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The rationale for motor learning in Parkinson's disease

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Parkinson's disease (PD) is a chronic progressive disorder mainly affecting the motor system. PD is only partially controlled by symptomatic dopaminergic treatment. Therefore, motor rehabilitation can be used in PD to reduce complications and to train patients in the use of compensatory movement strategies. Rehabilitative practice is largely dependent on the efficiency of motor learning, i.e. the acquisition of new abilities or the adaptation of pre-existing ones. Although patients with PD are able to improve their motor performance through practice, the amount and persistence of clinical benefit are uncertain. Both "implicit" (procedural) and "explicit" (declarative) features of motor learning have been extensively investigated in patients with PD using neuropsychological testing, serial reaction time paradigms, and analysis of reaching movements. Evidence from these studies suggests an early impairment of "explicit" learning in PD, while "implicit" learning is relatively preserved. The consolidation of learned motor tasks is defective in PD and the mechanisms of motor learning seem to be independent from dopamine-replacement therapy. The knowledge of motor learning in PD is critical in designing more effective rehabilitative protocols.

KEY WORDS: Parkinson disease - Rehabilitation - Exercise therapy - Memory.

Idiopathic Parkinson's disease (PD) is defined pathologically by the loss of dopaminergic neurons in the pars compacta of the *substantia nigra* (with the presence of neuronal inclusions, the Lewy bodies) and clinically by some combination of motor (rest tremor, rigidity, bradykinesia) as well as non-motor symptoms.[1] PD is a common neurodegenerative disorder affecting more than 250 patients per 100 000 [2] and can be considered as one of the major reasons of neurological disability, causing a significant economic burden. PD has a chronic progressive course**,** mainly affecting the motor system**,** and is responsible for a severe motor impairment. The cause of the disease is still unknown so that no "cure" or neuroprotective treatment is so far available. On the other hand, the symptomatic dopaminergic treatment is very effective in the early phases, but progressively loses its efficacy. In addition, there are symptoms (such as postural instability with falls, gait disturbances and freezing, and cognitive impairment) that are not responsive to dopaminergic stimulation; it has been demonstrated that the most disabling long-term problems of PD are related to the occurrence of symptoms that are not improved by levodopa.[3] Eventually, in spite of optimal medical/surgical management, patients' autonomy in daily living activities is severely reduced in the late phases and there is no rescue treatment for mobility and postural problems.

Therefore, there is a solid rationale for motor rehabilitation in PD which is aimed at improving quality of life. Recent evidence-based reviews [4, 5] demonstrated that multidisciplinary rehabilitation in PD can

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be effectively used to prevent or cut down secondary complications due to reduced mobility, but also to teach and train patients with PD in the use of compensatory movement strategies in order to optimize the residual functional capacities and compensate for their defective abilities.

Motor rehabilitation may be regarded as a process of relearning how to move in order to satisfy personal needs and it is based on the assumption that practice or training leads to improvement of skills.[6] Therefore, motor learning includes the acquisition of new "abilities" (movement programming and execution) as well as the adaptation of pre-existing and acquired "abilities".[7] The knowledge of the efficiency of motor learning in patients with PD is a critical issue in planning effective rehabilitation protocols.

Motor learning

Motor learning is the process of improving the motor skill through a relatively permanent change in behaviour that occurs as a result of experience and practice. Motor learning is essential for effortless execution of complex sequential movements (speaking, walking, typing, playing instruments) that constitute a critical part of everyday life activities, but it is also important for calibrating smoothness and accuracy of simple movements.

Different modalities of learning have been identified. "Implicit" or "procedural" learning has been characterized as a non-declarative process, where people are exposed to information, and acquire knowledge of that information simply through exposure. The acquisition of such motor skills can be documented by increased accuracy or speed of performance. On the other hand, "explicit" learning is characterized as an active process where people seek out the structure of any information that is presented to them. This declarative or explicit memory implies the conscious awareness of the learned information.

