

Motor rehabilitation and brain plasticity after hemiparetic stroke

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Abstract

This review intends to begin to build a bridge between our understanding of the effect of motor rehabilitation and brain plasticity on recovery after hemiparetic stroke. It discusses the impact of intensive post-stroke motor rehabilitation on motor recovery. This is followed by an overview of our current understanding, based on human brain mapping technologies, of brain plasticity underlying spontaneous recovery after hemiparetic stroke. These discussions lead to a descriptive review of human brain mapping studies that have begun to provide an understanding of the neural basis of rehabilitation-induced gains in motor function after stroke. Finally, it speculates on how a solid understanding of the neural underpinnings of spontaneous and rehabilitation-induced motor recovery will permit brain mapping technologies to be applied toward optimizing post-stroke motor rehabilitation.

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1. Introduction

Motor impairments, including hemiparesis, incoordination and spasticity, are the most common deficits after stroke.

Abbreviations: BOLD, blood oxygenation level-dependent; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; MEP, motor evoked potential; NIRS, near-infrared spectroscopy; PET, positron emission tomography; TMS, transcranial magnetic stimulation

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Most patients recover at least some of their lost motor function over time, though the degree of this recovery is variable. There is evidence that increasing the intensity of post-stroke therapy can enhance motor recovery. Brain mapping studies in patients have revealed that the brain reorganizes after stroke in relation to recovery of motor function. This review intends to begin to build a bridge between our understanding of rehabilitation efficacy and brain plasticity after stroke.

To this end, this review first discusses evidence that intensified motor therapy can improve motor recovery after stroke. Next, in order to best appreciate the study of brain

mechanisms underlying motor recovery in stroke patients, we discuss fundamental technical and conceptual features of those human brain mapping technologies that have contributed most to our current understanding of brain plasticity after stroke. This is followed by a descriptive review of what we have learned from these technologies about brain plasticity underlying spontaneous recovery after hemiparetic stroke. For further insights into brain plasticity associated with motor recovery, the reader is referred to other recent reviews on this topic (Herholz and Heiss, 2000; Boniface, 2001; Hallett, 2001; Thirumala et al., 2002; Calautti and Baron, 2003). We then provide a descriptive review of studies that have begun to provide an understanding of the neural basis of rehabilitation-induced gains in motor function after stroke. Finally, it speculates on how a solid understanding of the brain mechanisms underlying motor recovery occurring spontaneously and promoted by motor therapy will permit brain mapping technologies to be applied toward optimizing post-stroke motor rehabilitation in the future.

2. Motor rehabilitation after stroke

2.1. Standard motor rehabilitation

Standard motor rehabilitation after hemiparetic stroke typically involves an eclectic mix of approaches, including neurofacilitation techniques, task-specific training and task-oriented training. Neurofacilitation techniques encompass several approaches aimed at retraining motor control by promoting normal or inhibiting abnormal movement. Task-specific training is aimed at improving skill in performing selected movements or functional tasks. Task-oriented training focuses on retraining functional tasks by taking into account the interplay of many systems—including the musculoskeletal, perceptual, cognitive and neural systems.

The intensity of standard motor rehabilitation, involving physical and occupational therapies, varies considerably across patients in different post-stroke settings, though typically is about 30–60 min per day early after stroke, and tends to decrease later after stroke. The period of time during which stroke patients typically receive motor rehabilitation depends on their degree of impairment and functional deficits, though usually does not continue for more than 6 months. Under these typical conditions of post-stroke rehabilitative care, recovery of motor function has been observed to be most rapid during the first month post-stroke, to slow during subsequent months, and to plateau by 6 months post-stroke (Hendricks et al., 2002). Initial stroke severity substantially shifts this time course, such that stroke patients with milder motor deficits usually exhibit a truncated time course of motor recovery. After completing standard rehabilitation, approximately 50–60% of stroke patients still experience some degree of motor impairment (Hendricks et al., 2002), and approximately 50% are at least partially dependent in activities-of-daily-living (Gresham et al., 1995).

