

Improving Hand Function in Chronic Stroke

Wolf Muellbacher, MD; Coletta Richards, MD; Ulf Ziemann, MD; George Wittenberg, MD; Deborah Wetz, MD; Babak Boroojerdi, MD; Leonardo Cohen, MD; Mark Hallett, MD

Background: Recovery of function following stroke plateaus in about 1 year, typically leaving upper arm function better than that in the hand. Since there is competition among body parts for territory in the sensorimotor cortex, even limited activity of the upper arm might prevent the hand from gaining more control, particularly when the territory is reduced in size because of the stroke. Deafferentation of a body part in a healthy brain enhances cortical representations of adjacent body parts, and this effect is markedly increased by voluntary activity of the adjacent part.

Objective: To explore whether deafferentation of the upper arm, produced by a new technique of regional anesthesia during hand motor practice, helps recovery of

hand function in patients with long-term stable weakness of their hand following stroke.

Methods and Results: Deafferentation, produced by a new technique of regional anesthesia of the upper arm during hand motor practice, dramatically improved hand motor function including some activities of daily living. The improvement was associated with an increase in transcranial magnetic stimulation-evoked motor output to the practice hand muscles.

Conclusion: This is a novel therapeutic strategy that may help improve hand function in patients with long-term weakness after stroke.

Arch Neurol. 2002;59:1278-1282

RECOVERY OF function after stroke may occur, but it is unclear whether interventions can improve function beyond the spontaneous process. In particular, recovery of hand function plateaus in about 1 year, and common knowledge is that the patient will remain at that level for the rest of his or her life.^{1,2} Typically in such situations, upper arm function is better than that in the hand.³ An emerging concept in neural plasticity is that there is competition among body parts for territory in the brain.⁴⁻⁹ Thus, even limited activity of the upper arm might prevent the hand from gaining more control, particularly when the territory is reduced in size because of the stroke. Work in our laboratory and elsewhere has indicated that deafferentation (with deafferentation) of a body part in a healthy brain enhances cortical representations of adjacent body parts,¹⁰⁻¹⁷ an effect that is markedly increased by voluntary activity of that adjacent part.^{18,19} Based on these findings, we explored whether deafferentation of the upper arm, produced by a new technique of regional anesthesia during hand motor practice, helps re-

covery of hand function in patients with chronic stable weakness of their hand following stroke.

REPORT OF CASES

CASE 1

A 51-year-old, right-handed woman who had a right capsular stroke was studied 57 months after the ictus. She had left-sided hemiparesis, moderate spasticity of the arm and leg, and a discrete hemihypesthesia. Her hand grasp was weak (MRC Scale, 4-) with full-active mass flexion and some mass extension of all fingers. Assessment scale scores were Modified Rankin Scale, 2 (slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance; mean [SD] score, 2.1 [0.4]; range, 2-3); Barthel Activities of Daily Living (ADL) Index, 100 (range 0 [worse]-100 [best]; mean score [SD], 98 [3.9]; range, 90 [worse]-100 [best]); National Institutes of Health Stroke Scale (NIHSS), 3 (mean score [SD], 3.4 [1.4]; range, 2 [best]-6 [worse]); and Fugl-Meyer Hand Scale, 3 (mean score [SD], 8.4 [5.3]; range, 3 [best]-14 [worse]).

From the Human Motor Control Section (Drs Muellbacher, Ziemann, and Hallett), and the Human Cortical Physiology Section (Drs Ziemann, Wittenberg, Boroojerdi, and Cohen), National Institute of Neurological Disorders and Stroke, and the Department of Anesthesia (Drs Richards and Wetz), National Institutes of Health, Bethesda, Md; Department of Neurology, Ludwig Boltzmann Institute, Neurological Hospital of Vienna, Vienna, Austria (Dr Muellbacher); and the Clinic of Neurology, J. W. Goethe-University Frankfurt, Frankfurt am Main, Germany (Dr Ziemann).

PATIENTS AND METHODS

PATIENTS

The study protocol was approved by the National Institutes of Neurological Disorders and Stroke institutional review board. Seven patients (6 men and 1 woman; mean age, 58 years; age range, 51-63 years) with right or left hemiparesis gave their written informed consent to participate in the experiments that were started on average 37 months after stroke onset (range, 13-57 months).

