Increased reaction time predicts visual learning deficits in Parkinson's disease

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Abstract

To determine whether the process involved in movement preparation of patients in the early stages of Parkinson's disease (PD) shares attentional resources with visual learning, we tested 23 patients with PD and 13 normal controls with two different tasks. The first was a motor task where subjects were required to move as soon as possible to randomly presented targets by minimizing reaction time. The second was a visual learning task where targets were presented in a preset order and subjects were asked to learn the sequence order by attending to the display without moving. PD patients showed higher reaction and movement times, while visual learning was reduced compared to controls. For PD patients, reaction times, but not movement times, displayed an inverse significant correlation with the scores of visual learning. We conclude that visual declarative learning and movement preparation might share similar attentional and working memory resources.

Keywords:
Parkinson's Disease, executive function, attention, motor control

Introduction

Motor slowness in Parkinson's disease (PD) is a general term that encompasses: akinesia, a poverty of movement production and delay in movement initiation; bradykinesia, a reduction in movement speed; and hypokinesia, a reduction in movement size[1]. In experimental motor tasks, akinesia is reflected by increased reaction times, a finding often reported in patients with PD[1].

During the few hundred milliseconds between stimulus presentation and movement onset, many processes take place, including attentional and stimulus processing, decision making and movement programming. Some of these processes and resources are also engaged during visuospatial learning that occurs without movement[2]. In fact, activation of fronto-parietal areas, the likely neural substrate of these processes, occurs during many tasks, independently of the modality and of the learning load[3,4].

It is now well known that PD impairs not only motor functions but also attentional and learning processes[5]. However, the connection between the two deficits has not been explored. Here we hypothesize that if movement preparation shares neural resources with visual spatial learning, in PD patients abnormalities in reaction time and impairment of sequence learning that requires no movement should be correlated.

Methods

Twenty-three patients with idiopathic PD (17 men and 6 women, mean age±S.E.: 60.0±6.8 years) in early stages of the disease (Hoehn & Yahr stage I-II) and thirteen age-matched normal controls (6 men, 7 women, 56.5±2.7 years) participated in the study. All subjects were right-handed, underwent a clinical interview to determine that he or she did not meet the DSM-III-R criteria for depression or dementia, scored more than 27 at Mini-Mental State Examination and had a normal brain MRI.

Mean UPDRS score (part 3) of PD patients was 8.8 (1.8, S.E.). The most involved side was the right in ten patients; the left in the remaining thirteen.

At the time of testing all patients were in stable conditions. Thirteen patients were drug-naive; four had been treated with deprenyl alone, four with levodopa/carbidopa, and two with a combination of dopamine agonists and levodopa/carbidopa. However, all patients were drug-free for at least 12 hours before testing. Written informed consent was obtained from all participants under a protocol approved by the institutional review board of the participating institutions.

Detailed features of the tasks have been previously reported[6,7]. Briefly, in both tasks, one of eight targets appeared on a screen with a common starting point, in synchrony with a tone at 1-second intervals. Each trial block lasted for 90 seconds.

The two tasks, which were presented in a randomized order, were:

1) Motor task: targets were presented in a pseudorandom and unpredictable order. Movements were performed on a digitizing tablet with the right dominant hand. Instructions were to reach each target as soon as possible, minimizing reaction time but avoiding target anticipation. Target distance was 1.8 cm.

2) Visual learning task: subjects were instructed to learn the order of a repeating sequence of eight targets that was presented in the 90-second block. At the end of the block, verbal reports about the sequence order were collected[6,7].

For each movement we computed: reaction time; movement duration; peak velocity; hand-path length; spatial error[6,7].

At the end of the visual block, declarative scored were computed from 0 (unawareness of a sequence) to 8 (complete correct sequence)[6,7].

Factorial analysis of variance (ANOVA) was performed to compare PD patients and normal controls' values. Linear regression analyses were also performed to determine correlations between kinematic and other variables. Level of significance was $p<0.05$.

Results

There was no difference between the performance indices of treated and drug-naïve patients and between right and left hemiparkinsonian patients. Therefore, patients' data were combined and compared to those of controls.

Data are summarized in figure 1. On average, reaction times were prolonged in PD patients compared to controls ($F(1,34)=5.6$; $p=0.02$). Similarly, in PD patients movement durations were significantly longer ($F(1,34)=8.0$, $p=0.008$) and peak of velocity reduced ($F(1,34)=6.9$, $p=0.01$). Spatial accuracy, expressed by spatial error, was similar in the two groups ($F(1,34)=1.9$, $p=0.2$); however, hand-path lengths were reduced in PD patients compared to controls ($F(1,34)=9.0$, $p=0.005$).

The declarative scores reflecting visual learning were significantly lower in patients compared to controls ($F(1,34)=13.2$, $p=0.0009$), indicating impairment in visuo-spatial learning.

