Title

Relearning of writing skills in Parkinson's disease: a literature review on influential factors and optimal strategies

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Abstract

Patients with Parkinson's disease (PD) suffer from severe motor symptoms which can only be partly alleviated by means of dopaminergic medication. Motor rehabilitation, i.e. relearning of a known motor skill through intensive practice, can be an effective and lasting therapeutic supplement in chronic neurodegenerative diseases. Recent studies on motor learning in PD provide insights for the development of optimal motor rehabilitation strategies, with a particular focus on achieving consolidated learning and retention. In this review, findings from the last couple of years are discussed with specific interest in the potential benefits from cueing and feedback strategies as means to achieve lasting changes. In addition, current neuroscientific insights on the impact of dopamine and cognitive functioning on learning are summarized. Finally, the knowledge on these topics is combined to propose an optimal strategy for relearning of writing skills in PD, a frequently reported motor deficit also known as micrographia.

Keywords

Parkinson's disease; Motor learning; Dopamine; Cognition; Micrographia

1 Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder caused by the loss of dopaminergic neurons in the pars compacta of the substantia nigra and other neurological systems, leading to a combination of motor and non-motor symptoms (Jankovic, 2008). One of the first symptoms often is micrographia. Wagle Shukla et al. (2012) defined it as “*an impairment of a fine motor skill manifesting mainly as a progressive reduction in amplitude during a writing task*”. Recently, it was shown by using objective criteria that 63% of patients with PD suffer from micrographia (Wagle Shukla et al., 2012). **Figure 1** shows a typical sample of handwriting impairments in PD, compared to a healthy person collected during our pilot experiments. Both participants were asked to copy as much as they could of a Dutch text on a blank page within 5 minutes. **Panel B** shows a healthy control who adopted a naturally small letter size. However, the handwriting is legible in contrast to the handwriting of the PD patient, as is shown in **Panel A**. Furthermore, it has been reported that writing velocity and sentence length are reduced in PD and that there is an increase in interruptions and variability of movement size (Broderick et al., 2009; Lange et al., 2006; Ponsen et al., 2008; Van Gemmert et al., 2003; Van Gemmert et al., 1999). It has been shown that dopaminergic medication and subthalamic nucleus stimulation can only partially improve these writing problems (Lange et al., 2006; Tucha et al., 2006), suggesting that additional therapeutic strategies are warranted. As an adjunct to pharmaceutical management of the disease, motor rehabilitation can play an important role in improving quality of life of PD patients (Goodwin et al., 2008; Keus et al., 2007; Keus et al., 2009). According to the World Health Organizations' (WHO) International Classification of Functioning, Disability and Health (ICF), rehabilitation can be considered as a health strategy that aims “*to enable people with health conditions, experiencing or likely to experience disability, to achieve and maintain optimal functioning in interaction with the environment*” (Stucki, 2005).

Motor learning entails an important component of rehabilitation. Doyon et al. (2009) described two types of motor learning: (i) Motor Sequence Learning (MSL), which is a process by which a series of movement elements become an entity through practice; and (ii) Motor Adaptation (MA), which is a process that requires participants to adapt to environmental changes. The process of motor learning consists of several phases, starting with the acquisition of a motor skill, followed by automatization, transfer and retention of what was learned. These last three processes are considered hallmarks of consolidation of motor learning. Based upon brain imaging studies, Doyon et al. (2009) presented a model of normal motor skill learning. During the early acquisition phase of both MSL and MA, cerebral structures, i.e. the striatum, cerebellum, motor cortical regions, prefrontal cortex, parietal cortex and hippocampus, interact to establish the motor routines that are necessary for learning. The consolidation phase involves activation of the cortico-striatal circuit for MSL, whereas the cerebellum is no longer involved. For MA on the other hand, the cortico-cerebellar system is activated, but the striatum is no longer implicated.

From the model of Doyon et al. (2009) it is clear that the striatum is involved in almost all stages of motor learning, but particularly during consolidation of learned skills that have a sequencing component. This suggests that motor learning in PD will be affected throughout the learning process, but particularly during the consolidation phase, which raises the question whether PD patients are still capable of learning a motor skill. Recently, this question was addressed in two literature reviews, both showing that the capacity for motor learning is, at least partly, preserved in patients with PD (Felix et al., 2012; Nieuwboer, Rochester, et al., 2009). However, both reviews mostly addressed the learning of novel motor tasks, and mainly considered learning that was guided by visual feedback. Compared to acquiring a novel motor task, improving the execution of an existing motor skill does not require the creation of a new motor program but instead engages previously established programs. We will refer to this

type of learning as motor refinement, which is of particular importance when trying to regain movement coordination and control, which is lost due to the impact of a disease such as PD. As such, this question is highly relevant as it addresses the role of practice-induced functional neuroplasticity in the context of a chronic neurodegenerative disease.