EXPERIMENTS

Two experiments were conducted—hand motor practice (experiment 1, “practice”), and hand motor practice during regional anesthesia of the upper arm (experiment 2, “practice and anesthesia”). In experiment 1, we explored the effects of motor practice on hand function. This experiment included 3 practice episodes. Practices 1 and 2 were 30 minutes each with a 15-minute break for rest and test measurements. Practice 3 was 15 minutes every day for an average of 35 days (range, 7-71 days) and was started the day after practices 1 and 2 were completed and continued until the beginning of experiment 2. Practice 3 was performed at home after the patient received instruction; the patients were otherwise under continuous supervision. In experiment 2, we aimed to enhance the effects of motor practice by depriving the motor cortex representations of the upper arm from their sensory inputs by using a new technique of regional anesthesia. This experiment included 2 practice episodes. Practices 4 and 5 were 30 minutes each with a 15-minute break for rest and test measurements and included 6 patients from experiment 1 (patient 1 withdrew from invasive procedures). The final follow-up measures were completed 14 days after practice 5 was completed.

PRACTICING

The practice task was a metronome-paced pinch between the index finger and the thumb of the impaired hand (frequency individualized between 0.3 and 0.5 Hz). The patient aimed to do the pinching as quickly as possible because previous experiments in healthy volunteers showed that practicing such accelerated movements can result in improved hand function.²⁰

BEHAVIORAL MEASURES

Maximal pinch force of the index finger and thumb was measured with a pinch gauge (model 5083; AliMed Inc, Dedham, Mass) according to a standardized procedure described in detail elsewhere.²⁰ The acceleration of each thumb flexion during practicing (up to 1200 movements) was taken with a miniature, high-output charge, piezoelectric accelerometer with integral electronics (model 25A, ISOTRON PE Accelerometer, 4.575 mV/g sensitivity; Endevco Corp, San Juan Capistrano, Calif) firmly fixed to the proximal

phalanx of the thumb with tape. The signal was amplified by a battery-powered, low-noise signal conditioner (model 4416B ISOTRON Signal Conditioner; Endevco). The signal was digitized using a PCI-MIO-16E4 board (National Instruments Corp, Austin, Tex) at a rate of 2000 Hz.

MEASUREMENT OF MOTOR EXCITABILITY

Surface electromyogram was recorded (bandpass, 0.1-2.5 kHz) from the left flexor pollicis brevis muscle using an electromyographic machine (Counterpoint Electromyograph; Dantec Dynamics A/S, Skovlunde, Denmark). The motor cortex was excited with a figure 8-shaped stimulation coil connected to a magnetic stimulator (Magstim 200; MagstimCo Ltd; Whitland, South West Wales). Motor threshold was defined as the minimum stimulus intensity required to produce motor evoked potentials (MEPs) exceeding 50 μ V in at least 5 of 10 trials. Peak-to-peak MEP amplitude was determined at a stimulus intensity of 20% of maximum stimulator output above the individual motor threshold.

REGIONAL ANESTHESIA

A needle was inserted into the interscalene groove and electrical stimulation was delivered to localize the upper brachial plexus roots. Then, 10 to 20 mL of 1.5% lidocaine hydrochloride was injected. The regional effects of this procedure were determined 15 minutes after injection by (1) skin anesthesia of shoulder and upper arm (defined as no response to touch in at least 3 of 4 trials) with sparing of forearm and hand; (2) increase in sensory threshold in shoulder and upper arm with sparing of forearm and hand, which was expressed as an increase in monofilament diameter size (in millimeters; the diameters provide a logarithmic scale of force exerted, and, thus, a linear and interval scale of perceived intensity) (Semmes-Weinstein Von Frey Monofilaments; Stoelting Co, Wood Dale, Ill) necessary to produce sensation to touch in at least 3 of 4 trials; (3) decreased strength (Medical Research Council [MRC] Scale) of shoulder and upper arm muscles, with sparing of forearm and hand muscles; (4) no change in pinch force (pinch gauge) because of regional anesthesia; and (5) no change in MEP amplitude in the practice flexor pollicis brevis muscle because of regional anesthesia. The effects of anesthesia were assessed 15 minutes after the injection of the anesthetic (evaluation of anesthesia) and at the end of the final practice episode (end of anesthesia) (**Figure 1**).

