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TMS enhances retention of a motor skill in Parkinson's Disease

Clara Moisello¹, Daniella Blanco¹, Cecilia Fontanesi¹, Jing Lin¹, Milton Biagioni², Pawan Kumar², Mirosław Brys², Andrea Loggini³, Lucio Marinelli³, Giovanni Abbruzzese³, Angelo Quartarone^{1,2,4}, Giulio Tononi⁵, Alessandro Di Rocco², and Maria Felice Ghilardi^{1,2}

¹Dept. of Physiology, Pharmacology & Neuroscience, CUNY Medical School, New York, NY, USA, 10031

²Dept. of Neurology, Movement Disorders Center, NYU-Langone School of Medicine, New York, NY, 10016

³Department of Neurosciences, Ophthalmology and Genetics, University of Genova, Italy, 16132

⁴Dept. of Neurosciences, Psychiatry and Anaesthesiological Sciences, University of Messina, Messina, Italy, 98125

⁵Dept. of Psychiatry, University of Madison, WI, 53719

Abstract

Background—In Parkinson's disease (PD), skill retention is poor, even when acquisition rate is generally preserved. Recent work in normal subjects suggests that 5 Hz-repetitive transcranial magnetic stimulation (5Hz-rTMS) may induce phenomena of long-term potentiation at the cortical level.

Objective/Hypothesis—We thus verified whether, in PD, 5Hz-rTMS enhances retention of a visuo-motor skill that involves the activity of the right posterior parietal cortex.

Methods—A group of patients with PD was tested in two two-day sessions, separated by one week (treatment and placebo sessions). The first day of each session, they learned to adapt their movements to a step-wise 60° visual rotation. Immediately after the task, either real 5Hz-rTMS (treatment) or sham (placebo) stimulation was applied over the right posterior parietal cortex (P6). Retention of this motor skill was tested the following day.

Results—In patients with PD, adaptation achieved at the end of training was comparable in the treatment and placebo sessions and was similar to that of a group of age-matched controls. However, retention indices tested on the following day were significantly lower in the placebo compared to the treatment session in which retention indices were restored to the level of the

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Corresponding author: M. Felice Ghilardi, Dept. of Physiology, Pharmacology & Neuroscience, CUNY Medical School, 138th street & Convent Avenue, New York, NY, 10031, USA, Tel: +1 212 650 5814, Fax: +1 212 650 7726, lice.mg79@gmail.com.

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controls. Importantly, reaction and movement time as well as other kinematic measures were the same in the treatment and placebo sessions.

Conclusion—These results suggest that rTMS applied after the acquisition of a motor skill over specific areas involved in this process might enhance skill retention in PD.

Keywords

motor skills; adaptation; motor learning; consolidation

Introduction

Although acquisition of new motor skills is generally preserved in Parkinson's Disease (PD), short- and long-term skill retention is impaired in both drug-naïve and pharmacologically treated patients. This conclusion is based on the results of earlier studies from ours and other groups using an implicit learning task in which subjects adapted their movements to rotated visual displays [1,2,3,4]. Adaptation in this task requires the formation of new visuo-motor relationships and, thus, the creation of new memories or 'internal models' [5]. In this thoroughly characterized task [6,7,8,9], learning is evident as a constant decrease of directional error that occurs without subjects' awareness; retention is sleep-dependent and is reflected in after-effects, a trace of the achieved adaptation, and in faster rate of re-adaptation at successive exposures. Importantly, learning depends on the activity of right posterior parietal areas as demonstrated by imaging and electrophysiological studies [6,10,11,12]. Indeed, this area, which is involved in the integration of proprioceptive, visual and vestibular inputs, plays an important role in forming and maintaining new internal models used for movement planning. In particular, the binding of multisensory information as well as the development of memories or models such as those required for moving under new visuo-motor coordinates is reflected by activity changes occurring over this area [12,13,14,15]. Importantly, the degree of skill retention highly correlates with the magnitude of EEG changes during learning over the right posterior parietal area, as well as with the occurrence of slow wave activity in subsequent sleep over that same spot [10].