1.1 Scope of this review

Few studies have been conducted on the optimal practice strategies to achieve motor refinement in PD. Therefore, the current review will consider what is known so far on the effectiveness of the relearning of an existing and automatic motor skill, such as handwriting, in PD. We will begin with discussing recent findings on general motor learning in PD, followed by the impact of external cueing and the application of feedback. This is followed by a review of the literature on several critical disease-specific motor learning problems caused by the impairments in the basal ganglia, namely the effect of dopamine and cognitive functioning. Finally, we will synthesize findings from a more focused review of the literature regarding relearning of writing skills in PD. To investigate the effects of both cueing and visual feedback on handwriting we conducted a systematic literature review using PubMed. Search terms to examine the effects of cueing included ‘Parkinson’s disease’, ‘micrographia’, ‘writing’, ‘drawing’, ‘cueing’ and ‘motor learning’. To investigate the effect of visual feedback we included ‘Parkinson’s disease’, ‘motor adaptation’, ‘distorted feedback’ and ‘writing’ as search terms. Articles retrieved were screened based on the title, abstract and full content.

2 Motor learning in Parkinson’s disease

To investigate motor learning, it is important to make a distinction between immediate improvements (early phase) in motor performance during acquisition and long-term motor learning (late phase). Because motor learning cannot be measured directly, retention and/or

transfer tests are necessary (Salmoni et al., 1984). A retention test will evaluate the strength of the motor memory representation over time, while a transfer test involves testing whether what was learned during practice can be generalized to another task (Kantak & Winstein, 2012). Retention and/or transfer tests can be performed immediately ($<24\text{h}$) or after a delay ($\geq 24\text{h}$). However, immediate retention and/or transfer tests are not always good predictors for relatively permanent motor learning (for a review see (Kantak & Winstein, 2012)). In a recent paper by Nieuwboer et al. (2009), an overview was given on both behavioral and brain imaging studies regarding motor learning in PD. Results from behavioral studies showed a relatively preserved acquisition and retention of motor learning of a range of motor tasks in PD, although only short term retention was reported. These previous studies involved mostly novel goal-directed upper limb tasks, postural sequences or stepping tasks. In addition, some studies were discussed which required motor refinement of sit to standing, buttoning and reactive stepping to postural perturbations. Overall, PD patients presented slower learning-rates compared to controls. Brain imaging studies demonstrated an increase in neural activity in PD patients compared to healthy controls in the bilateral cerebellum, bilateral premotor areas, bilateral parietal cortex, bilateral precuneus and bilateral dorsolateral prefrontal cortex (Mentis et al., 2003; Wu & Hallett, 2005), suggesting a reduced neural efficiency of learning in PD.

Recently, Pendt et al. (2011) investigated learning of a novel skill in PD patients with an emphasis on short- and long-term retention of performance. Participants were trained on a throwing task: they were instructed to throw a ball in counter-clockwise direction around a vertical post in order to knock down a target on the other side of the post. As participants had to learn the mapping between the real arm movements and the ball's trajectory in the projected space, this task was considered a new motor skill. Five sessions were distributed across 5 days, of which the first 4 sessions occurred on 4 consecutive days and the 5th session

took place 5 days after the 4th session. Retention was tested 7 to 9 months after the final practice session. Results confirmed that early learning of a new motor skill is intact in PD patients. However, during both short- and long-term retention tests patients performed more poorly than healthy controls. This could be interpreted as either the result of problems with movement initiation at the beginning of a new session or poorer retention (Pendt et al., 2011). A recent meta-analysis by Felix et al. (2012) concentrated on the ability of PD patients to learn new upper extremity reaching tasks, for example reaching for a ball or reaching to a target on a digitizing tablet. This study focused on the effect of practice on movement time as a measure of learning. Results showed a consistent reduction in movement time as a result of practice for both PD patients and healthy controls, although improvements were greater in the healthy control group. Moreover, effects were not only present immediately after training, but were sustained, although to a lesser extent, after a period of time.