DATA ANALYSIS

The effects of practice and anesthesia on force, motor threshold, MEP amplitude, and sensory measures were assessed separately with analysis of variance using a model of repeated measures. For each time point, changes were expressed as ratio (postpractice/prepractice₁). Conditional to statistically significant ($P < .05$) values, post hoc paired t tests were performed. Simple regression analyses were done to study correlation between the practice-induced changes in motor behavior and motor excitability.

CASE 2

A 62-year-old man who had a left capsular stroke was studied 44 months after the ictus. He had a right-sided hemi-

paresis, with moderate spasticity in his arm and leg including sustained ankle clonus. He could raise his arm and hand against gravity, but his hand grasp was weak (MRC Scale, 4-); he had full-active finger flexion and could re-

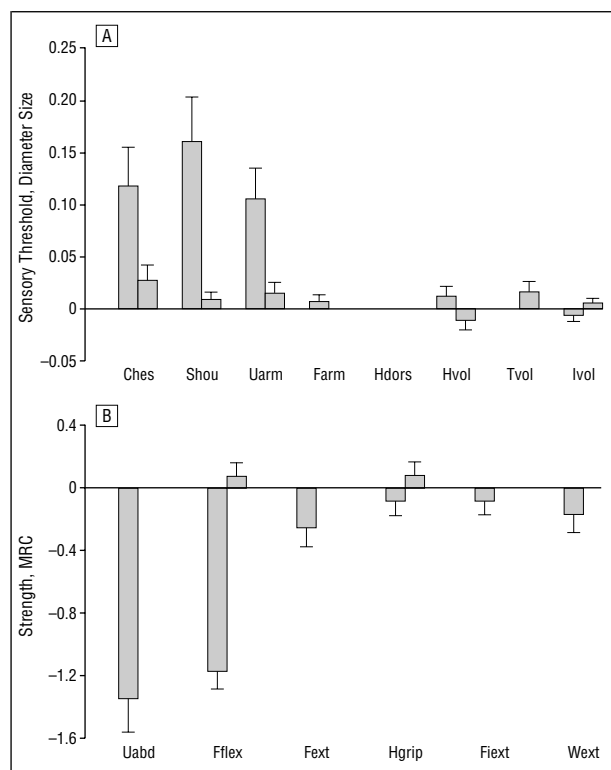


Figure 1. Effects of regional anesthesia on sensory threshold (A) and muscle strength in different body parts (B). Changes (during [first bar] and after [second bar] anesthesia) were expressed as difference in monofilament diameter size (A) and as difference in muscle strength (Medical Research Council [MRC] Scale) (B). Ches indicates upper chest; Shou, shoulder; Uarm, upper arm; Farm, forearm; Hdors, dorsal side of the hand; Hvol, volar surface of the hand; Tvol, volar surface of the thumb; Ivol, volar surface of the index finger; Uabd, upper arm abduction; Fflex, forearm flexion; Fext, forearm extension; Hgrip, handgrip; Fiext, finger extension; Wext, wrist extension; asterisks, $P < .05$; and error bar, SEM.

lease from an active mass flexion grasp. Assessment scale scores were Modified Rankin Scale, 2; Barthel ADL Index, 100; NIHSS, 3; and Fugl-Meyer Hand Scale, 3.

CASE 3

A 57-year-old, right-handed man who had a right-sided pontine stroke was studied 48 months after the ictus. He had slurred speech, left-sided facial weakness, and left-sided hemiparesis. His hand grasp was weak (MRC Scale, 4-), but he was able to grasp a small cylinder-shaped object; he could perform a good spherical grasp. Assessment scale scores were Modified Rankin Scale, 2; Barthel ADL Index, 100; NIHSS, 3; and Fugl-Meyer Hand Scale, 14.