Adaptation to a 30° rotation occurs similarly in patients with PD and age-matched controls: at the end of training, adaptation levels are similar in both groups [1,2,3]. However, re-adaptation, tested either immediately after training or one-two days later, is faster than in the first exposure only in normal controls [1,2,3]. A possible explanation is that formation of internal models and their retention is hampered in PD because of impaired induction of long-term potentiation (LTP)-related phenomena [3]. In fact, many studies in PD have now demonstrated deficits of LTP-like phenomena in the primary motor cortex [16,17,18,19,20]. A way to enhance LTP-like phenomena in vivo is the use of 5 Hz-repetitive transcranial magnetic stimulation (5Hz-rTMS): in normal subjects, 5Hz-rTMS increases the amplitude of muscle and cortical responses and produces local increases of slow wave activity in subsequent sleep [21,22,23,24]. More direct evidence of LTP induction comes from our animal study showing that 5Hz-rTMS increases expression of brain-derived neurotrophic factor, tyrosine-receptor-kinase-B and N-methyl-D-aspartate receptor that induce dendritic translation [25]. It is then plausible that, if LTP is impaired in PD, 5Hz-rTMS applied to an area involved in learning might enhance memory formation and retention in these patients.

Therefore, in this study, a group of patients with PD adapted to one of two rotation types in two separate sessions. After training, 5Hz-rTMS or sham-rTMS was applied to the right posterior parietal area. While adaptation at the end of training was comparable in the two sessions, retention on the following day was abnormal after sham-TMS but not after 5Hz-rTMS.

Methods

Subjects

We tested 19 patients with PD (14 men, age: 60.9 ± 5.4 yrs) and 19 age-matched (10 men, age 58.9 ± 8.7 yrs) controls. As shown in Table 1, all patients had mild to moderate PD and were treated with dopaminergic drugs. None of the patients and controls had severe medical illness or had recently received chronic treatment for sleep complaints. During all the experiments, all the patients were in ON state, in their regular medication schedule. All subjects were right-handed and were naïve to the motor task. The experiments were conducted with the approval of the participant institutes' IRBs. Written informed consent was obtained from all participants.

Experimental design

All patients with PD completed a real rTMS and a sham session, or Treatment and Placebo session, respectively. Each session encompassed two consecutive mornings. The two sessions were performed at least one week apart, in a counterbalanced order. During this period, the medication dosage and schedule were always the same. On day 1 of each session (i.e., training, see also Supplemental Material and Figure), patients adapted to a total of 60° rotation, either counterclockwise (CCW) or clockwise (CW). Importantly, CW and CCW rotations activate the same brain pattern; the rate of adaptation is the same in both; there is no transfer of learning from one to another and there is no interference on retention, if CCW and CW rotations are learned at least 24 hours apart [6, 7, 9]. At the end of day-1 training, patients underwent either a sham (in the placebo session) or a real 5Hz-rTMS (treatment session). On day 2 of each session (i.e., testing), patients repeated the same tasks with the same rotation as in day 1. The order of cursor rotation (CW or CCW) and sessions (treatment or placebo) was counterbalanced.

Control subjects completed only a two-day session: on day 1, they adapted to a 60° rotation (either CCW or CW); on day 2, they were tested with the same protocol.

All subjects were asked to keep a diary about sleep duration for the night between the two testing days of each session.

TMS

With a MAGSTIM Rapid Stimulator (Magstim, Whitland, Dyfed, UK) connected to a figure-of-eight shaped coil, we first identified the Left first dorsal interosseus (FDI) muscle representation on M1 using single-pulse TMS applied to the Right hemisphere as the position in which TMS elicited highest motor-evoked potentials (MEPs). Resting motor threshold (RMT) was measured at the relaxed left FDI, as the lowest intensity capable of

evoking 5 of 10 MEPs with amplitude of at least 50 μ V. RMT (mean $\pm$ SD) was similar in the treatment (55.5 ± 10.7) and placebo sessions (55.5 ± 10.7 ; $p=0.23$). The TMS output intensity was then adjusted to 90% of the RMT. For both the treatment and placebo sessions (see experimental design), the coil was positioned over the right posterior parietal cortex, corresponding to P6 in the 10–20 EEG system. In the treatment session, a total of 25 trains of pulses were applied through the tangentially oriented coil positioned over P6 area with the grip pointing backwards. Each train consisted of 50 single pulses of 5 Hz lasting for 10 s, with an inter-train interval of 2 s. The 25 trains were grouped into 5 blocks of 5 trains each, for a total of 1250 TMS pulses. Any two consecutive blocks were separated by a stimulus-free interval of 1 min. These stimulation parameters were chosen because they induce local signs of LTP-like plasticity in terms of increase of both motor response amplitude and local slow wave activity in subsequent sleep [21,22,23]. In the placebo session, the coil was placed at the same location as for the real rTMS in the treatment session but was rotated 90° about the axis of the handle and separated from the head by a 2 cm plastic spacer.