Studies in healthy adults suggested that non-invasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), can facilitate neuronal excitability and motor learning (for a review see (Tanaka et al., 2011)). Although the combination of motor training and non-invasive brain stimulation has not been investigated yet in PD, it has been shown that 8 sessions of anodal tDCS over motor and prefrontal cortices over a period of 2.5 weeks resulted in short term improvements of gait and long term improvements of upper limb bradykinesia (Benninger et al., 2010). Treatment with 50 Hz-rTMS over the primary motor cortex (M1) in 8 sessions over a period of 2 weeks was shown to be safe, though, it failed to improve motor performance in PD (Benninger et al., 2012). However, 1 Hz-rTMS over M1, preconditioned by anodal tDCS, resulted in beneficial effects on upper limb bradykinesia (Gruner et al., 2010).

In short, the abovementioned studies showed that PD patients can benefit from motor practice when learning novel goal-directed tasks and that non-invasive brain stimulation may in itself

improve performance. However, little is known about the retention effects of what was learned and about the relearning of internally-generated and well-rehearsed tasks which are predominantly affected by PD. During internally-driven movements the basal ganglia and supplementary motor areas are activated (Debaere et al., 2003; Jenkins et al., 2000), while during externally generated movements the cerebellum, parietal lobe and lateral premotor cortex are more engaged (Debaere et al., 2003; Jueptner & Weiller, 1998). Therefore, PD patients may benefit from the use of external stimuli, such as cueing and feedback to achieve a consolidated motor representation using compensatory brain networks that bypass the deficient brain structures.

2.1 Application of cueing in motor learning

Motor learning in PD has been shown to benefit from the use of cueing (Espay et al., 2010; Lohnes & Earhart, 2011; Rochester et al., 2010; Rochester et al., 2009). Cueing is defined as the use of external temporal or spatial stimuli to facilitate initiation and continuation of movement (Nieuwboer et al., 2007). The use of cues and their application in motor learning have been studied extensively in PD, particularly with respect to gait. Short-term carry-over effects of cueing were recently shown to extend to long-term effects, as gait training with external rhythmical cues increased single- and dual-task walking speed and step length, even at follow-up after 6 weeks (Rochester et al., 2010). However, this study did not compare the results to a control group of patients, who received training without cues. This point was addressed by Kadivar et al. (2011) who compared 6 weeks of multidirectional step training in PD, either externally-paced (EP), i.e. in time with an auditory cue at 1 of 3 speeds, or internally-paced (IP), i.e. at a self-selected internal pace. The effects of EP training generalized to improvements of the Dynamic Gait Index, which were maintained at least 4 weeks after training termination. IP training also led to improvements. However, these were not maintained as long as in the EP group. Positive results with regard to retention were also

obtained by Almeida & Bhatt (2012), who compared 6 weeks of cued gait training on a treadmill with cued training overground. Visual cues consisted of lines on the ground or on the treadmill, 70cm apart, to provide an indication for step length. In this study, it was found that improvements in gait were maintained through a retention period of 6 weeks for both programs. Aside from the visual and auditory cueing strategies, attentional cues such as the instructions “Take big steps” or “Take a big step in time to the beat” were also shown to enhance walking speed and stride length in both single and dual tasks in PD patients (Lohnes & Earhart, 2011; Rochester et al., 2009).

In contrast to the effects on gait, the effects of cueing on upper limb movements have not been studied extensively. Several studies investigated the effects of visual and auditory cueing on the training of bimanual movements, however, results are ambivalent. While some studies found improvements in bimanual coordination of PD patients in response to visual cues (Nieuwboer, Vercruysse, et al., 2009; Verschueren et al., 1997), others did not for auditory cues (Almeida et al., 2002; Swinnen et al., 2000). Research on cued learning of unimanual movements, such as writing or drawing, in PD is even rarer. Recently, Ringenbach et al. (2011) compared the use of verbal (“up” & “down”), auditory (high and low tones) and visual (target lines) cues during both unimanual and bimanual drawing tasks. Comparison of a PD group with a healthy elderly and young control group showed that bimanual performance of PD patients improved when following external cues. When comparing cue types, results indicated a benefit from both auditory and verbal cues, but not from visual cues. However, as a no-cue condition was not included, it could not be determined whether the use of visual cues was better than no cues.

Overall, these findings suggest that motor learning and particularly retention can benefit from the use of external cueing in PD. However, further research is needed to investigate how these cues can be used to improve the long-term motor learning of upper limb skills.