The two learning modalities can be selectively impaired in different populations and are likely to depend on distinct neural circuits.[8] Explicit memory has been associated with the functional activity of medial temporal lobes and of the diencephalic structures, while the anatomical and physiological substrates of implicit memory are more uncertain. However, imaging studies in normal subjects have shown the activation of striatum, premotor, and supplementary motor area during implicit learning tasks.[9] In particular, network analysis of the PET data [10] revealed distinct brain activation patterns associated with acquisition of performance (left dorsolateral prefrontal cortex, DLPFC; rostral supplementary motor area, SMA; anterior cingulate cortex; left caudate and putamen) and with retrieval of performance (bilateral premotor cortex; right precuneus and posterior parietal cortex).

In addition, an impairment of procedural motor learning has been consistently reported in patients with various movement disorders (Huntington's disease, Parkinson's disease, and dystonia) [11] suggesting that basal ganglia might be specifically involved in the neural circuits underlying implicit learning.

Motor learning in Parkinson's disease

Using an accurate neuropsychological testing, it is possible to demonstrate subtle signs of cognitive impairment even in the earliest stages of the disease.[12-15] Cognitive changes regard multiple domains, including particularly "frontal" executive functions: working memory, attentional set-shifting, temporal sequencing, and visuomotor processing.[16, 17] The mechanisms underlying these deficits are not fully understood and the relationship between cognitive signs and antiparkinsonian treatment is uncertain.[18] Nevertheless, the occurrence of cognitive deficits may worsen motor dysfunction of PD. In addition, they may affect the ability to learn and retain motor tasks raising the issue whether patients with PD are capable of and may benefit from motor learning.

Early studies provided inconsistent data about the possible impairment of motor learning in PD. Parkinsonian patients appeared able to improve their performance with practice, thus partially compensating bradykinesia and defective force production. However, they showed difficulties in the acquisition of new motor "set" [19] and the ability to use advance information ("pre-programming") required more practice than control subjects to achieve comparable levels of performance.[20, 21] Other studies suggested that patients with PD did not differ from normal subjects in the processes of motor adaptation and motor skill learning.[22, 23] In summary, Parkinson patients do benefit from practice but

the amount of benefit is generally lower than in normal control subjects.[24]

Several questions, however, remained unresolved. In particular, it was uncertain whether sequence learning was already affected in early PD, since defective learning was apparently correlated with the severity of motor signs (bradykinesia).[25] Finally, it was not clear whether PD was associated with an impairment of explicit sequence learning, where (at variance with implicit learning) working memory and attention play a major role.

Implicit memory in PD

Indeed, most of studies investigated motor learning capabilities by serial reaction time (SRT) paradigms.[26] In such paradigms, subjects are required to respond as quickly as possible to the presentation of visual stimuli in different spatial positions. Subjects are unaware that spatial localization of visual stimuli follows a repeated sequence. SRT induces mainly a sequence-specific learning, with minimal demands on working memory and is not associated with DLPFC activation.[27] The discrepancies between results of SRT studies (from normal to severely impaired learning) [28, 29] have been interpreted taking into account differences in patient's sampling (disease severity, therapeutic regimen), methodology, and possible frontal executive impairment.[30] A recent study [31] (using SRT methodology and neuropsychological testing of declarative memory, executive and visuospatial functions) showed small differences in sequence learning between patients and controls. However, patients with more advanced clinical symptoms tended to show worse performance, suggesting that "implicit" procedural learning impairment is not an early feature of PD, but emerges with progression of the disease (independently of cognitive dysfunction or dopaminergic medication).

