Jpn J Rehabil Med 2010 ; **47** : 463–469

2009 年／第 4 回 リハビリテーション科専門医会 学術集会／諏訪

《**Invited Lecture**》

Strategies to treat Swallowing Disorders and Dysphagia*1

Arthur J Miller, PhD*2 and Koichiro Matsuo, DDS, PhD*3

Introduction

Treatment of dysphagia can use several mechanisms including increasing sensory input relevant to inducing swallowing, enhancing the regions of the central nervous system not damaged, and strengthening the motor system including increasing the use of the muscles active in swallowing.

Sensory System

The sensory system can be used in a strategy to treat a patient with dysphagia, and can involve increasing the intensity or frequency of stimulation of the sensory pathway, pairing multiple sensory stimulus sites, or pairing peripheral sensory stimulation with central cortical stimulation. These approaches are designed to improve or lower the threshold to trigger a pharyngeal swallow, which is an "all or none" reflex. Enhanced sensory stimulation can be from the oral and pharyngeal regions innervated by the trigeminal, glossopharyngeal, and vagal nerves[1–7] (**Table**). Multiple-site stimulation can involve scenarios like stimulating the glossopharyngeal nerve[8–11] or its mucosal receptive field with airpuffs during and prior to stimulating the internal branch of the superior laryngeal nerve (iSLN) receptive fields with drops of water or sour fluid. Using surface skin electrical stimulation of the iSLN has not been shown to work to induce swallowing, but the mechanism may need further refinements using other stimulation approaches (*i.e.*, transmagnetic stimulation coils).

Experimental studies in the anesthetized adult cat show that rubbing and touching the anterior faucial pillars with a probe that is at ambient or cold temperatures does not induce swallowing.[12] However, simultaneously probing the anterior faucial pillars while stimulating the iSLN evokes more pharyngeal swallowing than with iSLN stimulation alone. These data suggest that the thermal stimulation to the pillars excite trigeminal sensory fibers innervating this region, which, somehow and through a longer synaptic loop, facilitate the interneurons in the nucleus tractus solitarius (NTS) of the brain stem, triggering pharyngeal swallowing. In humans, administering air pulses uni- or bilaterally to the peritonsillar area evokes an irrepressible urge to swallow, followed by a pharyngeal swallow.[13] Based on many different sensory studies of swallowing, an ideal stimulus could be a complex stimulus involving a moving, highly patterned and textured object that would disintegrate to a flu-

*1 This paper is based on the invited lecture (chairperson : Ichiro Fujishima) in the 4th Annual Meeting of the Japanese Board-certificated Physiatrist Association at Suwa on October 17, 2009
*2 Professor, Division of Orthodontics, Department of Orofacial Sciences, School of Dentistry, University of California at San Francisco, San Francisco, CA, USA
E-mail : art.miller@ucsf.edu
*3 Associate Professor, Department of Special Care Dentistry, Matsumoto Dental University and Dysphagia Rehabilitation Clinic, Matsumoto Dental University Hospital, Nagano, Japan

Table Potential factors involved with rehabilitation in patients with dysphagia

			References
Sensory systems			
	Nerves	Trigeminal	Sweazey and Bradley, 1989[5]
		Glossopharyngeal	Kitagawa et al, 2002[11]
		Internal branch of the superior laryngeal nerve	Sinclair, 1970, 1971[8,9]
	Stimuli	Airpuffs	Theurer et al, 2005[13]
		Water	Sweazey and Bradley, 1988[4]
		Sour taste	Logemann et al, 1995[14]
		Touch/pressure	Capra, 1995[1]
		Cold	Chi-Fishman et al, 1994[12]
		Electrical stimulation applied directly to the faucial pillars	Power et al, 2004[29]
	Sites	Anterior faucial pillars	Chi-Fishman et al, 1994[12]
		Peritonsillar area	Power et al, 2004[29]
		Pharyngeal mucosa	Sinclair, 1970, 1971[8,9]
Central nervous system			
	Stimuli	Excitatory amino acids and norepinephrine injected into the brain stem	Bieger, 1981, 1998[18,19]
		Transcranial magnetic stimulation applied near the sensorimotor cortex region	Hamdy et al, 1999, 2000[40,41]
	Sites	Brain stem	Jean, 1990[15]
		Nucleus tractus solitarius	Jean and Tell, 1994[17]
Motor pathway			
	Stimulation	Placing bipolar stimulating electrodes in selected muscles like the geniohyoid and stimulating at near tetanic contraction levels	Mann et al, 2002[32] Burnett et al, 2005[34]
	Exercises	Use muscles involved in swallowing in vocalization exercises	Fox et al, 2006[26]
		Strengthen muscles through tongue exercises	Robbins et al, 2005[27]