2.2 Application of feedback in motor learning

Besides cueing, motor learning in PD also benefits from the provision of augmented feedback (Swinnen et al., 2000; Verschueren et al., 1997). While cues provide a reference point for the execution of movements, feedback provides patients with knowledge about their own performance during or after the completion of a task. There are two types of feedback: (i) intrinsic feedback, i.e. sensory-perceptual information from internal sensory processes available as the result of an executed movement; and (ii) augmented feedback, i.e. extrinsic feedback from an outside source (Schmidt & Lee, 2011). Extrinsic feedback that provides information about the outcome of an action with regard to an environmental goal is called ‘Knowledge of Results (KR)’. On the other hand, extrinsic feedback providing knowledge about the quality or pattern of a movement underlying the goal outcome is referred to as ‘Knowledge of Performance (KP)’ (Schmidt & Lee, 2011). Winstein (1991) illustrated this difference using the example of rising from a seated position to standing: KR could be the amount of time it took to stand up, while KP could be the degree to which the subject leaned his or her trunk forward prior to rising from the chair.

Feedback in the context of motor learning usually involves information about the outcome of the movement (KR). In a study by Guadagnoli et al. (2002) it was shown that the frequency of feedback (KR) has an influence on motor learning in PD. In this study participants had to perform an arm pointing task as accurately as possible with regard to their goal movement time. Patients were given feedback (KR), either after each movement trial (100% feedback condition) or after every fifth trial (20% feedback condition). After trials that were to be followed by feedback, a computer screen displayed movement time errors (either moving too slow or too fast). During acquisition, four blocks of 15 trials were performed. The last trial was followed by an interval period of 10 minutes. Immediately after this, participants performed a retention test, consisting of 15 trials, during which no feedback was given.

Results showed that PD patients performed better in the retention test, when they had received feedback after every trial (100%) during the acquisition phase, compared to after every fifth trial (20%). Chiviacowsky et al. (2010) reported that, similar to healthy participants (Salmoni et al., 1984), PD patients performed even better on the retention test (without feedback), one day after practice of a linear position task, when they received feedback (KR) in 66% of the trials during acquisition compared to after every trial.

Onla-or & Winstein (2008) compared the effects of low demand practice (100% KR and block-design) and high demand practice (60% KR and random order) in a goal-directed arm movement task performed by PD patients, the premise being that high demand practice would involve more cognitive processing and as such facilitate consolidation. This task required participants to move a lever horizontally at the correct speed and distance to replicate the goal movement trajectory, displayed on the computer screen. Feedback consisted of an overall error score and a graphical representation of the response superimposed with the goal movement task. Learning was assessed with a recall test, in which the same movement was performed without feedback 1 day after practice. Results revealed that PD patients from the high demand practice group, but not those from the low demand group, showed comparable motor learning to healthy controls, but only when the context of the recall test was the same as that during practice. These results suggest that when augmented feedback is provided too frequently to PD patients, as in the low demand condition, it can cause a dependency and discourages the processing of intrinsic feedback in learners with PD, as well as healthy controls. The negative consequences of dependency on augmented feedback for retention have been investigated extensively by Schmidt and coworkers, as well as others (for an early review, see (Salmoni et al., 1984)).

In a study by Ondo and Satija (2007) the effect of complete withdrawal of visual feedback on micrographia was tested. Patients (both ON and OFF medication) and healthy controls were

tested while writing a sentence with both their eyes open and closed. Results showed that the writing length of patients OFF medication increased when their eyes were closed. These data suggest that micrographia is not only a motor hypokinetic feature, but that sensorimotor features are also affected in PD.

Overall, we can conclude that both the use of cues and augmented feedback can give rise to improvements in motor learning capacity. However, feedback overload and possibly also continuous cueing may lead to dependency and decreased long-term retention and/or transfer of learning. It should be investigated whether it is best to randomize the use of cues and no cues in the training phase, as was shown for healthy young adults (Lin et al., 2011), or whether it is best to incorporate a gradual reduction of cued learning to uncued learning. Generally, the findings so far have indicated a need for awareness of strategic implementation and gradual reduction of feedback-based and cued learning to unpredictable motor performance without cues or feedback to enhance automaticity, particularly in PD.

