

Dopaminergic effects on encoding of a motor memory in chronic stroke

Abstract—The effects of a single oral dose of levodopa administered in a randomized, double-blind, placebo-controlled cross-over design on formation of a motor memory were studied by a training protocol in patients with chronic stroke. Levodopa enhanced the ability of motor training to encode an elementary motor memory relative to placebo. Up-regulation of dopaminergic function may enhance motor memory formation, crucial for successful rehabilitative treatments in patients with chronic stroke.

NEUROLOGY 2005;65:472–474

A. Floel, MD; F. Hummel, MD; C. Breitenstein, PhD; S. Knecht, MD; and L.G. Cohen, MD

Chronic stroke is associated with substantial motor disability.¹ As part of rehabilitative interventions, it would be desirable to enhance memory formation and response to motor training protocols.^{1–3} Pharmacologic interventions have shown promise in modulating cortical plasticity and motor function.^{3,4} For example, amphetamines can enhance formation of motor memories but may do so at the expense of undesired side-effects (cardiac arrhythmias, hypertension, and addiction),⁴ possibly not tolerated by elder individuals with brain lesions.^{1,4} Dopaminergic agents (e.g., levodopa in combination with decarboxylase inhibitors or dopamine agonists) may have a superior risk–benefit ratio relative to D-amphetamines.^{1,2} In the subacute stage after stroke, levodopa appears to exert a beneficial effect on rehabilitative treatments.⁵ We thought to determine if levodopa could enhance training-dependent encoding of an elementary motor memory years after the stroke. If so, it is possible that this strategy could contribute to neurorehabilitative efforts in the chronic stage after stroke, when therapeutic options are scarce.

Methods. *Subjects.* Nine patients aged 55 to 85 years (mean \pm SD, 66.1 \pm 9.5 years; three of them women, all but one right-handed) with cerebral infarcts participated in the study. All participants had a single ischemic cerebral infarct (all subcortical) (table). All gave written informed consent to each experiment according to the Declaration of Helsinki (http://www.wma.net/e/policy/17-c_e.html), and the National Institute of Neurologic Disorders and Stroke Institutional Review Board approved the study protocol. Patients were tested at least 1 year after the stroke (3.7 \pm 0.7 years after the stroke; range 1 to 8 years).

All patients initially had a severe motor paresis (below Medical Research Council Scale⁶ grade 2) and recovered substantially

(range on Medical Research Council Scale from 4.2 to 4.9) to be able to perform both motor tasks (see table). Degree of spasticity was assessed with the Modified Ashworth Scale for grading spasticity⁷ and ranged from 0 to 3 (see table); muscle strength was assessed with the upper extremity section of the Fugl–Meyer Scale.⁸ None of the patients had overt somatosensory deficits, as assessed in the standard neurologic examination. All patients had visual perception within normal limits and a normal Mini-Mental State Examination (range 26 to 30 points). Additionally, all participating patients fulfilled the following inclusion criteria: 1) ability of transcranial magnetic stimulation (TMS) to elicit isolated thumb movements in the absence of movements of any other digits, wrist, or arm; 2) consistent (reproducible) direction of TMS-evoked thumb movements in the baseline condition; 3) absence of dopaminergic medications or drugs interfering with the absorption of levodopa from the gastric tract⁹; 4) age >52 years. As the ability to encode a motor memory with training alone differs depending on age,¹⁰ (see reference E-1 on the *Neurology* Web site at www.neurology.org) only patients older than 52¹⁰ were included in the current study to increase homogeneity.

Experimental protocol. All patients participated in two sessions, separated by at least 24 hours, testing the effects of levodopa (100 mg of levodopa and 25 mg of carbidopa, PO) + training and placebo (identical capsule, PO) + training on encoding of a motor memory. The order of the sessions was randomized between patients and counterbalanced. In each session, subjects fasted for at least 2 hours preceding levodopa/placebo intake and avoided other medications to prevent interference with drug absorption (reference E-2). Testing started 60 minutes after oral intake of levodopa/placebo, at a time that shows peak plasma concentrations of the drug (see reference E-2). Measurement of systolic and diastolic blood pressure and heart rate and subjects' rating of attention to the task and fatigue levels were taken four times during each session. Motor training kinematics were monitored along the experiment (see the "Experimental setup" material on the *Neurology* Web site at www.neurology.org).