id-like substance that includes a weak acid. Taste is an effective stimulus and sour substances have some affects to evoke swallowing.[14)]

Central Nervous System

The brain stem pathway for swallowing develops early, and in the prenatal period, well before cortical descending input becomes important. The brain stem central pathway controlling pharyngeal swallowing is almost like an imprinted neural circuit, which develops further postnatally. The major changes postnatally are that the cortex and higher central nervous system (CNS) regions become more important to modulating and affecting the threshold to induce swallowing and its intensity. The primary site for controlling the pharyngeal phase of swallowing is the nucleus tractus solitarius.[15,16)] Potentially, the NTS subnuclei could be altered by direct application of neural transmitters and growth factors as well as administering inhibitors to enzymes that degrade the neural transmitters.[17–19)] Injecting norepinephrine directly into the NTS in an experimental animal induces pharyngeal swallowing. The potential for microinjections of drugs into discrete regions of the brain, or specific arteries as with the vertebral blood supply, raise interesting questions on potential methods to induce swallowing. Ideally, a short-term application of a neurotransmitter, which would facilitate the brain stem swallowing pathway for a brief period without side effects, would be the most valuable approach.[19–21)] Even the placement of a long-term (*i.e.*, 2–3 month) biodegradable source of the neurotransmitter placed directly over the dorsal medullary region of the brain stem might prove valuable in rehabilitation.[22)] Among excitatory amino acid neural transmitters, glutamate can evoke a complete swallow or components of its response.[23,24)]

Motor Pathway

We can also alter the motor pathway as a method to improve swallowing in a patient with dysphagia. We can strengthen the motor output either by enhancing the synaptic drive to the motoneurons in a motoneuron pool that innervates a given muscle and/or strengthen the muscles innervated by the motoneuron pool. Muscles used in swallowing can be strengthened by exercises. The Lee Silverman Voice Treatment (LSVT) exercise has been shown to improve swallowing by its approach of improving vocal intensity and using a vocal exercise.[25] The oral transit time, the pharyngeal transit time, and vallecular residue decreased in Parkinson's patients who completed one month of the Lee Silverman Voice Treatment.[26] Tongue strength as well as swallowing improved with Parkinson's patients using the LSVT approach. Placing a subject on tongue exercises against resistance which involves applying pressure to a balloon-like object increases the strength and mass of tongue muscles, and as a result of this non-swallowing exercise, improves swallowing pressures on liquid boluses and reduces the penetration aspiration scores.[27] Exercises are effective in assisting the upper esophageal sphincter to open as the exercises strengthen the muscles that assist this opening, and the exercise develops a better biomechanical approach.[28] These exercises mean that a motoneuron is trained in one type of motor response that is not swallowing, but is more responsive during swallowing because its muscle fibers are stronger. But it is possible that just increased use of this motoneuron and the muscle fibers it innervates (*i.e.*, motor unit) enhance the central synaptic drive on this motoneuron. In addition, the type of use of the motor unit will modify the properties of its muscle fibers. Increasing the frequency of motoneuron use will enhance the blood supply to its muscle fibers and make them more fatigue resistant. Increasing force of contraction of the motor unit against a greater load will enhance the muscle fibers to develop greater cross-sectional area and, resultantly, more force.