3 Influence of basal ganglia deficiency on motor learning

Although several strategies improve motor learning of PD patients, the effect of basal ganglia deficiency on motor learning needs to be taken into account when developing an optimal strategy. In the following section we will discuss the impact of dopamine and cognitive functioning.

3.1 The impact of dopamine

Recently, it was shown that the basal ganglia are engaged in several types of learning, including reinforcement learning, i.e. the learning of action selection to maximize reward. An important property of reward is to block habitual control, i.e. automatic and unconscious behavior, in favor of goal-directed control, i.e. controlled and conscious behavior (Schneider & Chein, 2003). It was demonstrated that dopaminergic pathways projecting to the striatum

contribute to reward-processing (Balleine et al., 2007; Schultz, 2006). Redgrave et al. (2011) proposed two separate mechanisms to discover and exploit behavior that maximizes reward acquisition. They hypothesized that the first mechanism can be used to determine whether an unpredicted sensory event is caused by the agent and to discover the causal components of the agents' behavior. This is done by altering the sensitivity of the internal basal ganglia circuit, using phasic DA release, in response to specific inputs. In the second mechanism, reward can modulate early sensory processing in the major input nuclei of the basal ganglia, thereby blocking habitual control and favoring goal-directed learning. This can improve with the use of cues (Ikeda & Hikosaka, 2003), as cited by Redgrave et al. (2011). These reward-related modulations can bias future selections in the basal ganglia and maximize future reward acquisition.

The role of DA in reinforcement learning was further investigated in healthy adults receiving a low dose of Amisulpride, which in low doses is thought to facilitate DA activity (Jocham et al., 2011). Results showed that the initial reinforcement learning was not affected by Amisulpride, however, in the later transfer phase performance was improved. These results confirm the role of DA in reinforcement learning and also corroborate the views of Redgrave et al. (2011) that DA is involved in favoring choices based on previously gathered knowledge.

In patients with PD, evidence suggests that dopaminergic medication influences reward-based reinforcement learning. It was shown that PD patients OFF dopaminergic medication are impaired in learning from reward or positive feedback (Cools et al., 2006; Frank et al., 2004). On the other hand, while ON dopaminergic medication they showed impairments in learning from punishment (Bodi et al., 2009; Cools et al., 2006; Frank et al., 2004), because medication blocks the effects of a normal DA dip. More recently, a reinforcement task in two phases (an acquisition phase and performance testing), similar to the study of Jocham et al. (2011), was tested in patients with PD (Shiner et al., 2012). Patients tested in the OFF state

were able to retrieve learned contingencies, however, they were not able to use this knowledge to make correct choices when they had to select between new stimulus pairings. On the other hand when patients were OFF medication in the acquisition phase, but ON medication during the performance testing, they chose the correct answer significantly more often. These results suggest that DA replacement therapy influences the ability to generalize from learned information and are in line with Redgrave et al. (2011) who suggested that previously gained knowledge can be used to bias future reward selection. A limitation of this study is that no healthy control group was tested. Therefore, it is impossible to define whether the improvements in performance due to DA therapy in PD led to a normal performance level. Taken together, these results suggest that DA replacement therapy plays a key role in reinforcement learning in PD patients. Although the tasks used to investigate reinforcement learning in PD are more related to information processing, rather than motor learning per se, we hypothesize that by combining dopaminergic medication with an intensive training program to learn to identify a sensory cue as the causal factor of successful behavior, a pre-existing motor skill may be relearned and refined in PD. Furthermore, feedback provides patients with the ability to link their actions to an outcome of success. This reveals why both cueing and feedback can lead to an improvement of motor learning capacities of PD patients.

3.2 The impact of cognition

Cognitive impairments are common in PD, even in early stages of the disease (Muslimovic et al., 2005). A recent review indicated that mild cognitive impairment is present in 25.8% of PD patients (Aarsland et al., 2010). Deficits are most prominent in the domain of memory and executive functions, which entail cognitive flexibility, inhibition, response switching and working memory, but also problem-solving, reasoning and planning (Kehagia et al., 2010). While several studies showed that working memory and cognitive flexibility are impaired in PD, other executive functions such as planning and inhibition appear to stay at a level

comparable to healthy elderly controls (for a review see (Kudlicka et al., 2011)). This suggests that executive functioning is differentially affected, rather than generally impaired in PD.

