L-Dopa infusion does not improve explicit sequence learning in Parkinson’s disease

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Abstract

We have recently introduced a set of sequence learning tasks that emphasize explicit learning and target anticipation and involve the activation of frontal lobes. This type of learning is impaired even in the early stages of Parkinson’s disease (PD). Studies on the effects of L-Dopa on cognitive symptoms of PD have yielded controversial results. To verify whether L-Dopa acutely improves explicit sequence learning, we tested six normal subjects and seven PD patients both off-drug and during L-Dopa infusion with two tasks: SEQ, a motor task with multiple demands, where a sequence had to be learned while reaching for a target; VSEQ, a visual task where a sequence had to be learned by attending to a visual display without moving. Motor performance was assessed with simple motor tasks. L-Dopa improved motor scores and movement speed, but had no beneficial effect on either type of sequence learning.

Keywords: Attention; Learning; Cognition; L-Dopa infusion; Parkinson’s disease

1. Introduction

Cognitive changes, usually related to executive functions, working memory, attention, and visuomotor processing, are common even in early stages of Parkinson’s disease (PD) and in non-demented PD patients \cite{1,2}. Cognitive deficits affect the ability to learn and retain motor tasks and may worsen the motor dysfunction of PD. Although the underlying pathophysiology remains unclear, the results of various studies attribute cognitive decline in PD to frontal lobe dysfunction \cite{1–8}. Animal and human studies have demonstrated that blocking dopaminergic receptors in the frontal lobe induces alterations in attentional resources allocation, working memory and elaboration of internal strategies, similarly to what is seen in PD \cite{9–13}.

The effects of antiparkinsonian therapies on cognitive dysfunction have been controversial. L-Dopa is a highly effective treatment for the motor deficits of PD. However, dopaminergic agents have been reported to produce contrasting effects on cognitive and related functions in both animal and patients’ studies. In fact, acute or chronic dopaminergic treatment may worsen frontal lobe function (for a review see: \cite{14}).

We have recently used sequence-learning tasks in which instructions emphasized explicit learning, target anticipation and involve the activation of frontal lobes \cite{15,16}. With these tasks, normal subjects typically learn simple repeating sequences in 90 s or less, both when the sequence order is learned visually, without moving, and when learning occurs while reaching for targets. In patients with PD, sequence learning is generally slower for both tasks \cite{15}.

In this study, we evaluated the effects of constant infusion of L-Dopa on the learning of motor and visual sequences in patients with moderate to severe PD (Table 1).
Table 1

Subject characteristics

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age (year)</th>
<th>Sex</th>
<th>H &amp; Y Stage</th>
<th>Levodopa infusion dose (mg/h)</th>
<th>UPDRS^a Off/On (%)^b</th>
<th>Medications^c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>M</td>
<td>1</td>
<td>50</td>
<td>14/11 (21.4)</td>
<td>1, 2</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>2</td>
<td>70</td>
<td>20/13 (35.0)</td>
<td>1, 2</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>F</td>
<td>1.5</td>
<td>100</td>
<td>25/12 (52.0)</td>
<td>1, 2</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>F</td>
<td>2</td>
<td>100</td>
<td>35/27 (22.9)</td>
<td>1, 2</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>M</td>
<td>1</td>
<td>60</td>
<td>15/10 (33.3)</td>
<td>2, 3, 4</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>M</td>
<td>3</td>
<td>30</td>
<td>35/23 (34.3)</td>
<td>1, 2</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>M</td>
<td>2.5</td>
<td>60</td>
<td>32/27 (15.6)</td>
<td>1, 2</td>
</tr>
</tbody>
</table>

^aUnified Parkinson’s Disease Rating Scale (UPDRS) motor ratings (“off”/“on” levodopa).

^bClinical improvement, defined as ([levodopa “off” – “on”]/levodopa “off”) 100%.

^c1, levodopa/carbidopa; 2, dopamine agonist; 3, anticholinergic; 4, selegiline.