Encoding of a motor memory. Motor training, consisting of voluntary thumb movements performed at 1 Hz, in a consistent direction leads to formation of an elementary motor memory that encodes the kinematic details of the practiced motions in young healthy individuals (see reference E-3). In brief, this protocol evaluates the ability of such training to modulate the direction of TMS-evoked thumb movements elicited by stimulation of the primary motor cortex (see the "Encoding of a motor memory material" on the *Neurology* Web site). To quantify training effects, we defined a training target zone (TTZ) as a window of $\pm 20^\circ$ centered on the training direction (figure 1, TTZ 40°) and the increase in the percentage of TMS-evoked movements that fell within the TTZ after each intervention (30 minutes of training plus levodopa and 30 minutes of training plus placebo) as the endpoint measure (see reference E-3). By design, training was in the direction opposite to the baseline TMS-evoked thumb movement direction. Therefore, the percentage of TMS-evoked movements within the TTZ before training was very small (<5%).

Statistical analysis. Data analysis was performed by an investigator blind to the intervention type. Normal distribution (Kolmogorow–Smirnov test of normality) was assessed for all data. Repeated measures analysis of variance (ANOVA_{RM}) was used to test the influence of the repeated factors time_{base}, 10 min, 20 min, post and drug_{levodopa, placebo} on the percentage of TMS-evoked

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From the Human Cortical Physiology Section (Drs. Floel, Hummel, and Cohen), National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD; and Department of Neurology (Drs. Floel, Breitenstein, and Knecht), University of Muenster, Germany.

Disclosure: The authors report no conflicts of interest.

Received January 10, 2005. Accepted in final form April 13, 2005.

Address correspondence and reprint requests to Dr. L.G. Cohen, Human Cortical Physiology Section, NINDS, NIH, Bethesda, MD 20817; e-mail: cohenl@ninds.nih.gov

Table Clinical characteristics of stroke patients

Patient no.	Age, y	Sex	Years post stroke	Lesion site	Motor function		
					MRC	FMS, %	MAS
1	62	M	5	L-basal ganglia	4.5	79	3
2	85	M	8	L-basal ganglia	4.8	96	0
3	70	M	2	L-occipito-posterior junction centrum semiovale	4.7	91	1+
4	65	M	2	R-thalamus	4.9	95	0
5	63	F	1	R-temporal lobe, R centrum semiovale	4.5	92	0
6	74	F	3	R-basal ganglia	4.8	96	0
7	55	M	3	R-basal ganglia	4.9	97	0
8	57	F	6	R centrum semiovale and basal ganglia	4.6	92	0
9	60	M	3	R-MCA, hemorrhagic (aneurysm)	4.2	85	1

MRC = Medical Research Council Scale (see reference E-7); FMS = Fugl-Meyer Scale⁶; MAS = Modified Ashworth Scale⁷ for rating spasticity; L = left hemisphere; R = right hemisphere; MCA = middle cerebral artery.

movements in the TTZ (primary outcome measure), systolic blood pressure, diastolic blood pressure, heart rate, attention to the task, and fatigue over the course of the training. Measures of corticomotoneuronal excitability (motor threshold [MT] of the training agonist muscle [MT_{agonist}], MT of the training antagonist muscle [MT_{antagonist}], motor evoked potential (MEP) amplitude of the training agonist [MEP_{agonist}], and MEP amplitude of the training antagonist [MEP_{antagonist}]) were analyzed using ANOVA_{RM} with a polynomial contrast analysis for the factor time_{base, post} and the repeated factor drug_{levodopa, placebo}. Motor training kinematics (magnitude of first peak acceleration of training movement, angular difference between the training movement direction and the baseline direction vectors, dispersion of training movement directions) and movement threshold were compared between sessions (levodopa, placebo) using paired *t* tests. Data

were considered significant at a level of *p* < 0.05. All data are expressed as means ± SEM, unless stated otherwise.

Results. Attention to the task, fatigue (see table E-1) and motor training kinematics (see table E-2) reflecting training quality were comparable across sessions. Blood pressure and heart rate experienced a similar mild decrease over time in both sessions. Movement thresholds, motor thresholds, and MEP amplitudes were also similar in both sessions at baseline and after training, indicating comparable corticomotor excitability (see tables E-1 through E-3).