Motor sequence learning encompasses elements of cognitive functioning. Within motor learning a distinction can be made between explicit and implicit learning. Explicit learning is conscious, intentional learning in which cerebellum, parietal lobes and lateral premotor cortex are involved, while implicit learning is unconscious and incidental learning, during which supplementary motor areas and basal ganglia are activated (Passingham, 1997). Neuroimaging studies used the serial reaction time (SRT) task to show that the basal ganglia are involved in implicit learning in a healthy population (Hazeltine et al., 1997; Rauch et al., 1997; van der Graaf et al., 2006). In a typical SRT task participants had to respond as fast as possible to a stimulus presented in one of four locations (Nissen & Bullemer, 1987). During the acquisition phase of a SRT task an increased prefrontal activation was found in healthy adults (Hazeltine et al., 1997; van der Graaf et al., 2006). This led Price and Shin (2009) to formulate and investigate the hypothesis that executive functioning could play a role in SRT learning. Results showed that sequence learning was correlated to neuropsychological measures of executive functioning, namely spontaneous cognitive flexibility and the ability to shift attention. Consequently, limited executive functioning could weaken sequence learning and, as SRT tasks are used to test implicit learning, may explain the impairments in implicit motor learning found in PD (Siegert et al., 2006; van Tilborg & Hulstijn, 2010).

Preliminary evidence for such an association between cognitive functioning and implicit sequence learning in PD was found by Deroost and colleagues (2006). Also in a later study by Vandenbossche et al. (2009), more direct evidence was found for the relationship between SRT performance and the level of cognitive performance. PD patients with a high score on the Scales for Outcomes in Parkinson's disease-cognitive (SCOPA-COG) test were found to

have significantly lower error rates in the SRT task compared to patients with average and low score on this test. These findings suggest that cognitive functioning plays a role in motor sequence learning. Furthermore, it was found that PD patients needed more time for sequence learning and that their performance strongly correlated with their stage of the disease (Stephan et al., 2011).

Whereas motor symptoms were shown to be improved by levodopa therapy in PD, the results of its effects on cognitive performance are ambivalent (for a review see (Macdonald & Monchi, 2011)). Some cognitive functions are improved by dopaminergic therapy, whereas others are unaffected or even become impaired. For example dopaminergic medication compensates for the cognitive inflexibility found in PD (Cools et al., 2003). On the other hand, Ghilardi et al. (2007) investigated the effect of levodopa infusion on learning of both motor and visual sequences in patients with moderate to severe PD. Although levodopa improved motor scores and movement speed, no beneficial effects on either type of sequence learning were observed. Furthermore, the effects of non-invasive brain stimulation on cognition were also investigated in PD. It was shown that anodal tDCS of the left dorsolateral prefrontal cortex resulted in significant improvements in working memory of PD patients (Boggio et al., 2006). In addition, 1 session of 25 Hz-rTMS over the left and right inferior frontal gyri led to an increased speed of cognitive processing in PD patients (Srovnalova et al., 2011).

In summary, these findings suggest that cognitive functioning plays an important role in how motor learning occurs in PD. More research is needed to define which deficits are exactly playing a role and how this can be addressed and incorporated in learning protocols with and without supplementary non-invasive brain stimulation.

4 Relearning of writing skills in Parkinson's disease

Micrographia is a frequent and debilitating motor problem in PD which can only be partially restored with dopaminergic medication. Although writing can be considered a visually controlled motor task, it is also well-learned and highly automatically performed and therefore a hallmark motor deficit of PD (Wagle Shukla et al., 2012). The relearning of writing skills as a complementary therapy is thus necessary for many PD patients.

Similar to gait, recent studies also showed positive effects of cueing on handwriting. A more focused literature review resulted in five studies addressing writing practice with and without cues. **Table 1** summarizes these studies and shows that a limited number of patients were included. All studies involved case series designs in which practice was conducted in one session only, comparing PD patients with healthy controls. Already in 1997, Oliveira et al. (1997) investigated the effects of visual (a dot to indicate writing size) and verbal (“big”) cues on handwriting in PD and found that PD patients are capable of writing with a more normal amplitude when given these cues in one practice session. These improvements were maintained when patients were tested again on the free-writing task, which was performed on blank paper without cues, shortly after the cued conditions. More recently, a pilot study by Bryant et al. (2010) showed that the use of both parallel lines and grid lines improved letter size of PD patients compared to free writing. The sequence of practicing with parallel or grid lines was randomized. Participants started with the control free writing condition, followed by practice of one test condition (parallel or grid lines) 5 times. This was followed by 1 minute of rest and the free writing condition. After 5 minutes of rest, the same sequence was repeated with the other test condition (parallel or grid lines). Nieuwboer et al. (2009) tested a writing related task. In this test patients with and without Freezing Of Gait (FOG) were instructed to perform alternating upper limb movements in a rhythmical fashion at small and large amplitudes, both with and without parallel lines indicating the size of the amplitude. Results