CASE 4

A 63-year-old, right-handed man who had a left-sided anterior pontine stroke was studied 13 months after the ictus. He had mild right-sided hemiparesis. Hand grasp was weak (MRC scale, 4-), but he was able to grasp small objects and could perform a spherical grasp (pick up a small ball with his fingers). Assessment scale scores were Modified Rankin Scale, 2; Barthel ADL Index, 100; NIHSS, 6; and Fugl-Meyer Hand Scale, 14.

CASE 5

A 60-year-old, right-handed man who had a left-sided capsular stroke was studied 20 months after the ictus. He had right-sided facial weakness and mild weakness and spasticity in the right arm. His hand grasp was weak (MRC Scale, 4) with full-active mass flexion and some mass extension of all fingers. He could put his arm through the sleeve of an article of clothing, and he could carry some objects in his hand. Assessment scale scores were Modified Rankin Scale, 2; Barthel ADL Index, 100; NIHSS, 4; and Fugl-Meyer Hand Scale, 4.

CASE 6

A 53-year-old, right-handed man who had a left-sided capsular stroke was studied 50 months after the ictus. He had right-sided hemiparesis, was able to grasp a small object, and could perform a spherical grasp. He could pick up a fork or spoon and use it and was able to button a shirt. Assessment scale scores were Modified Rankin Scale, 2; Barthel ADL Index, 100; NIHSS, 2; and Fugl-Meyer Hand Scale, 14.

CASE 7

A 61-year-old, right-handed man who had a left-sided capsular stroke was studied 27 months after the ictus. He had right-sided hemiparesis with facial weakness and mild paresis of the arm and lower extremity with an almost normal gait. His hand grasp was weak (MRC Scale, 4), but he was able to grasp small objects and could perform a spherical grasp. Assessment scale scores were Modified Rankin Scale, 3; Barthel ADL Index, 90; NIHSS, 2; and Fugl-Meyer Hand Scale, 5.

RESULTS

No patient experienced any significant adverse effect.

EXPERIMENT 1

Figure 2 shows results of experiment 1 (Figure 2A) and experiment 2 (Figure 2B). Patients rapidly improved in peak pinch force and peak pinch acceleration after the first (postpractice 1) and second (postpractice 2) practice episode (peak force, $P = .004$; peak acceleration, $P < .001$; Figure 2A). Further practicing (practice 3) did not lead to additional improvement (average change in force because of practice 3 relative to practice 2 was as follows: 1.15; range, 0.74-2.05; $P = .46$; no significant correlation was found between motor performance and the number of training days during practice 3; $R = 0.12$; $P = .82$). Transcranial magnetic stimulation revealed no significant alteration in motor threshold or MEP amplitude in the practice flexor pollicis brevis muscle (Figure 2A).

EXPERIMENT 2

The regional anesthesia procedure provided a significant proximal (ie, upper chest, shoulder, and upper arm) but not distal (ie, forearm and hand) anesthesia (Figure 1):

regional effect of anesthesia on (1) skin anesthesia of shoulder and upper arm was present in all patients; (2) sensory threshold (Figure 1A), $P < .001$; (3) regional effect of anesthesia on strength (Figure 1B), $P < .001$; (4) effect of anesthesia on pinch force, $P = .41$ (mean [SD], 1.06 [0.05]; range, 0.94-1.11); and (5) effect of anesthesia on MEP size, $P = .48$ (mean [SD] MEP ratio during anesthesia/preanesthesia, 1.14 [0.43]; range, 0.67-1.74).

Hand motor practice during regional anesthesia produced an additional improvement in hand function as shown by a further significant increase in pinch force ($P = .02$) and pinch acceleration ($P < .001$) after practices 4 (postpractice 4) and 5 (postpractice 5) (Figure 2B). No significant change in pinch force was observed in the intact (contralateral) hand (mean [SD], 1.01 [0.06]; range, 0.92-1.06; $P = .21$). The behavioral improvement was associated with a significant increase in transcranial magnetic stimulation-evoked motor output to the practice muscle as indicated by a significant increase in MEP amplitude in the flexor pollicis brevis ($P = .02$; Figure 2B), whereas motor threshold was unchanged. The practice-induced increase in peak force during regional anesthesia was significantly correlated to the increase in MEP amplitude ($R = 0.86$; $P < .003$). Patients showed retention of the force gains 2 weeks later (mean [SD] force, 2.43 [1.09]; range, 1.43-4.09). At that time, 5 of the 6 patients reported significant functional benefits in some of their ADL: for example, "handgrip better"; "better hand control"; "can now hold pen, cup"; "hand strength better"; "hand feels more normal"; "thumb moves faster and in a new direction"; "can now hold small objects"; "writing a lot better and much longer"; "previously no such big steps"; and "helped in daily living."