2. Methods

2.1. Subjects

Patients were five men and two women (mean age: 58.4 years; range 55–66) with an established diagnosis of moderately severe PD. They were on long-term treatment with L-Dopa and a dopamine agonist, except for one patient who had milder PD and was treated with a combination of selegiline, a dopamine agonist, and anticholinergic agent. Controls were six normal subjects, five men and one woman (mean age: 56.9 years; range: 52–64). All subjects had scores greater than 27 on mini-mental status examination. Written informed consent was obtained from all participants. The experiments were conducted in accordance with the Declaration of Helsinki.

Patients and control subjects were tested in two consecutive days. On each day, patients were tested 12h off dopaminergic drugs. One day, patients were tested without medication (“OFF” state), the other during a continuous intravenous infusion of L-Dopa (“ON” state) that was individually titrated to a maximal clinical effect (mean L-Dopa infusion rate ± SD: 67.1 ± 25.6 mg/h, range: 30–100 mg/h). Dopamine agonists were not administered during either ON or OFF state. Clinical response was measured by serial motor UPDRS ratings every 30 min. Motor testing was performed after a steady state had been achieved as defined by less than 5% variation in consecutive motor UPDRS ratings. On the first testing day, four patients were tested OFF medication and the other three ON.

Patients also underwent a 40 min neuropsychological assessment prior to and during L-Dopa infusion. Testing consisted of: National Adult Reading Test (NART), Beck Depression Inventory (BDI), Digit Span, Brief test of Attention, Symbol Digit Modalities Test (SDMT), Controlled Oral Word Association and Hopkins Verbal Learning Test (HVLT). The second assessment was performed during infusion at peak dose, with the exclusion of NART and BDI. Neuropsychological test scores were converted to T-scores (μ = 50, SD = 10) based on published normative populations.

2.2. Motor tasks

General features of the motor tasks have been detailed previously [15,17]. Briefly, subjects moved a cursor on a digitizing tablet with their right hand out and back from a central starting point to one of eight radially arrayed targets. Subjects were instructed to make uncorrected movements with sharp reversal inside each target. Targets appeared on a computer screen in synchrony with a tone at a constant interval of 1.5 s. Target distance was 1.2 cm. Testing was done in separate trial blocks of 90 s each, for a total of 56 movements (seven movement cycles). All subjects learned to perform the tasks in one or two training sessions the day before testing. Training, which was conducted with all PD patients on their regular medication, was complete when performance became stable.

The following tasks were administered:

CCW: Targets appeared in a predictable counterclockwise order. Subjects had to reach the target in synchrony with the tone. Thus, they had to initiate each movement before the corresponding target and tone were presented.

RAN: Targets were presented in a non-repeating and unpredictable order. Instructions were to reach for each target “as soon as possible”, minimizing reaction time but avoiding target anticipation. For each subject, the floor value of the reaction time distribution, i.e., the lowest onset time, was used to define anticipatory movements in SEQ [15].

SEQ: The eight targets appeared in a repeating order. Subjects were informed that a sequence was to be presented, instructed to learn the order of the sequence while reaching for targets and to anticipate target appearance. At the end of the block, they were also asked to report the sequence order and a declarative score (from 0, unawareness of a repeating sequence, to 8, complete correct sequence) was computed [15].

VSEQ: A repeating sequence of eight targets was presented for 90 s (56 target appearances, seven complete cycles). Subjects were asked to learn the sequence order by attending to the display without moving. The degree of learning achieved was assessed with declarative scores, as per SEQ. All tasks were repeated twice in each day. Since no statistically significant difference was found between the two repetitions, we used average values for each subject. Performance of the control group in all tasks was the same in both days (all, p > 0.7). Thus, these data are presented as averages.

2.3. Data analysis

For each movement we computed: (1) movement extent, the length of the vector from movement onset to the reversal point; (2) movement time, the time from movement onset to the reversal point; (3) onset time, the time from target and tone presentation to movement onset.

For SEQ we also quantified the number of anticipatory movements, i.e., those with onset time lower than RAN floor value, directed to the correct targets. This number reflects explicit learning, as we have found that the number of correct anticipatory movements is a good predictor of declarative scores [15].