showed that visual cueing not only influenced the movement amplitude, but also decreased the number of upper limb freezing episodes. As previously mentioned, Ringenbach et al. (2011) showed that the use of auditory and verbal cues resulted in a lower coefficient of variance of cycle time and lowered the variability of amplitude and relative phase in PD patients during a drawing task. In a study by Swinnen et al. (2000) it was shown that PD patients benefitted from practice to improve their movement speed and consistency of the spatial trajectories in a triangle tracing task.

These results suggest that providing PD patients with an indication of the desired writing amplitude encourages them to achieve and maintain this amplitude. However, these improvements are only at the performance level. To date no studies have been conducted assessing the effects of long and intensive periods of relatively permanent motor learning, using retention and/or transfer tests.

In addition, visual feedback was shown to be an important factor that can influence upper limb motor learning (Swinnen et al., 2000; Verschueren et al., 1997). Therefore we also reviewed existing studies on the effect of visual feedback and consequently distorting visual feedback on handwriting of PD patients to check feedback dependency and consolidation of learning. Careful screening resulted in five studies (**Table 2**). When distortion occurred in both the horizontal en vertical display, PD patients were able to compensate their writing, however, to a lesser extent than controls (Fucetola & Smith, 1997). In a later study by Teulings et al. (2002) PD patients were compared to young and elderly controls in an adaptation task. Participants performed cursive loops, either at real size or vertically distorted (70% or 140%). Young controls gradually enlarged the loop size in the 70% distortion condition and reduced loop size in the 140% distortion condition. PD patients, however, amplified the effect of the distortion instead of correcting it. Elderly controls showed results in between those of the young control group and the PD group. On the other hand, Contreras-

Vidal et al. (2002) showed that PD patients are capable of visuo-motor adaptation. The conflicting outcomes may be explained by the fact that participants were able to see their own hand movements in the study of Teulings et al. (2002). The results of Contreras-Vidal et al. (2002) are in line with a recent study using an adaptation task in PD (Leow et al., 2012). In this study, participants moved a cursor from a start circle to a target circle on a digitizing tablet. This movement was first practiced with veridical visual feedback of the movement trajectory. Once practice criteria were met, the actual adaptation experiment began in which visual feedback was distorted. Similar to the writing experiments, initial adaptation occurred to the same extent in PD as in control subjects. However, PD patients showed less retention of previous learning, across successive adaptation blocks both within the same test session and between test sessions separated by 24h. This ‘retention of adaptation’ has been explained in the context of reinforcement learning: an adapted movement is reinforced by its association with previous successful outcomes (Huang et al., 2011). The previously described problems with reinforcement learning in PD could thus explain the deficiently retained adaptation in PD. The study of Leow et al. (2012) did not show an absolute deficit in reinforcement learning in PD patients. This suggests that continued repetition by PD patients could be associated with the outcome of success in the long run.

On balance, evidence regarding motor learning of writing skills is limited. The studies described here were pre-post studies and did not include a control intervention. Furthermore, it needs to be investigated whether the use of cues and feedback only improves immediate writing performance or also the consolidation of the learning process. Therefore, long-term training studies are needed, incorporating both long-term retention and transfer tests, to investigate whether relearning of writing skills can be an effective and lasting therapeutic supplement to improve handwriting of PD patients.

5 Conclusion

Review of the motor learning literature suggests that there is potential for motor refinement in PD, when taking a number of limitations inherent to the disease into account. By combining dopaminergic medication with an intensive training program and providing patients with an optimal frequency of feedback to learn to identify an external sensory cue as the causal factor of successful behavior, a pre-existing motor skill may be relearned. The cue can guide the patients' movements, thereby providing a substantial advantage, because reliance on movements that have to be initiated by internally-generated signals (known to be deficient in PD) is circumvented.