Explicit memory in PD

Studies of motor learning with SRT paradigms cannot completely discriminate between "explicit" and "implicit" learning.[32] Revisiting the SRT task, Moisello *et al.*[33] clarified that both explicit (reaction or onset time) and implicit (movement time) components characterize this approach. This conclusion is supported by the results of imaging studies.[34]

However, motor learning can be investigated also by methodologies other than SRT. One possible approach is the analysis of "reaching" movements, where subjects have to move a cursor on a digitizing tablet with their dominant hand, performing out and back movements from a central starting point to one of eight targets (circles) displayed on a computer screen (Figure 1). Subjects are instructed to make movements without corrections and reversing sharply inside each target circle; they receive a feedback of successful hits (greying of the target). A computer samples hand positions, elaborating movement trajectory and displaying it on the screen in front of the subjects (Figure 1). Different protocols can be designed (timed-response task, reaction time task, pseudorandom sequences). Early detection and anticipation of targets have a prominent explicit component with working memory engagement and activation of the DLPFC.[35]

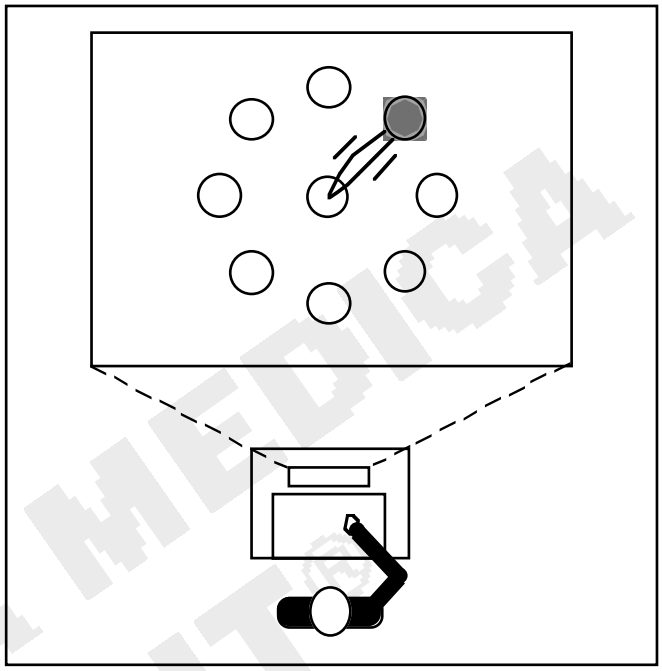

Figure 1.—Schematic representation of the experimental apparatus used to evaluate arm reaching movements. The lower part of the figure shows the patient sitting with the right arm on a digitizing tablet and moving a cursor (represented on the screen in front of him). The upper part of the figure represents the computer screen showing the eight targets. Solid lines show the hand trajectory of out and back movements (arrows indicate the movement direction) from the central starting point to the target (which turned grey).

Using such experimental protocol (appearance of targets within a repeated sequence and verbal reports

about the sequence order) it has been shown that shown that explicit sequence learning is impaired in early PD.[35] Patients showed a learning deficit both when targets reaching or sequence recognition were required. Such impairment is independent from slowness in motor execution (bradykinesia) and possibly reflects early deficits in attention and working memory resources. Indeed, network analysis [10] showed topographical abnormalities of brain activation during motor sequence learning in early stage PD patients: bilateralization of brain activation and additional cortical activation suggested compensatory mechanisms for abnormalities in basal ganglia function. It should be noticed that PD patients with amnestic mild cognitive impairment show a bilateral posterior cortical dysfunction.[36]

Memory consolidation in PD

Memory consolidation refers to processes of brain plasticity by which experiences result in enduring long-term changes in neural representations.[11]

In a recent study [37] we analyzed motor memory consolidation in a group of patients with PD. In the protocol, subjects were unaware that the display of the movement trajectory on the screen was rotated by 30°. Subjects can unconsciously compensate the fictive directional error by rotating movement trajectory in the opposite direction (training). PD patients and controls were able to adapt to rotation in the same way. However, when tested after 1-2 days, the directional error was greater in patients than in controls, documenting a deficit in the consolidation of implicit memory related to visuo-motor transformation (Figure 2). Such lack of consolidation was present in the early stages of the disease and independently from treatment.