2.2. Intensive motor rehabilitation

Evidence suggests that intensive motor rehabilitation favorably impacts motor recovery in hemiparetic stroke patients. Meta-analyses and systematic reviews have concluded that greater intensity of therapy, provided by increasing the amount of therapy during the post-stroke period, modestly improves functional outcomes in stroke patients (Kwakkel et al., 1997; Steultjens et al., 2003; Teasell et al., 2003). Systematic reviews of the post-stroke rehabilitation literature have also suggested that the efficacy of post-stroke motor therapy is related to the degree to which the neuromuscular system is challenged by repetitive volitional movement (Duncan, 1997; Richards and Pohl, 1999; Woldag and Hummelsheim, 2002; Barreca et al., 2003). There are several rehabilitation approaches that are considered, according to current practice standards, to provide intensive rehabilitation by increasing the neuromuscular challenge to stroke patients. Further, these intensive rehabilitations have shown efficacy in improving motor function after stroke. For example, lower limb strength and function have been shown to be increased by progressive aerobic conditioning (Smith et al., 1999; Teixeira-Salmela et al., 1999), resistance training (Teixeira-Salmela et al., 1999; Weiss et al., 2000), and circuit training (Dean et al., 2000). Upper limb motor control and function have been shown to be improved by constraint-induced movement therapy (Taub et al., 1993; Kunkel et al., 1999; Miltner et al., 1999), bilateral training (Mudie and Matyas, 1996; Altschuler et al., 1999; Whittall et al., 2000; Hesse et al., 2003), robot-assisted training (Aisen et al., 1997; Volpe et al., 2000; Lum et al., 2002; Fasoli et al., 2003), and virtual reality training (Holden et al., 1999; Merians et al., 2002).

While few studies have explicitly addressed whether certain intensive therapies are more beneficial than others to particular patient subgroups, there is some evidence that this is true. Constraint-induced movement therapy, a training that aims to overcome learned-nonuse of the stroke-affected limb (Taub, 1994), was shown to produce greater gains in dexterity and functional use of the affected upper limb of chronic stroke patients with sensory disorder or hemineglect, respectively, than a neurodevelopmental therapy-based training of equal amount of time (van der Lee et al., 1999). In severely impaired stroke patients, greater improvements in motor function of the affected upper limb were induced by bilateral training, in which the unaffected limb simultaneously practiced selected functional tasks, as compared to unilateral practice of the same functional tasks (Mudie and Matyas, 1996). In contrast, in mildly impaired stroke patients, bilateral training of selected motor tasks tended to be less efficacious in improving aiming movements of the affected upper limb than unilateral training of same motor tasks (Platz et al., 2001). A particular intensive motor therapy may be most appropriate for a patient due to the goodness-of-fit between the neural status of the patient and neural consequences of the therapy. However, rehabilitation

specialists are currently limited to clinical examination and experience in determining the most appropriate rehabilitation approach for a patient.

Human brain mapping technologies offer the possibility of providing objective information about the neural status of a patient and neural consequences of a motor therapy to assist in selecting the optimal rehabilitation protocol. Human brain mapping technologies are currently used as basic research tools to understand brain plasticity mediating motor recovery occurring spontaneously, and have begun to be used to understand brain plasticity underlying motor recovery promoted by rehabilitation. Succeeding at these tasks will be necessary before a role for human brain mapping can expand into guiding post-stroke therapies, as well as in developing new efficacious therapies.

3. Brain plasticity and motor recovery after stroke

3.1. Human brain mapping technologies

Our current understanding of brain plasticity underlying spontaneous motor recovery has largely come from three human brain mapping technologies: transcranial magnetic stimulation (TMS) and the functional neuroimaging technologies—positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

TMS can be applied to evaluate motor cortex excitability in stroke patients. Using TMS, a stimulating coil is placed on the scalp over where the motor cortex resides. A brief, high-current pulse is passed through the coil. This current pulse induces a magnetic field that penetrates painlessly through the scalp, skull and underlying brain tissue, resulting in an induced current in the brain tissue. This induced current activates, indirectly, pyramidal cells of the corticospinal tract. As action potentials traverse these neurons, motor evoked potentials (MEP) are detected by electromyography in a contralateral target muscle, typically a finger muscle. Several parameters of the MEP can be measured to provide indices of motor cortex excitability, including threshold, amplitude, and size of the cortical area from where the potentials are evoked. TMS is usually done with the target muscle initially at rest. Therefore, TMS measurements are not dependent on subjects performing a particular movement. This feature makes TMS a tool amenable to studying motor cortex excitability in stroke patients, even those with hemiplegia.