Electrical Stimulation

Electrical stimulation has proved to be one form of modulating the swallowing pathway. Applying electrical stimulation to the human faucial pillars for 10 minutes in normal subjects at different frequencies did not necessarily induce swallowing but did modify the evoked potential in pharyngeal muscles induced by transcranial magnetic stimulation (TMS) applied to the sensorimotor cortex.[29] Bipolar surface electrode stimulation overlying the submental and laryngeal regions were tested as to its effect on laryngeal and hyoid descent in ten normal subjects.[30] Applying the same stimulation during pharyngeal swallowing reduced the larynx and hyoid bone peak elevation with the swallows, and was judged less safe based on the National Institutes of Health-Swallowing Safety Scale.[31] Inserting fine wires directly into the genioglossus muscle and stimulating through these bipolar hooked electrodes resulted in a significant increase in the hypopharyngeal airway.[32] Placing monopolar hooked wires into the mylohyoid, thyrohyoid, and geniohyoid muscles in normal subjects produced significantly greater elevation of the larynx, and has real potential to assist subjects with dysphagia who cannot elevate their larynx during a normal pharyngeal swallow.[33,34]

Electrical stimulation applied longitudinally to striated muscles can also have a direct impact on strengthening the muscles as shown in animal studies. A denervated muscle in an experimental animal can be maintained without losing muscle mass by stimulating the muscle with high frequency (*i.e.*, 100 Hz) to obtain a near tetani-like contractions for short bursts (20 pulses) at a high intensity to obtain a near 90 % of maximum isometric tetanic contraction, and repeating this often over a 24 hour period (*i.e.*, 200 contractions in 24 hours).[35,36]

Cortex

Functional magnetic resonance imaging has shown that multiple sites of the cortex are active during swallowing and vary slightly as to whether it is a spontaneous swallow or voluntarily elicited.[37–40]

Other approaches have identified similar sites.[41)] Studies in the awake primate, using intracranial microelectrode stimulation, demonstrate that swallowing can be elicited in an area lateral to the primary motor cortical face area (MI) and the primary sensory cortical face area (SI), as well as an area immediately lateral and/or anterior to the face MI.[42)] This same region may receive mechanical sensory input from sensory stimulation in the oral cavity including the tongue contacting other oral tissue as well as a bolus. Swallowing impairment is more common with bilateral hemispheric strokes, but can also occur with a unilateral infarction of either hemisphere.[43)] These results suggest that one side of the cortex plays a dominant role, and that role would include more control over the initiation and intensity of the swallow.

Relearning in a damaged brain as with swallowing in a patient following a stroke, requires the brain to reorganize to restore function. The brain continuously remodels its circuitry in order to learn in the normal state, and those properties apply to the undamaged portion of the brain in a subject with a CNS stroke.[44–48)] After focal ischemic infarct in a rat or monkey cortex, the adjacent undamaged cortex needs to become more active.[49,50)] Retraining of skilled hand or limb use results in prevention of loss of hand or limb territory adjacent to the infarct of the cortex with the permanent damage. Rehabilitative training in skilled reaching tasks with a limb can prevent the adjacent cortical regions from losing function and can reorganize their neurons.[51)] Such training must involve repetition to induce and maintain the neural plasticity. Rehabilitative training can shape subsequent reorganization of the adjacent intact cortex so that undamaged motor cortex may play an important role in motor recovery.[52,53)]

Rehabilitation after a cortical stroke inducing dysphagia may be assisted by increasing the use of a second pathway (*i.e.*, another sensory input) to compensate for the loss of the descending pathway from the cortex, which could normally be facilitatory. Consistent stimulation with several trials daily over a period of days to weeks would be expected to improve the swallowing pathway. It could be postulated that increased attempts to elicit pharyngeal swallowing in a patient with a cortical stroke would use alternate, undamaged cortical sites, and that enhancing the sensory input to these undamaged sites without evoking swallowing would lead to these cortical regions incorporating neurons around the site of damage, or with the contralateral cortical region which would have a similar function.[54,55)]