ANOVA_{RM} showed an interaction of time by drug on the percentage of TMS-evoked movements falling in the TTZ ($F[1,16] = 4.89, p = 0.042$). Post-hoc testing showed that training under both placebo and levodopa increased the percentage of TMS-evoked thumb movements falling in the TTZ ($p = 0.028$ and $p = 0.011$). The magnitude of this increment with levodopa ($8.8 \pm 2.7\%$) was higher than with placebo ($2.6 \pm 1.0\%$; $p = 0.014$), and the effect was clearly identifiable in five of the nine subjects tested (figure 2).

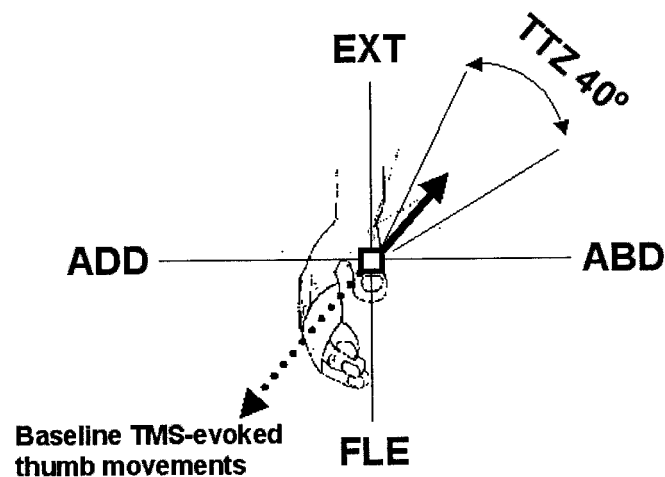


Figure 1. Diagram showing measurement of thumb movements with an accelerometer positioned on the distal interphalangeal joint (rectangle on the thumb). Baseline transcranial magnetic stimulation (TMS)-evoked thumb movements in this example fell in a flexion-adduction direction (dotted arrow). Training voluntary thumb motions were performed in the opposite direction (extension-abduction, solid arrow). At the end of the training period, we measured the percentage of TMS-evoked thumb movements falling in the training target zone, the endpoint measure of the study.

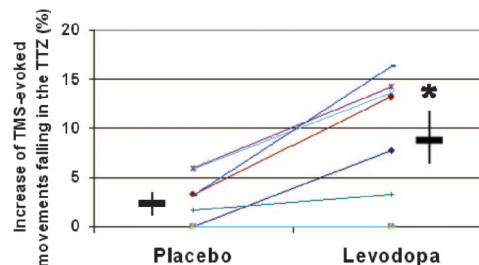


Figure 2. Thirty minutes of training under levodopa and under placebo led to an increase in transcranial magnetic stimulation (TMS)-evoked movements falling in the training target zone (TTZ). The increment in the percentage of TMS-evoked movements in the TTZ under levodopa was significantly higher than under placebo, an effect evident in five of the nine patients tested (each line denoting one patient; three patients showed zero increase under both placebo and levodopa). Black bars indicate means ± SE.

Discussion. Our results show that the primary motor cortex within the affected hemisphere of patients with chronic predominantly subcortical stroke retains the ability to encode a motor memory with training and that a single oral dose of levodopa significantly enhanced this effect relative to placebo. These results could not be explained by differences in training quality, attention, fatigue, blood pressure or heart rate levels or motor cortical excitability at baseline across intervention days.

Previous reports have documented enhancement in training effects with D-amphetamines in animal models,² healthy volunteers (see reference E-4), and in the subacute and chronic period in patients with stroke.^{3,4} One potential problem limiting the use of amphetamines in elder individuals with brain lesions has been the range of potentially undesirable effects.^{1,4} For this reason, the finding that dopaminergic agents could enhance training effects in the subacute period following stroke triggered enthusiasm. In healthy humans intake of levodopa increases motor memory formation (see reference E-1), whereas dopamine-receptor antagonists impair motor learning (see reference E-5). Mechanisms underlying these effects in humans are not clear but may relate to the documented facilitatory effects of dopaminergic neurotransmission (see reference E-6) on N-methyl-D-aspartate-dependent and -independent long-term potentiation induction, involved in memory formation.

Our findings demonstrate that beneficial effects of levodopa on training-dependent plasticity can be elicited not only in the subacute period after stroke⁵ but also in the chronic stage, when less therapeutic options are available. The magnitude of this effect across the spectrum of poststroke motor disability remains to be determined.

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