Impaired consolidation of learning a non-motor procedural task was already documented by a long term study in patients with PD.[38] The mechanisms underlying the lack of memory consolidation in PD are not fully clarified. However, it should be noticed that increasing evidence suggests a critical role of sleep in the consolidation of memory traces for newly learned sequences of movements.[10] Indeed, patients with PD are characterized by frequent sleep abnormalities and homeostatic processes are altered during sleep.[39]

In any case, the defective consolidation of motor memories in PD is relevant for planning of rehabilitation programs in these patients. It has been shown

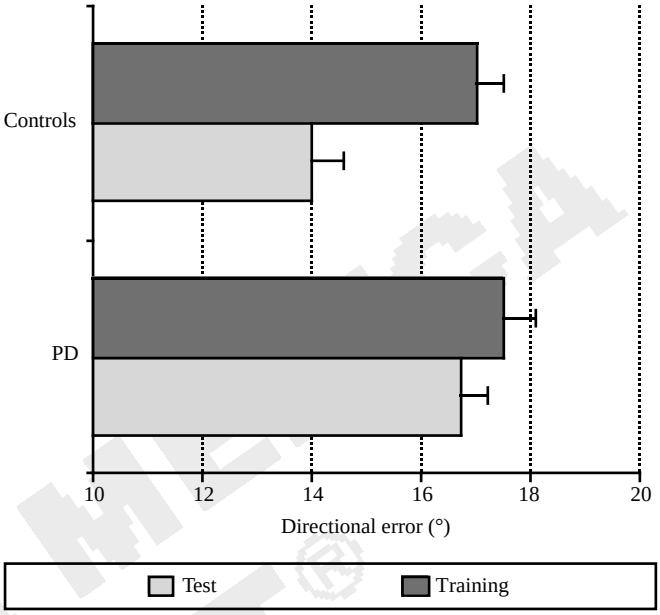

Figure 2. Effect of overnight consolidation on "implicit" learning in patients with Parkinson's disease (PD). The ability to compensate the directional error to 30° rotation was analysed. During the training session (black bars) the directional error reduction was similar between patients with PD and normal age-matched controls. One day after, during the test session (white bars), the improvement of directional error was significantly lower in patients with PD than in controls.

that PD patients do benefit from short-term practice similarly to normal controls, while prolonged practice is of scarce benefit in improving motor performance.[40]

Effect of antiparkinsonian treatment on motor learning

PET imaging has demonstrated that the release of endogenous dopamine is increased in the posterior putamen and in the anterior caudate of healthy volunteers during implicit or explicit task learning.[41] However, levodopa does not improve explicit sequence learning of parkinsonian patients, in spite of a significant benefit on motor scores and movement speed [42] and may even exert a detrimental effect on cognitive function through impairment in the activation of occipital association cortex.[43] Such observations are in keeping with functional imaging studies: while levodopa increased motor-related activation, an activation decrease was seen during the working mem-

ory task.[44] This might suggests that the mesocortical degeneration may not be predominantly involved in cognitive deficits of PD or differences in dopamine metabolism. On the other hand, deep brain stimulation of the internal pallidum is able to improve sequence learning performance and, at variance with levodopa, to increase DLPFC activation.[45-47]

Conclusions

Motor learning is a fundamental step in the rehabilitation process of patients with PD. Common experience suggests that Parkinsonian patients are able to improve their motor performance through practice although both amount and persistence of clinical benefit are variable and lower than in healthy subjects. Behavioural and imaging studies documented that plastic mechanisms within the corticostriatal system are defective in PD. In particular, explicit learning is impaired (early and independently of bradykinesia), while implicit learning is relatively preserved in the initial stages of the disease. In addition, the consolidation of motor memories looks defective in PD. Finally, the role of dopamine and of dopamine-replacement therapy in motor learning is still uncertain.

The knowledge of mechanisms underlying motor learning in PD is critical in designing more effective rehabilitative protocols and in choosing the optimal strategy to improve motor skills of Parkinsonian patients.