Linking the use of external cues to an outcome of success such as being able to maintain writing size, could thus potentially improve micrographia in PD. To the best of our knowledge, no long-term writing training studies have been performed, thereby testing carry-over to uncued performance. To limit cue-dependency in PD, it needs to be investigated whether it is best to randomize the presence or absence of cues in the training phase or whether it is preferred to incorporate a gradual reduction of cued learning to uncued learning (similar to fading augmented feedback schedules). Furthermore, long-term training studies are necessary to investigate whether the use of cues, augmented feedback and non-invasive neurostimulation techniques improve immediate task performance or can truly induce long-term effects that are at the heart of learning and neuroplasticity.

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Figure Captions

Figure 1

Figure 1: Example of the handwriting of a PD patient and healthy control

(A) Writing example of a 54 year old male with idiopathic Parkinson's disease, Hoehn & Yahr stage III. Writing was performed while on dopaminergic medication and with deep-brain stimulator on.

(B) Writing example of a 52 year old healthy female.

Tables

Table 1: Writing studies with cues in PD

Reference	Groups	Task paradigm	Cue type	Practice	Results PD patients
Oliveira et al. (1997)	11 PD (H&Y II-IV) 14 CTRL	Writing 3 lines of the cursive letter 'l' in each condition	No (blank page) Visual (dots) Verbal ("big")	Each condition was performed twice	Increased amplitude, maintained in the 2 nd No-cue condition
Swinnen et al. (2000)	13 PD (H&Y I-IV) 13 CTRL	Bimanual triangle tracing with and without vision	Auditory (metronome)	2 days, with vision	Improved movement speed and consistency of spatial trajectories due to practice No effect of cue
Nieuwboer et al. (2009)	10 PD (FOG) 10 PD (non-FOG) 5 CTRL	Bimanual, anti-phase line drawing (OFF medication)	Visual (parallel lines indicating the size of the amplitude)	Several practice trials with and without visual target	Cueing diminished amplitude variability, mainly in the PD group
Bryant et al. (2010)	11 PD	Write 3 words on blank page pre and post intervention	Visual (parallel lines and grid lines)	Practice with 2 types of cues	Increased letter size after practice with cues
Ringenbach et al. (2011)	15 PD 15 elderly CTRL 15 young CTRL	Unimanual & bimanual line drawing	Verbal ("up", "down") Auditory (high & low tone) Visual (target line) No-cue was not tested	Practice before experiment started	Lower variability of amplitude & relative phase with auditory & verbal cues, compared to visual cues
Abbreviations: PD: Parkinson's disease; CTRL: control; H&Y: Hoehn & Yahr; FOG: freezing of gait					

Table 2: Feedback-dependency and the effect of practice on writing-related tasks in PD

Reference	Groups	Task paradigm	Feedback	Practice	Results in PD patients
Fucetola & Smith (1997)	20 PD (H&Y I-III) 20 CTRL	Letter strokes	Real size Reduced by 50% Enlarged by 100%	3 practice trials at real size	Reduced FB: increase in stroke sizes, but smaller than CTRL Enlarged FB: decrease in stroke sizes, but larger than CTRL Improvements with practice, similar to CTRL
Teulings et al. (2002)	11 PD (H&Y I-III) 16 elderly CTRL 10 young CTRL	Cursive loops at 0.5 & 2cm Hand not visible	Real size Reduced to 70% Enlarged to 140%	1 practice trial at real size with guidelines	Reduced FB: decrease in stroke size Enlarged FB: increase in stroke size Patients lack trial by trial adaptation
Contreras-Vidal et al. (2002)	5 PD (H&Y I-III) 4 elderly CTRL 4 young CTRL	Cursive loops at 0.5 & 2cm Hand visible	Real size Reduced to 70% Enlarged to 140%	1 practice trial at real size with guidelines	Reduced FB: increase in stroke sizes Enlarged FB: decrease in stroke sizes Trial by trial adaptation, similar to CTRL
Leow et al. (2012) a	8 PD 8 CTRL	Move a cursor from start to target circle Hand not visible All tests on the same day	Real size 30° counterclockwise rotation	30 practice trials at real size	Initial adaptation similar to CTRL Larger directional error after de-adaptation
Leow et al. (2012) b	8 PD 8 CTRL	Move a cursor from start to target circle Hand not visible Tests separated by 24h	Real size 30° counterclockwise rotation	30 practice trials at real size	Similar adaptation to CTRL on day 1 Smaller directional error at day 2 for CTRL, not for PD
Abbreviations: PD: Parkinson's disease; CTRL: control; H&Y: Hoehn & Yahr; FB: feedback					