Activity enhances dopaminergic long-duration response in Parkinson disease

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ABSTRACT

Objective: We tested the hypothesis that dopamine-dependent motor learning mechanism underlies the long-duration response to levodopa in Parkinson disease (PD) based on our studies in a mouse model. By data-mining the motor task performance in dominant and nondominant hands of the subjects in a double-blind randomized trial of levodopa therapy, the effects of activity and dopamine therapy were examined.

Methods: We data-mined the Earlier versus Later Levodopa Therapy in Parkinson's Disease (ELLDOPA) study published in 2005 and performed statistical analysis comparing the effects of levodopa and dominance of handedness over 42 weeks.

Results: The mean change in finger-tapping counts from baseline before the initiation of therapy to predose at 9 weeks and 40 weeks increased more in the dominant compared to nondominant hand in levodopa-treated subjects in a dose-dependent fashion. There was no significant difference in dominant vs nondominant hands in the placebo group. The short-duration response assessed by the difference of postdose performance compared to predose performance at the same visit did not show any significant difference between dominant vs nondominant hands.

Conclusions: Active use of the dominant hand and dopamine replacement therapy produces synergistic effect on long-lasting motor task performance during "off" medication state. Such effect was confined to dopamine-responsive symptoms and not seen in dopamine-resistant symptoms such as gait and balance. We propose that long-lasting motor learning facilitated by activity and dopamine is a form of disease modification that is often seen in trials of medications that have symptomatic effects. ***Neurology*® 2012;78:1146–1149**

GLOSSARY

ELLDOPA = Earlier versus Later Levodopa Therapy in Parkinson's Disease; **LDR** = long-duration response; **PD** = Parkinson disease; **SDR** = short-duration response.

Long-duration response (LDR) in Parkinson disease (PD) pharmacologic therapy develops over days to weeks with chronic use of the drug, and gradually decays after the drug is stopped. LDR is distinct from short-duration response (SDR) that parallels the half-life of the drug (hours). LDR is a more beneficial and durable component of dopaminergic therapy without accompanying dyskinesia and motor fluctuations,[1,2] but its underlying mechanism is poorly understood. We reported that dopamine-dependent motor learning in a mouse model of PD produces the same phenomenon as LDR.[3] Learning motor tasks was dependent on both dopamine and task-training and occurred over a few days. In the absence of dopamine, task-training resulted in development of aberrant learning, leading to deterioration of performance over a few days.

Therefore, we hypothesized that LDR is facilitated by a combination of active training and dopamine to a greater magnitude than achievable by either one alone. The objective of this study was to test this hypothesis using previously published clinical trial data from the Earlier versus Later Levodopa Therapy in Parkinson's Disease (ELLDOPA) study that examined the effi-

Supplemental data at www.neurology.org

Supplemental Data

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Coinvestigators are listed on the *Neurology*® Web site at www.neurology.org.