Activation studies using PET or blood oxygenation level-dependent (BOLD) fMRI evaluate the brain's hemodynamic response to an "activation task" (e.g. a specified, repetitive hand movement). Brain areas with neurons actively involved in the activation task receive an increased supply of blood. PET and BOLD-fMRI exploit different aspects of this neurovascular response. PET relies directly on the increase in cerebral blood flow. A PET camera monitors emitted positrons just after intravenous injection of

a radioactive tracer substance, usually ^{15}O labeled water. The distribution of the radiolabeled substance is related directly to regional cerebral blood flow. BOLD-fMRI, in contrast, provides only an indirect measure of cerebral blood flow changes, relying on a complex and not yet fully understood set of physiologic events. BOLD-fMRI relies on the fact that oxygen consumption by active neurons is less than the increase in cerebral blood flow, resulting in a local net increase in oxygenated blood and net decrease in deoxygenated blood. The net decrease in deoxygenated hemoglobin iron in blood produces a change in magnetic susceptibility, resulting in an increase in magnetic resonance signal ($T2^*$) in brain tissue. Using PET or fMRI, brain areas with statistically significant increases in signal during the activation task, as compared to baseline (e.g. no movement) are interpreted as areas involved in processing information related to the activation task.

PET and fMRI have their particular advantages as methods for evaluating brain activation related to motor recovery after stroke. Functional MRI has the advantage of being non-invasive (i.e. no exposure to a radiolabeled substance). Further, the images collected using fMRI are of higher spatial and temporal resolution than PET (approximately 3 mm^3 versus 8 mm^3 ; approximately 2 s versus 5 min, respectively), permitting a more refined assessment of the spatial and temporal dynamics of brain activation associated with motor performance in stroke patients. However, the PET scanning environment is advantageous because it provides more physical space for subjects to perform limb movements and for ancillary equipment to monitor these movements. Further, the PET scanning environment provides more flexibility in the design of ancillary equipment because of the lack of high magnetic fields.

Other human brain mapping technologies have also begun to contribute to our understanding of brain plasticity associated with motor recovery after stroke, and each holds particular advantages that will be helpful in piecing together a complete understanding of the recovery process. Near-infrared spectroscopy (NIRS) is an emerging technology that non-invasively measures brain activation by monitoring changes in the absorption of near-infrared light by hemoglobin-containing species in cerebral blood. To its advantage, NIRS can be designed to be relatively insensitive to head motion, and uses compact instrumentation that makes it feasible for application in stroke patients at the bedside or in the rehabilitation facility. The temporal resolution of NIRS is similar to that of fMRI (approximately 1 s), though the sampling rate is typically several orders of magnitude greater than this, thereby allowing for more accurate detection of the evolution of the hemodynamic response. The disadvantages of NIRS, as compared to PET and fMRI, are its relatively poor spatial resolution (approximately 3 cm) and depth penetration (approximately 1 cm beneath the skull).

Magnetoencephalography (MEG) and electroencephalography (EEG) are methods that record the electromagnetic fields and induced electrical currents, respectively, generated

by neuronal activity. Whereas all the previously mentioned methods rely on a relatively slow hemodynamic response, MEG and EEG measures derive directly from neural activity signals that are significantly faster. MEG and EEG allow for measurement of brain activity with a high temporal resolution (approximately 1 ms), and like NIRS can be sampled at a much higher frequency. The spatial resolution of MEG/EEG, however, is relatively poor (approximately 5–10 mm). Efforts are currently being made to develop robust methods for combining from individual subjects high spatial resolution information of fMRI with high temporal resolution information of MEG/EEG. Such technical developments will aid in understanding the spatiotemporal processes underlying motor recovery in stroke patients.