Transcranial magnetic stimulation can be applied to the pharynx to induce cortical evoked potentials in the sensorimotor cortex.[55,56)] Peripheral stimulation of the pharynx will increase the cortical representation and improves swallowing in patients with stokes. In these studies, the pharyngeal mucosa was stimulated for 10 minutes at 10-Hz with bipolar ring electrodes placed in an intraluminal catheter. The authors felt that the pharyngeal stimulation for 10 minutes enhanced the cortex excitability and not the brain stem because the pharyngeal stimulation for 10 minutes did not enhance reflexes elicited from stimulating the sensory nerves that would go through the brain stem swallowing pathway. Transcranial magnetic stimulation can excite peripheral nerves.[56)] Trigeminal and vagal nerve stimulation occurred with a 50-mm outer diameter figure-eight coil placed over the face for the trigeminal nerve, and over the neck for the vagus nerve, 2-cm below the angle of the jaw at the anterior border of the stenocleidomastoid muscle. This type of electrode stimulates a region around 2-cm^2. The trigeminal nerve is stimulated by putting the center of the electrode over the supraorbital branch of the trigeminal nerve and induces a bilateral blink reflex. Stimulation to the peripheral nerves is often given at the maximum tolerated intensity. However, the most effective transcranial magnetic stimulation may be with the cortex.[57)] Rehabilitation of swallowing might work in which the cortex is stimulated simultaneously with the new oral or pharyngeal stimulus. Transcranial magnetic stimulation and electrical stimulation can enhance skill training when applied to the motor cortex, and when applied to the affected hemisphere of a subject with unilateral stroke, improving motor function for a period of time.[58,59] Transcranial magnetic stimulation to the motor cortex can increase its excitability as has been done with training on fine digit movement.[60–62] Pairing peripheral nerve stimulation with transcranial magnetic stimulation of the cortex for a muscle of the limb will enhance the cortical stimulation in the future in recruiting that muscle.[63] The same approach could conceivably be used with the cortex regions important to swallowing in dysphagic patients. Hamdy and his group of researchers have felt that when a unilateral cortical lesion affects the dominant swallowing cortical hemisphere, recovery includes an expansion of cortical swallowing areas in the non-damaged hemisphere.[64]

Summary

So many of the approaches used to rehabilitate patients with sensory and motor diseases can be effective in potentially treating dysphagic patients. Many of the strategies need to be designed to address an impaired central nervous system in which the remaining intact CNS develops new neural connections.