References

1. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79:368-76.
2. Morgante L, Rocca WA, Di Rosa AE, De Domenico P, Grigoletto F, Meneghini F *et al*. Prevalence of Parkinson's disease and other types of parkinsonism: a door-to-door survey in three Sicilian municipalities. The Sicilian Neuro-Epidemiologic Study (SNES) Group. Neurology 1992;42:1901-7.
3. Hely MA, Morris JGL, Reid WGJ, Trafficante R. Sydney Multicenter Study of Parkinson's Disease: non-L-Dopa–responsive problems dominate at 15 years. Mov Disord 2004;20:190-9.
4. Keus SH, Bloem BR, Hendriks EJ, Bredero-Cohen AB, Munneke M. Evidence-based analysis of physical therapy in Parklinson's disease with recommendations for practice and research. Mov Disord 2007;22:451-60
5. Suchowersky O, Gronseth G, Perlmutter J, Reich S, Zesiewicz T, Weiner WJ. Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006;66:976-82.
6. Krakauer JW. Motor learning: its relevance to stroke recovery and neurorehabilitation. Curr Opin Neurol 2006;19:84-90.
7. Shadmehr R, Wise SP. The computational neurobiology of reaching and pointing: a foundation for motor learning. Cambridge: MIT Press; 2005.
8. Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 1992;99:195-231.
9. Doyon J, Owen AM, Petrides, Sziklas V, Evans AC. Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. Eur J Neurosci 1996;8:637-48.
10. Nakamura T, Ghilardi MF, Mentis M, Dhawan V, Fukuda M, Hacking A *et al*. Functional networks in motor sequence learning: anbnormal topographies in Parkinson's disease. Hum Brain Mapp 2001;12:42-60.
11. Doyon J. Motor sequence learning and movement disorders. Curr Opin Neurol 2008;21:478-83.
12. Owen AM, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, *et al*. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain 1992;115:1727-51.
13. Owen AM, Beksinska M, James M, Leigh PN, Summers BA, Marsden CD *et al*. Visuospatial memory deficits at different stages of Parkinson's disease. Neuropsychologia 1993;31:627-44.
14. Owen AM, Iddon JL, Hodges JR, Summers BA, Robbins TW. Spatial and non-spatial working memory at different stages of Parkinson's disease. Neuropsychologia 1997;35:519-32.
15. Brown RG, Marsden CD. Neuropsychology and cognitive function in Parkinson's disease: an overview. In: Marsden CD, Fahn S, editors. Movement disorders 2. London: Butterworths; 1987. p. 99-123.
16. Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease. The cortical focus of neostriatal outflow. Brain 1986;109:845-83.
17. Taylor AE, Saint-Cyr JA, Lang AE. Memory and learning in early Parkinson's disease: evidence for a "frontal lobe syndrome". Brain Cogn 1990;13:211-32.
18. Carbon M, Marié RM. Functional imaging of cognition in Parkinson's disease. Curr Opin Neurol 2003;16:475-80.
19. Frith CD, Bloxham CA, Carpenter KN. Impairments in the learning and performance of a new manual skill in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1986;49:661-8.
20. Worringham CJ, Stelmach GE. Practice effects on the preprogramming of discrete movements in Parkinson's disease. J Neurol Neurosurg Psychiatry 1990;53:702-4.
21. Soliveri P, Brown RG, Jahanshahi M, Marsden CD. Effect of practice on performance of a skilled motor task in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1992;55:454-60.
22. Agostino R, Sanes JN, Hallet M. Motor skill learning in Parkinson's disease. J Neurol Sci 1996;139:218-26.
23. Behrman AL, Cauraugh JH, Light KE. Practice as an intervention to improve speeded motor performance and motor learning in Parkinson's disease. J Neurol Sci 2000;174:127-36.
24. Swinnen SP, Steyvers M, Van Den Bergh L, Stelmach E. Motor learning and Parkinson's disease: refinement of within-limb and between-limb coordination as a result of practice. Behav Brain Res 2000;111:45-9.
25. Smith JG,. McDowall J. The implicit sequence learning deficit in patients with Parkinson's disease: a matter of impaired sequence integration? Neuropsychologia 2006;44:275-88.
26. Nissen MJ, Bullemer P. Attentional requirements of learning: evidence from performance measures. Cogn Psychol 1987;19:1-32.
27. Grafton S, Hazeltine E, Ivry R. Functional mapping of sequence learning in normal humans. J Cogn Neurosci 1995;7:497-510.
28. Jackson GM, Jackson SR, Harrison J, Henderson L, Kennard C. Serial reaction time learning and parkinson's disease: evidence for a procedural learning deficit. Neuropsychologia 1995;33:577-93.
29. Smith J, Siegert RJ, McDowall J, Abernethy D. Preserved implicit learning on both the serial reaction time task and artificial grammar in patients with Parkinson's disease. Brain Cogn 2001;45:378-91.