COMMENT

The main result of this open-label experiment is that regional anesthesia of the upper arm during hand motor practice potentiates practice-induced improvements in hand motor function in patients with chronic stroke. In experiment 1 (practice), patients rapidly improved in hand motor function as indicated by a significant increase in peak pinch force and pinch acceleration after the first practice episode. They showed both retention of this improvement and additional improvement during the second practice episode, but further practicing did not lead to additional improvement indicating that the behavioral gain had quickly reached a plateau by the second practice episode.

In experiment 2 (practice and anesthesia), we aimed to enhance the effects of motor practice on hand function by depriving the motor cortex representations of the upper arm from their sensory inputs. We hypothesized that regional deafferentation-deafferentation of the upper arm during hand motor practice would enhance the cortical motor output to the hand, and that this enhancement would lead to an additional improvement in hand function that had reached a plateau by the previous practice episodes. This idea was based on recent studies that demonstrated that deafferentation-deafferentation of a body part in a healthy brain enhances cortical representations of adjacent body parts,¹⁰⁻¹⁷ and that this effect is increased by motor practice of the adjacent part.^{18,19} While

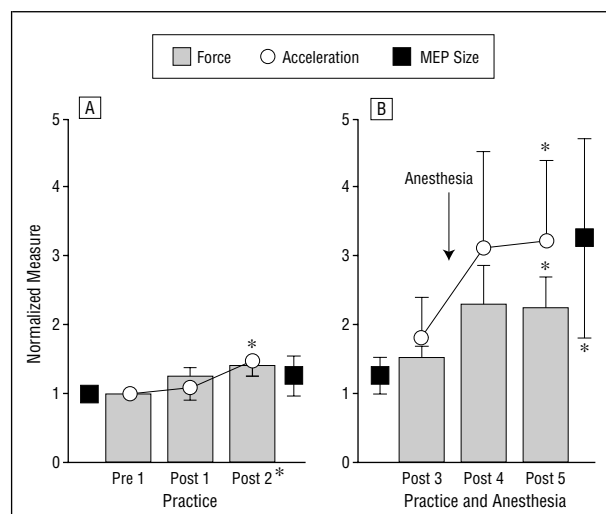


Figure 2. Effects of motor practice (A) and motor practice and anesthesia (B) on motor behavior and motor excitability in patients with long-term stroke. Data were normalized to the initial (prepractice 1) measure and given a value of 1.0. The numbers refer to the respective practice episode. MEP indicates motor evoked potentials; asterisks, $P < .05$; error bar, SEM; pre, before the initial practice session; and post, after each designated practice session.

this is a preliminary and uncontrolled study, in some sense by its design, the patients served as their own control group in experiment 1. Moreover, experiment 2 was biased against the anesthesia effect because if there was a limit to the extent of plasticity, all possible improvement might well have occurred in the first experiment.

Hand motor practice during regional anesthesia of the upper arm led to additional improvement in hand function as shown by a further significant increase in pinch force and pinch acceleration that had reached a plateau by the previous practice episodes. The failure to demonstrate significant changes in pinch force in the intact (contralateral) hand rules out nonspecific influences that are known to influence behavioral test measurements. Patients showed retention of the behavioral improvement on follow-up 2 weeks later, and at that time, 5 of the 6 patients reported functional benefits in some of their ADL.