Repeated-measures and mixed model analysis of variance (ANOVA) with post hoc comparisons were performed to assess the effects of L-Dopa and differences from normal controls. All analyses were considered significant for p < 0.05 with Bonferroni correction for multiple comparisons.

3. Results

3.1. UPDRS and neuropsychological tests

During L-Dopa infusion, UPDRS motor ratings decreased from 25.7 (+9.9 SE) to 16.6 (+6.7 SE) equivalent...
to 30.6% improvement ($p = 0.002$). Overall, there was no significant effect of L-Dopa on cognitive function measured with neuropsychological tests. However, we found a greater number of false-positive errors in the recognition portion of HVLT test ($p = 0.019$).

3.2. Motor tasks

In the patient group, durations of movements directed to predictable targets (CCW) were significantly reduced following L-Dopa infusion (Fig. 1, $p < 0.01$). In this task, there was also a parallel change in onset time (Fig. 1, $p < 0.02$) and a small, though significant, increase in movement extent ($1.17 \pm 0.05$ vs. $1.31 \pm 0.01$ cm; $p < 0.005$). Movement and onset time of patients in ON condition approached those of normal controls (Fig. 1).

L-Dopa produced similar effects on movements to random, unpredictable targets (RAN), with a decrease in both movement times ($495.4 \pm 51.2$: $436.1 \pm 59.7$ ms, $p < 0.002$) and reaction times ($331.5 \pm 39.6$: $295.9 \pm 33.1$ ms, $p < 0.001$). However, both movement times and reaction times remained significantly longer than those of normal subjects ($280.22 \pm 35.9$: $211.95 \pm 19.7$ ms, respectively).

3.3. Sequence learning

Similarly to CCW and RAN, SEQ movement times in patients were significantly shorter in ON compared to OFF drug condition (ON: $459 \pm 95$ ms; OFF: $504 \pm 85$ ms; $p < 0.0001$). Learning in SEQ was evident in both normal subjects and parkinsonian patients as a significant decrease in onset time across the 90 s block, with a corresponding increase in the number of correct anticipatory responses (Fig. 2). Onset time decreased significantly in patients in both drug conditions ($p < 0.001$), without significant difference between the two. However, onset time of patients were higher than those of normal controls ($p < 0.0001$). In the last movement cycle, controls performed an average of seven correct anticipatory movements ($\pm 0.34$, 87% of the sequence), while patients with PD performed only 3–4 of such movements both ON and OFF drug (37% to 45% of the sequence). Interestingly, in PD patients, onset time were lower and the total number of correctly anticipatory movements per block was greater in ON compared to OFF drug condition, although these differences did not achieve significance (Fig. 2). Declarative scores obtained at the end of the block were higher in normal controls (Fig. 3). In patients, scores were lowest following L-Dopa administration (ON: $2.6 \pm 1.3$; OFF: $3.9 \pm 2.2$). In four out of seven patients, these scores worsened in the ON condition and stayed the same in two others. As in previous studies, declarative scores in SEQ were significantly correlated with the corresponding number of correct anticipatory movements ($R^2 = 0.7p < 0.0001$).

Visual learning in VSEQ was measured with declarative scores. In patients with PD, VSEQ scores were higher than SEQ scores (Fig. 3, $p = 0.0005$) and did not improve, but rather decreased with L-Dopa (Fig. 3). Declarative scores of normal controls were significantly higher than those of patients during L-Dopa infusion, but not when tested OFF drug (Fig. 3).
sequence learning and aspects of neuropsychological performance.

Prior clinical observations and many studies using a variety of motor tasks have demonstrated that L-Dopa greatly improves motor performance in PD. Only few studies have assessed the effects of L-Dopa on sequence learning, and none has been done on explicit sequence learning. In the present study, the levels of L-Dopa for each subject were titrated in order to achieve maximal motor UPDRS improvement. Correspondingly, patients’ motor performance in the two reaching tasks, CCW and RAN, improved both spatially and temporally, with increases in movement length and decreases in reaction times and movement duration. CCW and RAN are motor tasks with different processing requirements. RAN is a choice reaction time task exploring stimulus-response processes. In CCW, a timed-response task with predictable targets [17], subjects were to reach the target when the tone was sounded and, thus, they had to predict tone presentation. Both in the OFF and ON status, parkinsonian patients ended the movements with temporal accuracy similar to that of normal subjects (see onset and movement times in Fig. 1). However, during L-Dopa infusion, there was a decrease in movement time, which reflects the clinical improvement in bradykinesia, which was accompanied by an increase in average movement range. Thus, with L-Dopa, movements became faster and less hypometric. In addition, there was an improvement in reaction time during the random choice task (RAN), suggesting a beneficial effect of L-Dopa on akinesia and movement planning.