References

1) Capra NF : Mechanisms of oral sensation. Dysphagia 1995 ; **10** : 235–247
2) Sweazey R, Bradley R : Responses of neurons in the lamb nucleus tractus solitarius to stimulation of the caudal oral cavity and epiglottis with different stimulus modalities. Brain Res 1989 ; **480** : 133–150
3) Sweazey R, Bradley R : Central connections of the lingual-tonsillar branch of the glossopharyngeal nerve and the superior laryngeal nerve in lamb. J Comp Neurol 1986 ; **245** : 471–482
4) Sweazey R, Bradley R : Response of lamb nucleus of the solitary tract neurons to chemical stimulation of the epiglottis. Brain Res 1988 ; **439** : 195–210
5) Sweazey R, Bradley R : Response characteristics of lamb trigeminal neurons to stimulation of the oral cavity and epiglottis with different sensory modalities. Brain Res Bull 1989 ; **22** : 883–891
6) Sweazey RD : Distribution of aspartate and glutamate in the nucleus of the solitary tract of the lamb. Exp Brain Res 1995 ; **105** : 241–53
7) Sweazey RD, Bradley RM : Response characteristics of lamb pontine neurons to stimulation of the oral cavity and epiglottis with different sensory modalities. J Neurophysiol 1993 ; **70** : 1168–1180
8) Sinclair W : Initiaion of reflex swallowing from the naso- and oropharnx. Am J Physiol. 1970 ; 221 : 956–90
9) Sinclair W : Role of the pharyngeal plexus in initiation of swallowing. Am J Physiol 1971 ; **221** : 1260–1263
10) Sinclair W : The pharyngeal plexus : an anatomical, histological and single unit analysis in the cat. [Ph. D. Thesis] : University of Toronto, 1975
11) Kitagawa J, Shingai T, Takahashi Y, Yamada Y : Pharyngeal branch of the glossopharyngeal nerve plays a major role in reflex swallowing from the pharynx. Am J Physiol Regul Integr Comp Physiol 2002 ; **282** : R1342–R1347
12) Chi-Fishman G, Capra NF, McCall GN : Thermomechanical facilitation of swallowing evoked by electrical nerve stimulation in cats. Dysphagia 1994 ; **9** : 149–155
13) Theurer JA, Bihari F, Barr AM, Martin RE : Oropharyngeal stimulation with air-pulse trains increases swallowing frequency in healthy adults. Dysphagia 2005 ; **20** : 254–260
14) Logemann JA, Pauloski BR, Colangelo L, Lazarus C, Fujiu M, Kahrilas PJ : Effects of a sour bolus on oropharyngeal swallowing measures in patients with neurogenic dysphagia. J Speech Hear Res 1995 ; **38** : 556–563
15) Jean A : Brainstem control of swallowing : localization and organization of the central pattern generator for swallowing. *in* Neurophysiology of the Jaws and Teeth (ed by Taylor A). MacMillan Press, London, 1990
16) Jean A, Car A : Inputs to the swallowing medullary neurons from the peripheral afferent fibers and the swallowing cortical area. Brain Res 1979 ; **178** : 567–572
17) Jean A KJ-P, Tell F : Nucleus tractus solitarii and deglutition : monoamines, excitatory amino acids and cellular properties. *in* Nucleus of the Solitary Tract (ed by Barraco IRA). Boca CRC Press, Raton, FL, 1994 ; pp 361–375
18) Bieger D : Role of bulbar serotonergic neurotransmission in the initiation of swallowing in the rat. Neuropharmacology 1981 ; **20** : 1073–1083
19) Bieger D : Deglutitive pharmacotherapy–a new angle ? Dysphagia 1998 ; **13** : 17–18
20) Bieger D : Hopkins DA : Viscerotopic representation of the upper alimentary tract in the medulla oblongata in the rat : the nucleus ambiguus. J Comp Neurol 1987 ; **262** : 546–562
21) Bieger D : Neuropharmacologic correlates of deglutition : lessons from fictive swallowing. Dysphagia 1991 ; **6** : 147–164
22) Byrd KE, Sukay MJ, Dieterle MW, Yang L, Marting TC, Teomim D, et al : Craniofacial and TMJ effects after glutamate and TRH microsphere implantation in proximity to trigeminal motoneurons of growing rats. J Dent Res 1997 ; **76** : 1437–1452
23) Hashim M, D B : Excitatory action of 5-HT on deglutitive substrates in the rat solitary complex. Brain Res Bull 1987 ; **18** : 355–363
24) Hashim MA, Bolger GT, Bieger D : Modulation of soli-