The behavioral improvement was associated with a significant increase in transcranial magnetic stimulation-evoked cortical motor output to the practice muscles as shown by a significant increase in MEP amplitude in the training muscle, whereas motor threshold remained unchanged. This is analogous to the results reported in the biceps muscle during acute ischemic hand deafferentation-deafferentation,²¹ the conventional model to study rapid deafferentation-deafferentation-induced motor cortical reorganization in humans.^{14,22}

The cortical changes observed here may result from rapid alterations in the balance of excitation and inhibition which likely depend on the observation that neural representations have a larger region of anatomical connectivity than their territory of usual functional influence. Some motor cortical output zones may be kept in check by tonic inhibition (eg, via cutaneous inputs), and if the inhibition is removed (eg, by anesthesia), the region of influence can be increased rapidly.²³ It was shown that, following application of the γ -aminobutyric acid (GABA) antagonist bicuculline to the forelimb motor cor-

tex area of the rat, stimulation of the adjacent vibrissa area led to forelimb movements, suggesting that GABAergic neurons are critical for maintaining motor cortical representations.²⁴ In humans, application of the GABA agonist lorazepam inhibited practice-induced motor cortex reorganization.^{18,25} Another mechanism is strengthening or weakening of existing synapses, such as or long-term depression, 2 forms of synaptic plasticity described in the motor cortex^{26,27} as well as in other cortical areas. The dissociation of motor threshold (no change) and MEP amplitude (significant increase) in the present experiments suggests that the practice-induced changes in motor cortex excitability were primarily caused by changes in synaptic excitability, since MEP amplitude at suprathreshold stimulus intensity is particularly sensitive to changes in synaptic and postsynaptic excitability of cortical neural elements activated by transcranial magnetic stimulation. This is compatible with a long-term potentiationlike mechanism. A further possibility of anatomical changes (eg, synaptic proliferation)²⁸ is unlikely because of the rapid time course.

Independent of the precise mechanisms, our results illustrate that the principles of brain plasticity can have practical applications in stroke rehabilitation. Further controlled trials are necessary to prove the implications of these preliminary open-label experiments.

Accepted for publication March 25, 2002.

Author contributions: Study concept and design (Drs Muellbacher, Wittenberg, Boroojerdi, Cohen, and Hallett); acquisition of data (Drs Muellbacher, Richards, Ziemann, Wetz, and Boroojerdi); analysis and interpretation of data (Drs Muellbacher and Ziemann); drafting of the manuscript (Drs Muellbacher, Richards, Wetz, Boroojerdi, and Hallett); critical revision of the manuscript for important intellectual content (Drs Ziemann, Boroojerdi, Cohen, and Hallett); statistical expertise (Drs Muellbacher and Cohen); obtained funding (Drs Cohen and Hallett); administrative, technical, and material support (Drs Cohen and Hallett); study supervision (Drs Cohen and Hallett).

This study was supported by the Max-Kade-Foundation, Bonn, Germany (Dr Muellbacher).

We thank our patients for their cooperation; E. Consideine and P. Shelton for assistance; and D. G. Schoenberg, MSc, for skillful editing.

Corresponding author: Mark Hallett, MD, National Institutes of Health, National Institute of Neurological Disorders and Stroke, 10 Center Dr, Bldg 10, Room 5N226, Bethesda, MD 20892 (e-mail: hallettm@ninds.nih.gov).