Tasks

All subjects performed two motor tasks, RAN and ROT [10, 12]. In both tasks, one of eight radially-arrayed targets (distance from center: 4 cm) displayed on a screen as circles (1 cm radius), flashed for 400 ms at a fixed 1.5 s interval (Figure 1A). The order of targets appearance was random and unpredictable. Subjects were asked to reach the target from the central starting point by moving a cursor on a digitizing tablet (sampling rate 200 Hz) with their right dominant hand. Instructions were to make movements as fast and as possible, without corrections. An opaque shield at shoulder level prevented subjects from seeing their limb. Cursor and target positions were visible on the screen at all times. In ROT, unbeknownst to subjects, the screen cursor was rotated either CW or CCW relative to the hand position by a total of 60° in six incremental steps of 10° each (Figure 1C). Subjects were never informed about the cursor rotation. In RAN, there was no discrepancy between the direction of the screen cursor and that of the moving hand. As detailed above and illustrated in Supplemental Material and Figure, each session encompassed two consecutive mornings. On Day 1, subjects were exposed for the first time to a 60° step-wise rotation adaptation (training): in the order, subjects performed three RAN blocks of 56 movements each, followed by twelve ROT blocks in six incremental steps of 10° (two blocks per step, equal to 112 movements, per step) separated by 1–2 minute rest. On day 2, they perform three RAN blocks followed by a complete 60° step-wise ROT, exactly as in day 1 (testing) and we measured the after-effects and gain in re-adaptation (see below and Supplemental Material and Figure).

When questioned at the end of the two sessions, none of the subjects reported awareness of the rotation. Moreover, inspection of the data, and in particular of reaction time values, revealed that none of the subjects implemented cognitive strategies, thus suggesting that adaptation to the rotated display was entirely implicit. Also, the majority of patients did not report any difference in the stimulation intensity of the two sessions, three of them guessed correctly and two guessed wrongly. Separate analyses of the data of the three patients that guessed correctly did not show any significant difference compared to the other data set.

Analysis

As in previous studies [2, 3, 8, 12, 26], for each movement, we measured: reaction time (Figure 1A); movement time (Figure 1A); directional error at the peak velocity, which represents a directional planning error (Figure 1B); temporal symmetry index of the velocity profile, i.e. the ratio between the time at peak velocity and total duration of the movement. The ideal bell-shaped velocity profile from a ballistic movement without correction has a symmetry index equal to 50% (Figure 1A).

We then computed one measure of adaptation achieved on day-1 training and two indices of retention on day 2 (after-effects and gains in re-adaptation), all derived from directional error. The details of these measures and their application to a set of data are reported in Supplemental Material and Figure.

As illustrated in Supplemental Figure part C., the adaptation reached by the end of training on day 1 was measured based on the average directional error of the last eight movements ($DirErr_1$) of the last 60° ROT block and expressed in percentage, as:

$$\%Adaptation = [1 - (DirErr_1 / 60)] * 100.$$

After-effects (Supplemental Figure part C.) were measured based on $\%Adaptation$ and the mean directional error of the first eight movements of the first RAN block at the beginning of day 2 testing ($DirErr_2$), as:

$$\%After-effects = [DirErr_2 / (60 - DirErr_1)] * 100.$$

Finally, we measured gains in re-adaptation based on the average of the adaptation curves of day 1 and 2 as detailed in Supplemental Material and Figure part B. Since they were normalized by the levels of day 1 adaptation, both after effects and re-adaptation were independent of the level of adaptation reached on day 1 and could be thus compared across sessions and patients.

ANOVAs were performed on all measures. Post-hoc tests (with Bonferroni correction for multiple comparisons when appropriate) were used to verify the effects of treatment in the PD group and the differences between controls and PD. In particular, to compare day 1-adaptation in the six steps of rotation in the treatment and placebo conditions (two conditions), we used a mixed model ANOVA (two conditions, six steps). We did not find any difference between the two conditions. Therefore, we compared day 1 adaptation of the averaged treatment and placebo sessions in PD to the session of the control group (mixed-model ANOVA with two groups, six steps). For $\%Adaptation$, $\%After-effects$ and re-adaptation gains as well as for kinematic variables on day 1 and their percentage changes on day 2, we compared the data of treatment, placebo and controls with one-way ANOVA. Pearson coefficients were used to explore significant correlations between performance and clinical measures in PD as well as between after-effects and re-adaptation gains.