30. Siegert RJ, Taylor KD, Weatherall M, Abernethy DA. Is implicit sequence learning impaired in parkinson's disease? a meta-analysis. Neuropsychology 2006;20:490-5.
31. Muslimovic D, Post B, Speelman JD, Schmand B. Motor procedural learning in Parkinson's disease. Brain 2007;130:2887-97.
32. Seidler RD, Tuite P, Ashe J. Selective impairments in implicit learning in Parkinson's disease. Brain Res 2007;1137:104-10.
33. Moisello C, Crupi D, Tunik E, Quartarone A, Bove M, Tononi G *et al*. The serial reaction time task revisited: a study of motor sequenze learning with an arm-reaching task. Ecp Brain Res 2009 [In press].
34. Schendan HE, Searl MM, Melrose RJ, Stern CE. An fMRI study of the role of the medial temporal lobe in implicit and explicit sequence learning. Neuron 2003;37:1013-25.
35. Ghilardi M, Eidelberg D, Silvestri G, Ghez C. The differential effect of PD and normal aging on early explicit sequence learning. Neurology 2003;60:1313-9.
36. Nobili F, Abbruzzese G, Morbelli S, Marchese R, Girtler N, Dessi B *et al*. Amnestic mild cognitive impairment in Parkinson's disease: a brain perfusion SPECT study. Mov Disord 2009;24:414-21.
37. 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;2009;15:6-11.
38. Cohen H, Pourcher E. Intact encoding, impaired consolidation in procedural learning in Parkinson's disease. Exp Brain Res 2007;179:703-8.
39. Arnulf I, Leu S, Oudiette D. Abnormal sleep and sleepiness in Parkinson's disease. Curr Opin Neurol 2008;21:472-7.
40. Agostino R, Curra` A, Soldati G, Dinapoli L, Chiacchieri L, Modugno N *et al*. Prolonged practice is of scarce benefit in improving motor performance in Parkinson's Disease. Mov Disord 2004;19:285-93.
41. Badgayian RD, Fischman AJ, Alpert NM. Explicit motor memory activates the striatal dopamine system. Neuroreport 2008;19:409-12.
42. Ghilardi MF, Feigin AS, Battaglia F, Silvestri G, Mattis P, Eidelberg D *et al*. L-Dopa infusion does not improve explicit sequence learning in Parkinson's disease. Parkinsonism Relat Disord 2007;13:146-51.
43. Feigin A, Ghilardi MF, Carbon M, Edwards C, Fukuda M, Dhawan V *et al*. Effects of levodopa on motor sequence learning in Parkinson's disease. Neurology 2003;60:1744-9.
44. Mattay VS, Tessitore A, Callicott JH, Bertolino A, Goldberg TE, Chase TN *et al*. Dopaminergic modulation of cortical function in patients with Parkinson's disease. Ann Neurol 2002;51:156-64.
45. Fukuda M, Ghilardi MF, Carbon M, Carbon M, Dhawan V, Ma Y, Feigin A *et al*. Pallidal stimulation for parkinsonism: improved brain activation during sequence learning. Ann Neurol 2002;52:144-52.
46. Carbon M, Ghilardi MF, Feigin A, Fukuda M, Silvestri G, Mentis MJ *et al*. Therapeutic modulation of motor sequence learning networks with GPi DBS. Hum Brain Mapp 2003;19:197-211.
47. Carbon M, Eidelberg D. Functional imaging of sequence learning in Parkinson's disease. J Neurol Sci 2006;248:72-7.