Whereas motor performance improved with L-Dopa infusion, neuropsychological tests and sequence learning did not. In fact, false-positive identifications increased in a verbal learning task; motor as well as visual sequence learning indexes either deteriorated or did not improve. Dissociation between motor and cognitive performance has been reported in a study of de-novo PD patients during oral L-Dopa therapy with improvement of reaction time but not of the event-related P300, a marker of cognition [18]. From its introduction in PD treatment, L-Dopa has been known to cause psychiatric symptoms and neuropsychological deficits, but also to improve specific cognitive functions such as verbal fluency and set-shifting [19,20]. However, L-Dopa may impair high speed memory scanning, associative conditional learning, visual learning, reversal, subject-ordered pointing and highly demanding executive tasks (for a review see: [14]). Moreover, human and animal studies [9–13] have shown that L-Dopa may have adverse effects on attention and working memory, cognitive aspects of great importance for successful performance in tasks such as our sequence learning tasks [16,21]. Interestingly, L-Dopa affected more profoundly the performance in the combined motor learning task (SEQ) rather than in the simple visual learning task (VSEQ). This suggests that L-Dopa negative effects might become more evident with increased attentional demands.

4. Discussion

Our study shows that in non-demented patients with moderate PD, intravenous dopaminergic treatment acutely improves both motor UPDRS scores and reaction and movement times of reaching movements. However, it fails to improve and, in some cases, further impairs explicit
In fact, VSEQ has fewer attentional and working memory requirements than SEQ, as VSEQ does not require that learning occurs with concurrent movements.

Our sequence learning tasks activate the putamen and the caudate [16,22]—which in PD shows a profound dopaminergic deficit [23]—as well as the dorsolateral prefrontal cortex (DLPFC) [16,22]. Our parallel imaging studies with positron emission tomography and O15 did not reveal significant changes in DLPFC during L-Dopa infusion [24], probably due to the small sample of patients tested and their non-homogeneous performance. However, during L-Dopa infusion we found a decrease in the activation of the brain network that includes DLPFC and caudate and that directly modulates sequence learning [22]. DLPFC, which in PD shows more variable degree of dopaminergic loss, receives projections both from the caudate [25] and the ventral tegmental area (VTA) [26]. Both pathways are involved in several aspects of cognitive processing; in particular, the projections from VTA facilitate sustained attention and spatial working memory [27,28]. Animal studies have shown that either excessive or insufficient dopamine receptor stimulation may impair cognitive tests related to DLPFC function [10,11]. Therefore, it is possible that the dopaminergic levels that improved motor performance through the motor loop [29] produced concomitant over stimulation of receptors in the DLPFC and caused attentional and/or working memory deficits. This may explain the decline of declarative scores during L-Dopa infusion in most of our patients.

Indeed, our findings need to be confirmed with controlled studies in larger patient populations. In fact, we have studied a small patient group with moderately severe PD. In addition, because of the study’s open label approach, we cannot exclude a placebo effect on the performance of some of our patients. Finally, our study design did not take into account the possible negative effect of the infusion procedure, such as discomfort, on the outcome of the learning tasks. Nevertheless, our results are in agreement with those of other studies showing that acute dopaminergic treatment may worsen frontal lobe function [14].

In summary, we found that L-Dopa improves motor signs but it may impair explicit sequence learning. These results suggest that motor and cognitive tasks engage different pathways and each pathway may require different level of dopaminergic activation to properly modulate their functions. Pharmacological modification of DLPFC and its efferent projections may interfere with the normal transfer of information that is fundamental to explicit learning [30].

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References