Results

No subject experienced adverse effects of the rTMS procedure. Importantly, the amount of sleep was the same across groups and sessions: in the night before re-adaptation, patients slept an average of 6.25 ± 1.5 hours in the placebo session and 6.30 ± 1.2 hours in the treatment session (paired-t test $p=0.88$), not differently from controls (6.66 ± 1.0 hours, unpaired t-test: $p=0.4$).

In all the experimental sessions, movements were essentially straight with a bell shaped velocity profile in both patients with PD and in controls, as suggested by inspection of the mean values of the symmetry index, a measure of temporal shape of the velocity profile (Table 2).

On day 1, all subjects adapted to the step-wise rotation by decreasing the directional error. Example from a single subject is illustrated in the Supplemental Material. As shown in Figure 2, the average adaptation varied between steps (range from 70 to 80%) with constantly lower values in the 10° step (ANOVA: step: $F(5, 54)=12.3$; $p<0.0001$). Importantly, in PD patients, the course of adaptation was basically overlapping in the treatment and placebo sessions (session: $F(1, 36)=0.02$, $p=0.88$) with a similar effect of rotation steps (step: $F(5, 36)=6.6$; $p<0.0001$; session X step: $F(1, 5)=1.44$, $p=0.22$). Therefore, the data of day 1 from the patients' treatment and placebo sessions were averaged to compare day 1 adaptation of PD and control groups. We found no statistical differences between groups (group: $F(1, 36)=2.3$, $p=0.14$; step: $F(5, 36)=11.9$; $p<0.0001$; group X step: $F(1, 5)=0.89$, $p=0.49$). Adaptation in the last step was greater in controls (about 4% corresponding to 2° ; post-hoc $p=0.03$). This slight difference was reflected in the final adaptation achieved (i.e., the directional error of the last eight movements, Supplemental Figure C). As illustrated in figure 3A, this index was slightly greater in the controls compared to patients in both treatment and placebo sessions ($F(2, 56)=3.2$, $p=0.04$), although post hoc comparisons did not reveal significant differences between PD and controls (treatment vs. controls, $p=0.09$; placebo vs. controls: $p=0.07$). Again, there were no differences between treatment and placebo sessions in PD ($p=0.90$). Altogether, these results show that the time course and the level of adaptation reached at the end of day 1 were very similar in the two groups. Most importantly, they suggest that day-1 adaptation was virtually overlapping in the two patient sessions.

The focus of this paper is skill retention and its modulation by rTMS. We thus analyzed the magnitude of %After-effects on day 2, representing a memory trace carried over from the first exposure to rotation on day 1. %After-effects in the placebo session were significantly lower compared to the control group (ANOVA: $F(2, 56)=31.9$; $p<0.0001$; post-hoc: $p<0.00001$, Figure 3B). After rTMS, they significantly increased compared to the placebo (post-hoc: $p=0.00003$), reaching the range of the controls ($p=0.61$, Figure 3B). Single-subject analysis revealed that the increase in the treatment session was present in all but one patient (Figure 3D). Similar results were seen for gains in re-adaptation (ANOVA: $F(2, 56)=13.3$; $p<0.0001$): in the treatment session, they were significantly higher than in the placebo ($p=0.00006$), reaching the range of controls ($p=0.83$, Figure 2C). The two retention indices, i.e., %after-effects and gains in re-adaptation, were not significantly correlated

($r < 0.2$) suggesting that they reflect different processes. In fact, as discussed in the following paragraphs, the former likely represents short-term memory formation and the latter the prompt retrieval of the appropriate internal model.

Finally, we ascertained whether rTMS had an effect also on kinematic indices. The results are reported in Table 2. Briefly, we found that reaction and movement times in PD were higher than in controls but without differences between placebo and treatment sessions. Importantly, the changes between day 1 and 2 of reaction and movement times as well as of symmetry indices were similar in all the groups (p always > 0.5) suggesting that there were no rTMS-induced changes on the kinematic variables. Thus, altogether these results suggest that rTMS on the right posterior parietal area induced selective effects on directional error-based indices of retention.

Adaptation, after-effects and re-adaptation indices did not correlate with clinical scores, disease duration, amount of levodopa equivalents or other PD characteristics (absolute r values always < 0.1 $p > 0.2$). This is in agreement with previous reports showing that adaptation and retention of a rotation task was not influenced by disease status or medication [2, 3]. Finally, there was no effect of session order (treatment or placebo) or type of rotation (CCW or CW) for any of the adaptation, retention and kinematic measures (p always > 0.3).

Discussion

The main result of this study is that application of 5 Hz-rTMS to the right posterior parietal area after adaptation to a visuo-motor rotation enhances indices of skill retention in patients with PD. Importantly, this effect was confined to the retention of new visuo-motor coordinates without affecting the kinematic characteristics.