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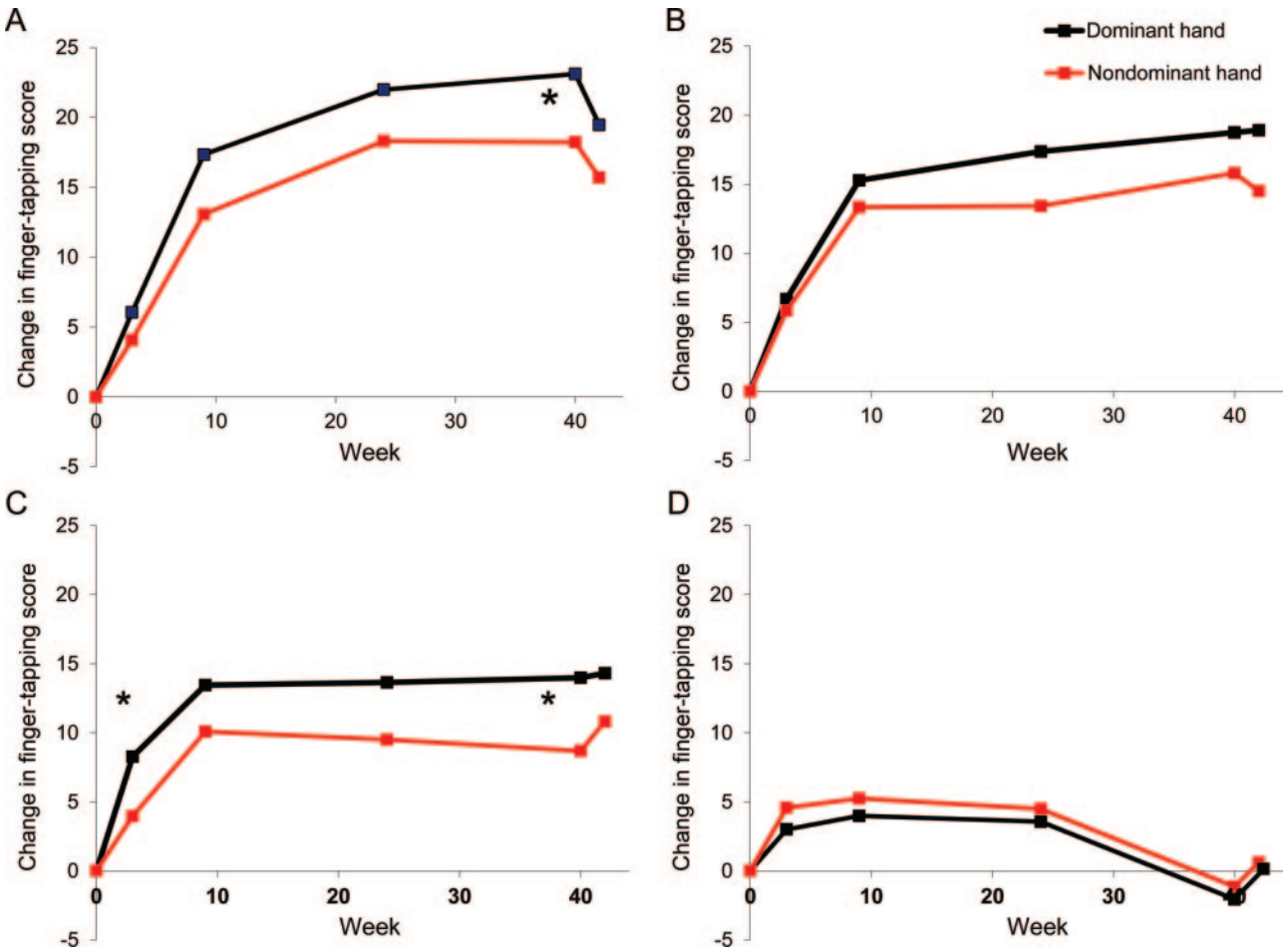
cacy of levodopa.[4] We reasoned that the preferred activity of the dominant hand can be used as a proxy for active learning experience that is reflected in motor performance tests during a clinical trial visit.

METHODS The ELLDOPA study enrolled 361 patients with early, untreated PD who were randomized to various dosages of carbidopa/levodopa or placebo.[4] Motor performance data were obtained at the baseline visit and before and 1 hour after administration of the first daily dose at the 3-, 9-, 24-, and 40-week visits and 2 weeks after stopping the study medication at the 42-week follow-up visit. Subjects performed 2-point finger-tapping using mechanical counters mounted 20 cm apart on a table and alternatively touched them over 1 minute as many times as possible. The change in predose finger-tapping counts at subsequent visits compared to baseline was used as a measure of LDR. The SDR was measured as the difference in scores between pre- vs postdoses at the same visit. Patients reported their hand dominance and more vs less affected hand since their symptoms were often asymmetric. Those who noted no hand dominance were excluded from the analysis (n = 3). Those with normal $^{[123]}\beta$-CIT scans without evidence of dopamine deficiency (SWEDD) (21 of 142 who underwent the imaging) or deemed to have less than 90% likelihood of PD at follow-up (n = 14) were excluded from our analyses.

The effect of hand dominance and asymmetry of symptoms on LDR were analyzed by a repeated-measures mixed model with a 3-way interaction including duration of treatment. The effects of levodopa treatment, duration of treatment, and hand dominance on LDR were tested with a 3-way interaction. Paired *t* tests were used to compare handedness of LDR and SDR at each visit and the change from the 40-week predose to the 42-week washout visit as well as mean changes in posture, gait, postural balance, and Hoehn & Yahr stage from baseline to the week 42 washout visit. Bonferroni correction was applied to account for multiple comparisons in determining statistical significance resulting in an adjusted α of 0.0125. SAS v9.2 software was used for analyses.

