task, i.e. doing up buttons while using foot tapping as a concurrent secondary task. They showed that although initially interference effects were greater in PD than in controls, secondary task interference decreased with learning at similar levels in both groups, albeit more slowly in PD. Kelly and colleagues [36] compared serial reaction time task learning under dual task conditions between patients and controls. PD-patients had greater deficits on both the primary and the secondary task but similar learning increments were apparent in both groups. A recent pilot study showed that velocity of multi-task walking was improved after multi-task gait training and that these effects were retained after 3 weeks follow-up [37]. However, secondary task performance was not measured in this study. Although the evidence is limited so far, learning a dual task and achieving automatization seem possible in PD.

2.3. Cued motor learning

Traditionally, cueing is seen as a compensatory rehabilitation method to improve motor output by bypassing the deficient internal motor generation system in PD [38]. This bypassing theory is based on studies which underscore the existence of a distinctive medial and lateral system, both having different anatomical connectivity and functional significance [39–43]. The medial system, including the supplementary motor area (SMA) and basal ganglia (BG), would support the generation of actions based on intention and a person's internal reference frame. The lateral system, including the premotor (PMC) and parietal cortex and the cerebellum, would dominate during externally-generated movements, i.e. responsive actions driven by the presence of specific stimuli or objects in the immediate environment.

Cueing as applied in the clinical setting does not involve feedback but rather provides a reference, target or external trigger for movement generation [44]. Here, we pose the contention that cueing may also be conceptualized as a motor learning tool. There is abundant evidence that cueing helps the performance of more normal walking in PD in one single session. To address acquisition, we have summarized in table 3 the 8 studies [45–52] in which short-term carry-over of cueing effects were tested in uncued conditions, immediately after the intervention. The results demonstrate that cueing effects were remarkably maintained. However, when tested the next day [45] or after 3 weeks [46] no left-over effects were shown. This may indicate, what Doyen et al. called an 'intermediate phase of learning' [11], in which the improvements of cueing were consolidated in motor memory after 6–8 hours without training. Alternatively, these results may be

Table 3
Cross-sectional cueing studies in PD – immediate carry-over

Reference	Groups	Task paradigm	Immediate carry-over
Morris et al. 1996 [45]	16 PD (H&Y?)	Walking with and without visual cues	Carry-over for speed and stride length. Not maintained next day
McIntosh et al. 1997 [47]	21 PD (H&Y II–IV) 20 CTR	Walking with and without auditory cues	Carry-over for speed stride length and cadence
Freedland et al. 2002 [48]	16 PD (H&Y?)	Walking on electronic walkway with/without pulsed auditory stimulation	Carry-over for speed, step length and cadence
Rochester et al. 2005 [49]	20 PD (H&Y I.5–IV) 10 CTR	Single and dual walking using rhythmical auditory and visual	Carry-over for speed and step length in dual task in PD only
Rochester et al. 2007 [46]	153 PD (H&Y II–IV)	Single and dual task walking with and without auditory, visual and somatosensory cues	Carry-over for speed and step length in single and dual task; Not maintained after 3 weeks
Hausdorff et al. 2007 [50]	29 PD (H&Y II–III) 26 CTR	Walking with and without rhythmic auditory stimulation	Carry-over for speed, stride length and stride time variability
Baker et al. 2007, 2008 [51,52]	15 PD (H&Y II–IV) 12 CTR	Single and dual walking tasks with and without auditory cue and attentional strategies	Carry-over for step length in dual task; Retention for gait variability in single and dual task

CTR: controls; PD: Parkinson's disease; H&Y: Hoehn & Yahr stage

interpreted as unspecific effects of cues, due to post-cue heightened attention and arousal. Interestingly, in 4 out of the 8 studies summarized in table 3, the cues were applied in both single- and dual-task paradigms [46,49,51,52]. Not only did the cues improve dual-task performance, but also carry-over effects were even more pronounced during dual than single task conditions.