Twenty-four hours after the initial training, skill retention measured with both after-effects and re-adaptation gains were lower in patients during the placebo session compared to controls, confirming that motor skill retention is impaired in PD [1,2,3]. As in previous works with 30° rotation [3], impaired retention was independent of disease duration, UPDRS scores, and medications. Importantly, the two retention indices, %after-effects and re-adaptation, were independent from the level of adaptation during training (see methods), thus allowing for comparison between groups and sessions. After-effects represent a memory trace of the newly formed internal models and the level of achieved adaptation, which normally decays with time [27]. During initial training, movement planning becomes more accurate and directional errors smaller as, with learning, new internal models are formed or modified. A fast decay and thus, the decay of the memory of the “rotated state”, produces a fast return towards the default “un-rotated” state and suggests an impairment of short-term memory formation. But there is another aspect that influences retention, that is, the capacity of retrieving promptly the appropriate internal model. In fact, during subsequent exposures to the same rotation, the previously acquired internal models need to be retrieved efficiently for faster re-adaptation, accurate movement planning and low directional errors. The other index of retention we used, i.e., the difference between adaptation and re-adaptation, is a composite measure that captures, at least in part, the successful retrieval of stored memories or internal models. The fact that both retention indices were lower in PD

after sham rTMS confirms previous results with 30° rotation showing decrements of both after-effects and adaptation gains, immediately after training as well as 24 and 48 hours later [1,2,3]. They further suggest that one of the main reasons of decreased retention in PD is a disruption of the processes leading to the formation of new internal models immediately after training. This disruption might be linked to impairment of cortical potentiation present in this disease [16,17,18,19,20].

The most important new finding is that, although adaptation at the end of training was the same in both sessions, retention in PD reached normal values only following rTMS. The basic mechanism underlying these results might be that 5Hz-rTMS enhances LTP-like phenomena. Indeed, when applied over the motor cortex, 5Hz-TMS produces long-lasting increases of TMS-evoked responses from the muscle [23] and the motor cortex [21], local increases of regional cerebral blood flow and glucose [28, 29] and local increase of slow wave activity in subsequent sleep over the motor cortex [22]. Therefore, it is plausible that 5Hz-rTMS induces local facilitatory effects that are expression of enhanced plasticity and LTP-related changes. This is also supported by direct evidence from animal studies [25]. Those animal studies demonstrated that 5Hz-rTMS induces plastic changes promoted by the basic mechanisms underlying synaptogenesis and activity-dependent forms of synaptic plasticity [25], which are cellular counterparts of memory formation [30]. The present study in PD, a disease with reduced cortical plasticity [16,17,18,19,20], demonstrates that 5Hz-rTMS specifically increases skill retention, behavioral manifestation of enhanced LTP-like phenomena, without affecting reaction and movement time. This focal effect is likely due to the choice of the target, the right posterior parietal area, and the time of intervention. The choice of this spot was based on previous high-density EEG studies with this task that showed activity relevant to visuo-motor adaptation and retention processes around electrode P6 [10,11,12,31]. The stimulation spot was defined with the 10–20 EEG system. Indeed, target localization on the bases of individual MRI would have been more accurate and might have led to greater improvements. Nevertheless, despite this limitation, we found significant improvement of retention in PD with rather uniform results. That the right posterior parietal cortex is involved in the learning of new visuo-motor mapping during rotation adaptation has been amply shown by imaging, EEG and sleep studies [6, 10,11,12, 31]. Indeed, activity of this region is required for many spatial tasks such as the present one and is crucial for spatial, attentional and multisensory integration processes needed for motor planning and visuo-motor adaptation [12,13,14,15]. Moreover, in normal subjects, this area plays an important role in the formation of internal models during successful rotation adaptation [12]. The present results further support the notion that first, this area is specifically involved the formation of visuo-motor memory but not in the change of kinematic characteristics and second, that impaired retention in PD could be due to deficient LTP-like phenomena in this area. Future studies should determine whether rTMS treatment also induced activation of regions that are functionally connected with the right parietal cortex and whether such activation played a role in increasing skill retention.