Figure 1 **Mean change in 2-point finger-tapping counts from baseline to various time points**



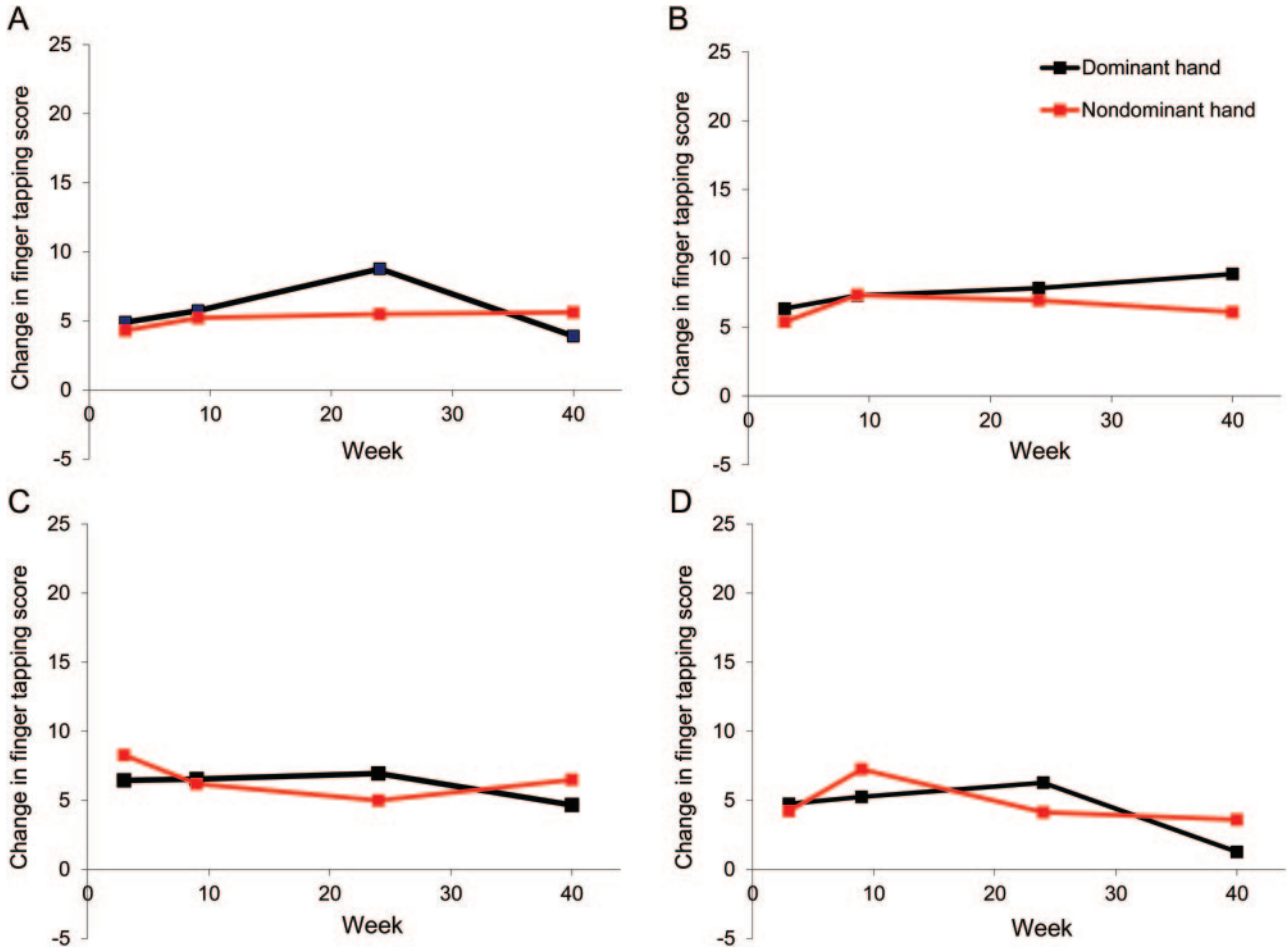
Changes in finger-tapping scores from baseline to predose measurements of various time points in 600 mg levodopa (A), 300 mg (B), 150 mg (C), and placebo-treated groups (D). These represent long-duration response (LDR). Levodopa treatment, time on treatment, and dominance of hand have significant effect on the magnitude of LDR ($p < 0.0001$ by 3-way interaction). There was also a significant interaction of treatment and dominance of hand ($p < 0.05$). There were significantly greater LDR in dominant hands compared to the nondominant hands at 40-week visit in the 600-mg group (A) and at 3- and 40-week visits in the 150-mg levodopa group (C) (given in 3 divided doses per day with carbidopa) (*$p < 0.0125$, which was the preset significance level considering Bonferroni correction for multiple testing using paired *t* test). At the 42-week visit, the finger-tapping score remained significantly higher than baseline in all 3 levodopa-treated groups ($p < 0.001$ by paired *t* tests), but not in the placebo group.