REFERENCES

- Katz S, Ford AB. Prognosis after stroke, II: long-term course of 159 patients. *Medicine (Baltimore)*. 1966;45:236-246.
- Andrews K, Brocklehurst JC, Richards B, Laycock PJ. The rate of recovery from stroke—its measurement. *Int Rehabil Med*. 1981;3:155-161.
- Twitchell T. The restoration of motor function following hemiplegia in man. *Brain*. 1951;74:443-480.
- Merzenich MM, Nelson RJ, Stryker MP, Cynader MS, Schoppmann A, Zook JM. Somatosensory cortical map changes following digit amputation in adult monkeys. *J Comp Neurol*. 1984;224:591-605.
- Kaas JH. Plasticity of sensory and motor maps in adult mammals. *Annu Rev Neurosci*. 1991;14:137-167.
- Weinberger NM. Dynamic regulation of receptive fields and maps in the adult sensory cortex. *Annu Rev Neurosci*. 1995;18:129-158.
- Gilbert CD. Plasticity in visual perception and physiology. *Curr Opin Neurobiol*. 1996;6:269-274.
- Sanes JN, Suner S, Lando JF, Donoghue JP. Rapid reorganization of adult rat motor cortex somatic representation patterns after motor nerve injury. *Proc Natl Acad Sci U S A*. 1988;85:2003-2007.
- Donoghue JP, Suner S, Sanes JN. Dynamic organization of primary motor cortex output to target muscles in adult rats, II: rapid reorganization following motor nerve lesions. *Exp Brain Res*. 1990;79:492-503.
- Merzenich MM, Kaas JH, Wall J, Nelson RJ, Sur, Felleman D. Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation. *Neuroscience*. 1983;8:33-55.
- Donoghue JP, Sanes JN. Peripheral nerve injury in developing rats reorganizes representation pattern in motor cortex. *Proc Natl Acad Sci U S A*. 1987;84:1123-1126.
- Cohen LG, Bandinelli S, Findley TW, Hallett M. Motor reorganization after upper limb amputation in man: a study with focal magnetic stimulation. *Brain*. 1991;114:615-627.
- Kew JJ, Ridding MC, Rothwell JC, et al. Reorganization of cortical blood flow and transcranial magnetic stimulation maps in human subjects after upper limb amputation. *J Neurophysiol*. 1994;72:2517-2524.
- Sadato N, Zeffiro TA, Campbell G, Konishi J, Shibasaki H, Hallett M. Regional cerebral blood flow changes in motor cortical areas after transient anesthesia of the forearm. *Ann Neurol*. 1995;37:74-81.
- Kew JJ, Halligan PW, Marshall JC, et al. Abnormal access of axial vibrotactile input to deafferented somatosensory cortex in human upper limb amputees. *J Neurophysiol*. 1997;77:2753-2764.
- Pascual-Leone A, Peris M, Tormos JM, Pascual AP, Catala MD. Reorganization of human cortical motor output maps following traumatic forearm amputation. *Neuroreport*. 1996;7:2068-2070.
- Ziemann U, Hallett M, Cohen LG. Mechanisms of deafferentation-induced plasticity in human motor cortex. *J Neurosci*. 1998;18:7000-7007.
- Ziemann U, Muellbacher W, Hallett M, Cohen L. Enhancing practice-dependent plasticity in human motor cortex [abstract]. *Soc Neurosci Abstr*. 1999;25:788.
- Ziemann U, Muellbacher W, Hallett M, Cohen LG. Modulating practice-dependent motor cortical plasticity. *Brain*. 2001;124:1171-1181.
- Muellbacher W, Ziemann U, Boroojerdi B, Cohen L, Hallett M. Role of human primary motor cortex in rapid motor learning. *Exp Brain Res*. 2001;136:431-438.
- Ziemann U, Corwell B, Cohen LG. Modulation of plasticity in human motor cortex after forearm ischemic nerve block. *J Neurosci*. 1998;18:1115-1123.
- Brasil-Neto JP, Valls-Sole J, Pascual-Leone A, et al. Rapid modulation of human cortical motor outputs following ischaemic nerve block. *Brain*. 1993;116:511-525.
- Hallett M, Chen R, Ziemann U, Cohen LG. Reorganization in motor cortex in amputees and in normal volunteers after ischemic limb deafferentation. *Electroencephalogr Clin Neurophysiol Suppl*. 1999;51:183-187.
- Jacobs KM, Donoghue JP. Reshaping the cortical motor map by unmasking latent intracortical connections. *Science*. 1991;251:944-947.
- Butefisch CM, Lang DF, Gutmann L. Mechanisms of use-dependent plasticity in the human motor cortex. *Proc Natl Acad Sci U S A*. 2000;97:3661-3665.
- Abbott LF, Varela JA, Sen K, Nelson SB. Synaptic depression and cortical gain control [comments]. *Science*. 1997;275:220-224.
- Hess G, Donoghue JP. Long-term potentiation and long-term depression of horizontal connections in rat motor cortex. *Acta Neurobiol Exp (Warsz)*. 1996;56:397-405.
- Keller A, Arissian K, Asanuma H. Synaptic proliferation in the motor cortex of adult cats after long-term thalamic stimulation. *J Neurophysiol*. 1992;68:295-308.