It is important to remark that our patients underwent both session in ON state on their regular medication schedule that was kept constant throughout the experiment. The decreased retention in the placebo session confirms previous findings that dopaminergic therapy per se is not enough to reach the retention levels of controls [3]. However, as

suggested by the results of studies in PD with similar rTMS procedures [32], it is possible that rTMS treatment without dopaminergic therapy would not be as effective in promoting skill retention. If dopaminergic treatment is a requirement for improving retention, its most likely site of action might be in regions other than the posterior parietal cortex. These regions might include the basal ganglia, as our previous finding in drug-naïve patients show that dopamine-transporter binding of the right caudate and putamen is highly correlated with short-term retention of rotation adaptation [2].

The choice of applying 5Hz-rTMS after training was driven by the following speculation. We reasoned that in PD, the neural activity resulting from the performance during training might not be enough to reach the threshold to start efficient LTP cascade signaling. Nevertheless, even in PD, training might induce a weak neural activity that might be enough to function as a tag or priming effect. The addition of 5Hz-TMS pulses might boost this weak training-induced signal in this specific area so that the threshold for the LTP cascade can be reached within the tagged area. The results of this study indicate that this is indeed a possible scenario. Irrespectively of the time of the intervention, based upon these results, we further speculate that the close temporal proximity of TMS with a behavioral task activating the neural pathways in a “naturalistic” way might represent a powerful approach to enhance plasticity in PD and in other neurological and psychiatric conditions. Indeed, further studies are needed to prove this point and to verify whether a different temporal application of rTMS to the right parietal and other areas in the fronto-parietal network involved in this type of learning produce similar effects.

In summary, this study establishes an association between impairment in skill retention, disruption of LTP-like phenomena and cortical plasticity in PD. By showing that local rTMS following specific training does indeed enhance memory consolidation, this study provides the bases for targeting specific symptoms or dysfunction with interventions aimed to enhance, in a circumscribed area, LTP-like phenomena and cortical plasticity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PD	Parkinson's disease
5Hz-rTMS	5 Hz-repetitive transcranial magnetic stimulation

References

1. Bedard P, Sanes JN. Basal ganglia-dependent processes in recalling learned visual-motor adaptations. *Exp Brain Res*. 2011; 209:385–93. [PubMed: 21311878]

2. Isaias IU, Moisello C, Marotta G, Schiavella M, Canesi M, Perfetti B, et al. Dopaminergic striatal innervation predicts interlimb transfer of a visuomotor skill. *J Neurosci.* 2011; 31:14458–62. [PubMed: 21994362]
3. Marinelli L, Crupi D, Di Rocco A, Bove M, Eidelberg D, Abbruzzese G, et al. Learning and consolidation of visuo-motor adaptation in Parkinson's disease. *Parkinsonism Relat Disord.* 2009; 15:6–11. [PubMed: 18424221]
4. Venkatakrishnan A, Banquet JP, Burnod Y, Contreras-vidal JL. Parkinson's disease differentially affects adaptation to gradual as compared to sudden visuomotor distortions. *Hum Mov Sci.* 2011; 30:760–9. [PubMed: 21414678]
5. Kawato M. Internal models for motor control and trajectory planning. *Curr Opin Neurobiol.* 1999; 9:718–27. [PubMed: 10607637]
6. Ghilardi M, Ghez C, Dhawan V, Moeller J, Mentis M, Nakamura T, et al. Patterns of regional brain activation associated with different forms of motor learning. *Brain Res.* 2000; 871:127–45. [PubMed: 10882792]
7. Krakauer JW, Ghez C, Ghilardi MF. Adaptation to visuomotor transformations: consolidation, interference, and forgetting. *J Neurosci.* 2005; 25:473–78. [PubMed: 15647491]
8. Krakauer JW, Ghilardi MF, Ghez C. Independent learning of internal models for kinematic and dynamic control of reaching. *Nat Neurosci.* 1999; 2:1026–31. [PubMed: 10526344]
9. Krakauer JW, Pine ZM, Ghilardi MF, Ghez C. Learning of visuomotor transformations for vectorial planning of reaching trajectories. *J Neurosci.* 2000; 20:8916–24. [PubMed: 11102502]
10. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. *Nature.* 2004; 430:78–81. [PubMed: 15184907]
11. Landsness EC, Ferrarelli F, Sarasso S, Goldstein MR, Riedner BA, Cirelli C, et al. Electrophysiological traces of visuomotor learning and their renormalization after sleep. *Clin Neurophysiol.* 2011; 122:2418–25. [PubMed: 21652261]
12. Perfetti B, Moisello C, Landsness EC, Kvint S, Lanzafame S, Onofri M, et al. Modulation of gamma and theta spectral amplitude and phase synchronization is associated with the development of visuo-motor learning. *J Neurosci.* 2011; 31:14810–19. [PubMed: 21994398]
13. Batista AP, Buneo CA, Snyder LH, Andersen RA. Reach plans in eye-centered coordinates. *Science.* 1999; 285:257–60. [PubMed: 10398603]
14. Sabes PN. The planning and control of reaching movements. *Curr Opin Neurobiol.* 2000; 10:740–6. [PubMed: 11240283]
15. Van Der Werf J, Jensen O, Fries P, Medendorp WP. Neuronal synchronization in human posterior parietal cortex during reach planning. *J Neurosci.* 2010; 30:1402–12. [PubMed: 20107066]
16. Kishore A, Joseph T, Velayudhan B, Popa T, Meunier S. Early, severe and bilateral loss of LTP and LTD-like plasticity in motor cortex (M1) in de novo Parkinson's disease. *Clin Neurophysiol.* 2012; 123:822–8. [PubMed: 21945457]
17. Kojovic M, Bologna M, Kassavetis P, Murase N, Palomar FJ, Berardelli A, et al. Functional reorganization of sensorimotor cortex in early Parkinson disease. *Neurology.* 2012; 78:1441–8. [PubMed: 22517098]
18. Morgante F, Espay AJ, Gunraj C, Lang AE, Chen R. Motor cortex plasticity in Parkinson's disease and levodopa-induced dyskinesias. *Brain.* 2006; 129:1059–69. [PubMed: 16476674]
19. Suppa A, Marsili L, Belvisi D, Conte A, Iezzi E, Modugno N, et al. Lack of LTP-like plasticity in primary motor cortex in Parkinson's disease. *Exp Neurol.* 2011; 227:296–301. [PubMed: 21145888]
20. Ueki Y, Mima T, Kotb MA, Sawada H, Saiki H, Ikeda A, et al. Altered plasticity of the human motor cortex in Parkinson's disease. *Ann Neurol.* 2006; 59:60–71. [PubMed: 16240372]
21. Esser SK, Huber R, Massimini M, Peterson MJ, Ferrarelli F, Tononi G. A direct demonstration of cortical LTP in humans: a combined TMS/EEG study. *Brain Res Bull.* 2006; 69:86–94. [PubMed: 16464689]
22. Huber R, Esser SK, Ferrarelli F, Massimini M, Peterson MJ, Tononi G. TMS-induced cortical potentiation during wakefulness locally increases slow wave activity during sleep. *PLoS One.* 2007; 2:e276. [PubMed: 17342210]