The RESCUE-study addressed the effect a 3-week period of cued gait training without controlling for uncued training. This study focused on the transfer of cued learning to non-cued outcomes in a variety of functional domains and retention after a 6-week follow-up period [44]. Although, significant training effects were shown on gait, transfer to other functional tasks was limited and retention was not demonstrated. The only study actually comparing uncued versus cued training in a randomised fashion in PD was carried out by Mak and colleagues [14]. This study investigated the effect of cued sit-to-standing using a visual trigger on computer screen. Not only did cued sit-stand training show greater effects than uncued training, but retention of cued training was maintained during uncued tests up till 2 weeks after intervention. On the down side, performance deterioration when augmented visual feedback was withdrawn, was evident in the study by Verschueren and colleagues [15].

Overall the findings on carry-over effects of cueing suggest that, acquisition of motor learning may be greater in PD (or performance improvements may be larger) when it becomes associated with external stimuli, which may become embedded in or part of the central motor representation, at least for the short term. As such, cue-augmented learning may only be evidenced when cues are present, allowing online access to the acquired motor skills. This specificity of learning has obvious clinical implications.

3. Evidence from imaging studies

Whereas behavioural studies show more or less intact motor learning throughout the learning process, several brain imaging studies indicate that this requires increased recruitment of neural resources and different neural networks in PD [53–56]. Similar findings have been shown in studies on aged individuals and stroke patients [57,58]. Mentis and colleagues (2003) studied early acquisition of a sequential task (target hitting with the right hand) [53]. It was shown with positron emission tomography (PET) scans that to achieve equal acquisition, patients recruited four times as many brain voxels and more bilateral activity than controls. Patients with PD additionally activated the left dorsolateral prefrontal cortex, the left anterior cingulate, the left orbitofrontal area and the bilateral cerebellum. Wu & Hallett (2005) investigated the ability to automatize a sequential finger task in PD with functional magnetic resonance imaging before and after a short training period [54]. Practice improved performance in both patients and controls, but patients displayed greater difficulty to switch to the automatic stage of learning. This was also reflected in the brain imaging data. Unlike in controls, brain activity became only a little more efficient in patients when learning to perform a single task automatically. However, several brain regions remained more active bilaterally in patients than controls, i.e. the cerebellum, premotor area, parietal cortex, precuneus and dorsal lateral prefrontal cortex. In a follow-up study, it was shown that PD patients activated more brain regions than healthy controls during dual-task performance [55]. After dual-task training, reduced interference was accompanied by a decrease in brain activity, although this was attenuated in PD compared to controls. Summarizing a series of PET-scanning studies on sequence learning in PD, Carbon and Eidelberg (2006) showed positive effects of deep brain stimulation but less predictable effects of dopaminergic treatment on acquisition [56]. Even over a period of 21 months, sequence learning declined in PD, a performance deterioration which was associated with a shift of brain activity from regions involved in normal learning towards areas not normally utilized [56].

Taken together, the above findings suggest potential for brain plasticity to compensate for neurodegeneration but also point to limitations in the sense of reaching a ceiling of learning. On a more positive note, within this overall increased neural compensation, a reduction of brain activity was observed even after limited practice and extending to automatization.

4. Translation to rehabilitation

How can the above findings on relatively preserved acquisition and consolidation of learning be translated to the clinical setting? Several authors point to the importance of an early start of motor learning in the disease process [1,56]. Although this seems self-evident, novel, relevant and motivating training modes are still to be developed which serve this purpose. All interventions under review used focused task or skill practice with higher repetition rates than usual in rehabilitation [14–24]. However, training intensities seemed compatible with the average clinical setting. PD patients do seem to need more time to achieve learning, especially to achieve

automatization. This review also suggested that particularly in the later stages, explicit learning methods, sensory information and cues may be adopted to enhance learning, acknowledging that there is a risk of developing cue-dependence. This implies that therapists need to build in a weaning-off stage to dissociate learning from the augmented sensory information or provide permanent reference points or cues to tap into the learning increments. The context-specificity of learning may be addressed by matching the learning environment as closely as possible to the daily functional situation.

5. Conclusion

There seems to be potential and limitations of motor learning in PD. The reduced flexibility of learning as the disease progresses needs to be accommodated using explicit learning methods and augmented sensory input, and by focusing on familiar environments and functionally important tasks. However, motor learning indicates a dynamic process, even against the background of a neurodegenerative condition as PD.

Acknowledgements

Conflict of interests

The authors have no conflicts of interest to report.

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