tarial deglutitive N-methyl-D-aspartate receptors by dihydropyridines. Neuropharmacol 1989 ; **28** : 923–929
25) Sharkawi A, Rmaig L, Logemann J, Pauloski BR, Rademaker AW, Smith CH, Pawlas A, Baum S, Werner C : Swallowing and voice effects of Lee Silverman Voice Treatment (LSVT) : a pilot study. J Neurol Neurosurg Psychiatry 2002 ; **72** : 31–36
26) Fox CM, Ramig LO, Ciucci MR, Sapir S, McFarland DH, Farley BG : The science and practice of LSVT/LOUD : neural plasticity-principled approach to treating individuals with Parkinson disease and other neurological disorders. Semin Speech Lang 2006 ; **27** : 283–299
27) Robbins J, Gangnon RE, Theis SM, Kays SA, Hewitt AL, Hind JA : The effects of lingual exercise on swallowing in older adults. J Am Geriatr Soc 2005 ; **53** : 1483–1489
28) Shaker R, Kern M, Bardan E, Taylor A, Stewart ET, Hoffmann RG : et al : Augmentation of deglutitive upper esophageal sphincter opening in the elderly by exercise. Am J Physiol 1997 ; **272** (6 Pt 1) : G1518–G1522
29) Power M, Fraser C, Hobson A, Rothwell JC, Mistry S, Nicholson DA, et al : Changes in pharyngeal corticobulbar excitability and swallowing behavior after oral stimulation. Am J Physiol Gastrointest Liver Physiol 2004 ; **286** : G45–G50
30) Ludlow CL, Humbert I, Saxon K, Poletto C, Sonies B, Crujido L : Effects of surface electrical stimulation both at rest and during swallowing in chronic pharyngeal dysphagia. Dysphagia 2007 ; **22** : 1–10
31) Humbert IA, Poletto CJ, Saxon KG, Kearney PR, Crujido L, Wright-Harp W, et al : The effect of surface electrical stimulation on hyolaryngeal movement in normal individuals at rest and during swallowing. J Appl Physiol 2006 ; **101** : 1657–1663
32) Mann EA, Burnett T, Cornell S, Ludlow CL : The effect of neuromuscular stimulation of the genioglossus on the hypopharyngeal airway. Laryngoscope 2002 ; **112** : 351–356
33) Burnett TA, Mann EA, Cornell SA, Ludlow CL : Laryngeal elevation achieved by neuromuscular stimulation at rest. J Appl Physiol 2003 ; **94** : 128–134
34) Burnett TA, Mann EA, Stoklosa JB, Ludlow CL : Self-triggered functional electrical stimulation during swallowing. J Neurophysiol 2005 ; **94** : 4011–4018
35) Dow DE, Carlson BM, Hassett CA, Dennis RG, Faulkner JA : Electrical stimulation of denervated muscles of rats maintains mass and force, but not recovery following grafting. Restor Neurol Neurosci 2006 ; **24** : 41–54
36) Dow DE, Dennis RG, Faulkner JA : Electrical stimulation attenuates denervation and age-related atrophy in extensor digitorum longus muscles of old rats. J Gerontol A Biol Sci Med Sci 2005 ; **60** : 416–424
37) Martin RE, MacIntosh BJ, Smith RC, Barr AM, Stevens TK, Gati JS, et al : Cerebral areas processing swallowing and tongue movement are overlapping but distinct : a functional magnetic resonance imaging study. J Neurophysiol 2004 ; **92** : 2428–2443
38) Martin RE, Sessle BJ : The role of the cerebral cortex in swallowing. Dysphagia 1993 ; **8** : 195–202
39) Martin RE, Goodyear BG, Gati JS, Menon RS : Cerebral cortical representation of automatic and volitional swallowing in humans. J Neurophysiol 2001 ; **85** : 938– 950
40) Hamdy S, Mikulis DJ, Crawley A, Xue S, Lau H, Henry S, et al : Cortical activation during human volitional swallowing : an event-related fMRI study. Am J Physiol 1999 ; **277** (1 Pt 1) : G219–G225
41) Hamdy S, Rothwell JC, Aziz Q, Thompson DG : Organization and reorganization of human swallowing motor cortex : implications for recovery after stroke. Clin Sci (Lond) 2000 ; **99** : 151–157
42) Martin RE, Kemppainen P, Masuda Y, Yao D, Murray GM, Sessle BJ : Features of cortically evoked swallowing in the awake primate (*Macaca fascicularis*). J Neurophysiol 1999 ; **82** : 1529–1541
43) Robbins J, Levine RL, Maser A, Rosenbek JC, GB K : Swallowing after unilateral stroke of the cerebral hemisphere. Arch Phys Med Rehabil 1993 ; **74** : 1295–1300
44) Monfils MH, VandenBerg PM, Kleim JA, Teskey GC : Long-term potentiation induces expanded movement representations and dendritic hypertrophy in layer V of rat sensorimotor neocortex. Cereb Cortex 2004 ; **14** : 586–593
45) Nudo RJ : Mechanisms for recovery of motor function following cortical damage. Curr Opin Neurobiol 2006 ; **16** : 638–644
46) Nudo RJ. Postinfarct cortical plasticity and behavioral recovery. Stroke 2007 ; **38** (2 Suppl) : 840–845
47) Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, et al : Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain 2005 ; **128** (Pt 3) : 490–499
48) Kleim JA, Barbay S, Cooper NR, Hogg TM, Reidel CN, Remple MS, et al : Motor learning-dependent synaptogenesis is localized to functionally reorganized motor cortex. Neurobiol Learn Mem 2002 ; **77** : 63–77
49) Kleim JA, Bruneau R, VandenBerg P, MacDonald E, Mulrooney R, Pocock D : Motor cortex stimulation enhances motor recovery and reduces peri-infarct dysfunction following ischemic insult. Neurol Res 2003 ; **25** : 789–793
50) Kleim JA, Jones TA, Schallert T : Motor enrichment and the induction of plasticity before or after brain injury. Neurochem Res 2003 ; **28** : 1757–1769
51) Taub E, Morris DM : Constraint-induced movement therapy to enhance recovery after stroke. Curr Atheroscler Rep 2001 ; **3** : 279–286
52) Hamdy S, Aziz Q, Thompson DG, Rothwell JC : Physiology and pathophysiology of the swallowing area of human motor cortex. Neural Plast 2001 ; **8** : 91–97
53) Hamdy S : The organisation and re-organisation of human swallowing motor cortex. Suppl Clin Neurophysiol 2003 ; **56** : 204–210
54) Hamdy S, Rothwell JC, Aziz Q, Singh KD, Thompson