23. Quartarone A, Bagnato S, Rizzo V, Morgante F, Sant'angelo A, Battaglia F, et al. Distinct changes in cortical and spinal excitability following high-frequency repetitive TMS to the human motor cortex. *Exp Brain Res*. 2005; 161:114–24. [PubMed: 15578171]
24. Quartarone A, Rizzo V, Bagnato S, Morgante F, Sant'Angelo A, Girlanda P, et al. Rapid-rate paired associative stimulation of the median nerve and motor cortex can produce long-lasting changes in motor cortical excitability in humans. *J Physiol*. 2006; 575:657–70. [PubMed: 16825301]
25. Wang HY, Crupi D, Liu J, Stucky A, Cruciata G, Di Rocco A, et al. Repetitive transcranial magnetic stimulation enhances BDNF-TrkB signaling in both brain and lymphocyte. *J Neurosci*. 2011; 31:11044–54. [PubMed: 21795553]
26. Ghilardi MF, Alberoni M, Rossi M, Franceschi M, Mariani C, Fazio F. Visual feedback has differential effects on reaching movements in Parkinson's and Alzheimer's disease. *Brain Res*. 2000; 876:112–23. [PubMed: 10973599]
27. Kitago T, Ryan SL, Mazzoni P, Krakauer JW, Haith AM. Unlearning versus savings in visuomotor adaptation: comparing effects of washout, passage of time, and removal of errors on motor memory. *Front Hum Neurosci*. 2013; 7:307. [PubMed: 23874277]
28. Siebner HR, Peller M, Willoch F, Minoshima S, Boecker H, Auer C, et al. Lasting cortical activation after repetitive TMS of the motor cortex: a glucose metabolic study. *Neurology*. 2000; 54:956–63. [PubMed: 10690992]
29. Siebner HR, Takano B, Peinemann A, Schwaiger M, Conrad B, Drzezga A. Continuous transcranial magnetic stimulation during positron emission tomography: a suitable tool for imaging regional excitability of the human cortex. *Neuroimage*. 2001; 14:883–90. [PubMed: 11554807]
30. Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, Pattwell SS, et al. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. *Science*. 2010; 327:863–6. [PubMed: 20075215]
31. Landsness EC, Crupi D, Hulse BK, Peterson MJ, Huber R, Ansari H, et al. Sleep-dependent improvement in visuomotor learning: a causal role for slow waves. *Sleep*. 2009; 32:1273–84. [PubMed: 19848357]
32. Suppa A, Iezzi E, Conte A, Belvisi D, Marsili L, Modugno N, et al. Dopamine influences primary motor cortex plasticity and dorsal premotor-to-motor connectivity in Parkinson's disease. *Cereb Cortex*. 2010; 20:2224–33. [PubMed: 20051362]