RESULTS The specific hypothesis tested was that LDR is greater in the dominant hand than in the nondominant hand. Since many patients also had asymmetric involvement of their symptoms, the effect of more or less affected side on LDR and its interaction with hand dominance was first tested. LDR was affected by hand dominance ($p = 0.007$), but not by whether the hand was more or less affected ($p = 0.52$) in the 600 mg group. Therefore, we analyzed data combining more and less affected sides. The mean LDR was greater in the dominant compared to nondominant hand at 9 and 40 weeks in those who were treated with 600 mg (figure 1A) and at 3, 9, and 40 weeks in the 150 mg group (figure 1C). The magnitudes of LDR were dose-dependent at 9, 24, and 40 weeks, showing a linear trend determined by including treatment assignment as a continuous variable in the linear regression models ($p < 0.001$). There was no significant difference between the dominant and nondominant hand in the placebo group at any visit. There was consistently greater magnitude of improvement of Unified Parkinson's Disease Rating Scale hand item scores in the dominant hand than nondominant hand as well, but the differences were not statistically significant at a preset level of $p < 0.0125$ since these scores were low in this early PD cohort (table e-1 on the *Neurology*® Web site at www.neurology.org).

The deterioration of finger-tapping scores during the 2-week washout phase was not significantly different in the dominant hand vs the nondominant hand, and finger-tapping scores at the end of the study remained significantly improved compared to those at the baseline in both hands ($p < 0.001$, figure 1). This is in contrast to measures such as posture, gait, postural instability scores, and Hoehn & Yahr stage that did not improve from the baseline to the end of the study (table e-2).

Levodopa effects on SDR were not distinguishable from placebo effect and there were no differences between dominant and nondominant hands (figure 2).

Figure 2 **Changes in 2-point finger-tapping scores from predose to 1 hour postdose**



Changes from predose measurements of finger-tapping scores to 1 hour postdose at various time points represent short-duration response in 600-mg levodopa (A), 300 mg (B), 150 mg (C), and placebo-treated groups (D). There were no statistically significant effects of levodopa treatment, duration of treatment, and dominance of hands.

DISCUSSION Our analysis shows that active use of the dominant hand produces greater magnitude of improvement in motor performance compared to the relative inactivity of the nondominant hand in the presence of levodopa, consistent with our hypothesis that activity and dopamine enhances LDR synergistically. The dose dependence and the lack of difference between the dominant and nondominant hands in the absence of dopamine replacement in the placebo group provide additional evidence for synergy of activity and dopamine. The improvement occurred gradually over 9 weeks and plateaued, and higher doses showed continuing increase up to 40 weeks albeit at a slower rate. This time course of LDR is much longer than that observed in previous studies, in patients who were more advanced than this cohort and in experimental settings when medications were discontinued.[5,6] Our analysis also shows that the effect of levodopa mainly manifests as LDR and SDR is not significantly different from placebo effect in this early PD cohort.

Studies to demonstrate the disease-modifying effect of various therapies have been complicated by the long-lasting benefits even after withdrawing medications that produce symptomatic effects.[4,7] This observation of long-lasting benefits raised controversy as to whether they represent disease modification. Disease modification may imply slowing of the degenerative process, but such evidence is lacking. Nondopaminergic mechanism of compensation was also suggested.[8] We propose a specific alternative mechanism of disease modification by dopaminergic agents in producing slow and long-lasting motor learning. Dopamine-resistant symptoms deteriorated or remained unchanged (table e-2) whereas dopamine-dependent motor scores remained significantly improved compared to baseline even after drug withdrawal, supporting the notion that dopamine-dependent motor learning is responsible for the residual benefit rather than general neuroprotection. Such plasticity has been noted in experimental studies as long-term potentiation or long-term depression, depending on the level of dopamine and other conditions of the stimulus,[9] and underlies motor learning.[10] The limitation of the study is that this was a data-mining study that used daily activities of hand dominance as a proxy for active training and assumed that finger-tapping scores reflect such activities. Future studies with prospective designs for specific motor tasks will address the role of motor learning and provide a stronger rationale for possible benefit of early dopaminergic treatment to enhance beneficial plasticity in PD.

AUTHOR CONTRIBUTIONS

U.J.K. conceived the idea, secured funding, planned the analysis, interpreted the analysis, and drafted and revised the manuscript. P.A. assisted with planning of the analysis, performed statistical analysis of the data, and revised the manuscript. The PSG ELLDOPA Study Investigators were responsible for the original study that provided the data for this study.

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DISCLOSURE

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