We then ascertained whether declarative scores in the visual task were associated to kinematic measurements. In PD patients, declarative scores were negatively correlated with reaction times: the higher the reaction time, the lower the declarative score ($r=-0.66$, $p=0.0006$). No significant correlations were found between declarative scores versus movement times ($r=-0.23$, $p=0.3$), peak velocity ($r=0.05$, $p=0.8$) or hand-path length ($r=-0.20$, $p=0.4$). In addition, there were no correlations between UPDRS (part 3) scores and either reaction times ($r=0.06$, $p=0.8$), movement times ($r=0.12$, $p=0.7$), hand-path length ($r=0.21$, $p=0.5$) or declarative scores ($r=-0.13$, $p=0.7$). In PD patients there was no significant correlation between reaction times and movement duration or peak velocity ($r=0.29$, $p=0.2$). As expected, movement time and peak velocity values were instead highly correlated ($r=-0.87$. $p<0.0001$).

Finally, in normal controls we did not find any correlation between learning scores with either reaction time ($r=0.39$, $p=0.2$) or movement time ($r=0.004$, $p=1.0$).

Discussion

This study shows that, in agreement with previous work, in patients with early stage PD increased reaction times and impaired visual sequence learning are significantly correlated: patients with higher reaction times are also more impaired in sequence learning, suggesting that movement preparation shares resources with learning of visuo-spatial sequences.
Increased reaction time in PD patients is considered the experimental hallmark of akinesia[1]. Our motor task also captured other characteristic features of PD: hypokinesia,with reduced hand-path length, and bradikinesia[1], with significant increases in movement time and reductions of peak velocity. Interestingly, the clinical motor UPDRS scores did not correlated with any of the kinematic measures. This lack of correspondence is likely due to the fact that motor UPDRS scores reflect global motor impairment, as this scale embraces multiple motor aspects. Interestingly, in our PD population, reaction and movement time did not correlate, adding evidence that their respective neural mechanisms may not overlap.
As previously shown[5,6], our PD patients display abnormal visual sequence learning, a learning that is declarative and explicit in nature, requires no motor involvement but loads working memory and attention buffers, possibly like movement preparation. PD patients also show alteration in visuo-spatial and central executive abilities[8]. It has been suggested that all these deficits stem from malfunction of the frontoparietal network[9]. In fact, this network is engaged in many and various facets of cognitive control, as it might be responsible for the active representation of attended and goal-relevant stimuli, and thus for promoting adequate domain-dependent information processing[2]. In fact, even the simple shift between attended stimuli leads to an update of this network[10].
The exclusive correlation of declarative scores with reaction times, but not with other kinematic parameters, suggests that, first, the neural resources for movement preparation and those for visuo-spatial learning partly overlap and, second, PD significantly hampers such resources. Moreover, these data suggest that motor and cognitive functions are not completely independent processes but share similar resources, implying that some motor and non-motor parkinsonian signs might have common neural bases. Such results are important in designing novel rehabilitative approaches to improve specific aspects of motor performance and the quality of life of patients.

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Author roles

L Marinelli: research project organization and execution, writing the first draft of the manuscript.

B Perfetti: statistical analysis design and execution, manuscript critique.

C Moisello: statistical analysis design and execution, manuscript critique.

A Di Rocco: statistical analysis review and critique, manuscript review and critique.

D Eidelberg: research project conception, statistical analysis review and critique, manuscript review and critique.

G Abbruzzese: statistical analysis review and critique, manuscript review and critique.

MF Ghilardi: research project conception, statistical analysis review and critique, manuscript review and critique.

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References

1. Berardelli A, Rothwell JC, Thompson PD, Hallett M. Pathophysiology of bradykinesia in Parkinson's disease. Brain 2001;124:2131-2146.
2. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001;24:167-202.
3. Funahashi S. Prefrontal cortex and working memory processes. Neuroscience 2006;139:251-261.
4. Rounis E, Stephan KE, Lee L, et al. Acute changes in frontoparietal activity after repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex in a cued reaction time task. J Neurosci 2006;26:9629-9638.
5. Doyon J. Motor sequence learning and movement disorders. Curr Opin Neurol 2008;21:478-483.
6. Ghilardi M, Eidelberg D, Silvestri G, Ghez C. The differential effect of PD and normal aging on early explicit sequence learning. Neurology 2003;60:1313-1319.
7. Ghilardi MF, Silvestri G, Feigin A, et al. Implicit and explicit aspects of sequence learning in pre-symptomatic Huntington's disease. Parkinsonism Relat Disord 2008;14:457-464.
8. Kemps E, Szmalec A, Vandierendonck A, Crevits L. Visuo-spatial processing in Parkinson's disease: evidence for diminished visuo-spatial sketch pad and central executive resources. Parkinsonism Relat Disord 2005;11:181-186.
9. Nakamura T, Ghilardi MF, Mentis M, et al. Functional networks in motor sequence learning: abnormal topographies in Parkinson's disease. Hum Brain Mapp 2001;12:42-60.
10. Hon N, Epstein RA, Owen AM, Duncan J. Frontoparietal activity with minimal decision and control. J Neurosci 2006;26:9805-9809.

Figure legends

Figure 1

Title: Kinematic and learning indices

Mean ± SE of kinematic and learning indices (* see text for statistics).