DG : Long-term reorganization of human motor cortex driven by short-term sensory stimulation. Nat Neurosci 1998 ; **1** : 64–68

55) Fraser C, Power M, Hamdy S, Rothwell J, Hobday D, Hollander I, et al : Driving plasticity in human adult motor cortex is associated with improved motor function after brain injury. Neuron 2002 ; **34** : 831–840

56) Hamdy S, Aziz Q, Rothwell JC, Hobson A, Barlow J, Thompson DG : Cranial nerve modulation of human cortical swallowing motor pathways. Am J Physiol 1997 ; **272**（4 Pt 1）: G802–G808

57) Hummel F, Cohen LG : Improvement of motor function with noninvasive cortical stimulation in a patient with chronic stroke. Neurorehabil Neural Repair 2005 ; **19** : 14–19

58) Hummel FC, Cohen LG. Drivers of brain plasticity. Curr Opin Neurol 2005 ; **18** : 667–674

59) Hummel FC, Cohen LG : Non-invasive brain stimulation : a new strategy to improve neurorehabilitation after stroke ? Lancet Neurol 2006 ; **5** : 708–712

60) Pascual-Leone A, Cammarota A, Wassermann EM, Brasil-Neto JP, Cohen LG, Hallett M : Modulation of motor cortical outputs to the reading hand of braille readers. Ann Neurol 1993 ; **34** : 33–37

61) Pascual-Leone A, Cohen LG, Brasil-Neto JP, Hallett M : Non-invasive differentiation of motor cortical representation of hand muscles by mapping of optimal current directions. Electroencephalogr Clin Neurophysiol 1994 ; **93** : 42–42

62) Pascual-Leone A, Nguyet D, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M : Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. J Neurophysiol 1995 ; **74** : 1037–1045

63) Stefan K, Kunesch E, Benecke R, Cohen LG, Classen J : Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. J Physiol 2002 ; **543**（Pt 2）: 699–708

64) Hamdy S, Aziz Q, Rothwell JC, Singh KD, Barlow J, Hughes DG, et al : The cortical topography of human swallowing musculature in health and disease. Nat Med 1996 ; **2** : 1217–1224