Highlights

- Retention of a visuomotor skill is impaired in PD
- Retention in PD improves after rTMS to the right parietal cortex
- rTMS to the right posterior parietal cortex does not affect kinematics

Figure 1.

A. The bottom part represents the screen display with the 8-target array during target appearance (first square) and at the end of the out-going movement (in gray) to the presented target. The asterisk on the hand path represents the point of peak velocity. The top part illustrates the temporal profile of velocity (asterisk on the peak) with the time of movement onset (empty circle) and end (gray-filled circle). Reaction time (difference between target appearance and movement onset) and movement time (difference between movement onset and end) are depicted together with the time to peak velocity (time to PV). The symmetry index is the ratio between the time to PV and the total duration of the movement expressed in percentage. The ideal bell-shaped velocity profile from a ballistic movement without correction has a symmetry index equal to 50%. B. The directional error at the peak velocity of a hand path is computed as the difference between the direction of the vector from the start point to the target and the direction of the vector from the start to the peak velocity point (marked by an asterisk). C. Illustration of the progressive reduction of the directional error during rotation adaptation (from 1. to 3.).

Figure 2.

Average of the course of adaptation to a 60° step-wise rotation during day 1. On the y-axis we report the mean $\pm$ S.D. of adaptation (expressed as the percentage of the imposed rotation) for each of the 10° rotation steps for the PD patients in the placebo (empty circles) and treatment (filled circles) sessions and for the normal controls (filled diamonds). The dotted line indicates the average of the placebo and treatment sessions. In the 60° step, controls showed slightly but greater adaptation than patients (post hoc for controls versus averaged values of placebo and treatment sessions in PD: $p=0.03$).

Figure 3.

A. B. C. Mean $\pm$ S.D. of A. % Adaptation, B. % After-Effects, C. % Re-Adaptation Gains for the PD patients in the placebo (empty circles) and treatment (filled circles) sessions and for the normal controls (filled diamonds). The dotted lines indicate significance with $p < 0.05$ with Bonferroni correction. D. % After-Effects are shown for each patient with PD in the placebo and treatment session with a symbol linked by a line. Notice that values in the treatment session are always greater than in the placebo with the exception of one patient. The % After-Effects of each control is indicated with a filled diamond.

Table 1

Patients' characteristics

Patients	Age	PD Duration (yrs)	Hoehn & Yahr Stage	Levodopa Equivalents (mg)
1	67	14	2.5	990
2	58	11	2	875
3	63	17	2.5	750
4	68	4	2	595
5	64	4	2	650
6	56	3	2	400
7	61	5	2	550
8	62	6	2	475
9	59	11	3	1125
10	68	8	3	300
11	61	8	2	920
12	63	10	2	260
13	63	2	2	223
14	61	9	2.5	860
15	66	18	2	100
16	49	4	2	750
17	51	6	2	685
18	54	4	2	300
19	64	6	2	600

Table 2

Kinematic variables.

A. Day 1: Mean±SD (ms)		Placebo	Treatment	Controls	ANOVA	
					F(2,56)	p
Reaction Time (ms)		282.8±41.2	281.4±42.1	247.7±30.9 *	5.09	0.0100
Movement Time (ms)		481.9±154.6	470.4±147.4	311.2±83.8 *	9.85	0.0002
Symmetry Index (%)		45.7±6.6	46.7±5.2	47.6±3.7	0.60	0.5502

B. Day 2: Mean±SD (% difference Day2-Day1)		Placebo	Treatment	Controls	ANOVA	
					F(2,56)	p
Reaction Time		-2.06±4.70	-0.73±5.96	0.90±4.84	1.55	0.22
Movement Time		-6.52±14.8	-4.98±22.20	-7.08±13.11	0.08	0.93
Symmetry Index		0.50±1.78	0.06±1.79	0.49±2.32	0.30	0.75

* post-hoc test corrected for multiple comparisons: controls versus PD; p<0.03