3.2. Brain plasticity during spontaneous recovery from hemiparetic stroke

Human brain mapping studies conducted in hemiparetic patients have provided insight, albeit incomplete, into changes in brain function that parallel the natural history of motor recovery after stroke. TMS studies have observed early abnormalities in the excitability of ipsilesional motor cortex (i.e. motor cortex on the same side as the stroke) that tend to wane over time in association with motor recovery. Early after stroke (approximately 2 weeks), [Turton et al. \(1996\)](#) found reduced excitability of ipsilesional motor cortex, as compared to that of contralesional motor cortex, evidenced by an elevated threshold, reduced amplitude, and prolonged latency of MEP recorded from the contralateral paretic hand. Follow-up testing over the first year post-stroke showed improved MEP recorded from the paretic hand that coincided with or just preceded recovery of its motor function. In contrast, MEP recorded from the unaffected hand were relatively stable over this time period, suggesting that normalization of ipsilesional motor cortex excitability was functionally linked to recovery of paretic hand motor function. [Traversa et al. \(1997, 1998\)](#) similarly observed that early after stroke (approximately 2 months) the excitability of ipsilesional motor cortex was reduced, and also observed that the size of its motor map was reduced. Later after stroke (approximately 4 months) in association with improved clinical scores, ipsilesional motor cortex excitability and motor map size increased toward that measured in normal control subjects. Further, in the subgroup of patients with subcortical stroke, the extent of map size increase over time was correlated with the degree of motor recovery of the paretic hand ([Traversa et al., 1997](#)).

Several functional neuroimaging studies suggest that activity within the sensorimotor network, not exclusively ipsilesional motor cortex, is most abnormal early after hemiparetic stroke, and that motor recovery is related to normalization of its activity. [Calautti et al. \(2001a\)](#) observed that early after stroke (approximately 7 weeks), activation in several areas of the bilateral sensorimotor network was greater during paretic hand movement of patients

than hand movement of normal control subjects. Later after stroke (approximately 31 weeks) when the patients had experienced some motor recovery, activation in the sensorimotor network during paretic hand movement had somewhat normalized, though a restricted number of brain areas (ipsilesional premotor cortex, prefrontal cortex, putamen) newly exhibited excessive activation. Overall, [Calautti et al. \(2001b\)](#) found that from approximately 2–8 months post-stroke, greater gains in motor function of the paretic hand were associated with more normalization of hemispheric activation. In a study of chronic stroke patients, [Ward et al. \(2003a\)](#) found that poorer functional outcome was correlated with greater increases in several sensorimotor areas during paretic hand movement relative to that during hand movement of normal control subjects. In a subsequent longitudinal study by [Ward et al. \(2003b\)](#), activation early after stroke was observed to be increased in several sensorimotor areas during paretic hand movement as compared to that during hand movement of normal control subjects, and the magnitude of the excessive activation in patients was positively correlated with the initial severity of functional deficit. The degree of functional recovery over time in patients was correlated with decreased brain activation, toward a more normal pattern; there was no time effect in normal control subjects. In individual patients, some brain areas exhibited increased activation in relation to functional recovery, though these differences were not significant in group-level analysis. Cumulatively, these studies suggest that normalization of activation in the sensorimotor network, following early excessive activation, is generally linked to better motor recovery after stroke. Patient-specific increases in brain activation associated with motor recovery may reflect individual compensatory mechanisms for achieving improved motor control.

Some functional neuroimaging studies point more specifically to normalization in the laterality of activation in ipsilesional relative to contralesional sensorimotor cortex as related to recovery of motor function after stroke. [Marshall et al. \(2000\)](#) reported that early after stroke (less than 1 week), the laterality of activation in primary sensorimotor cortex during paretic hand movement was shifted toward the ipsilateral (contralesional) hemisphere, in comparison to the strongly contralateral activation during unaffected hand movement. Later after stroke (3–6 months) when these patients had experienced good recovery of motor function, primary sensorimotor cortex activation during affected hand movement had shifted toward normality, due to increased activation in ipsilesional primary sensorimotor cortex and decreased activation in contralesional primary sensorimotor cortex. In contrast, the laterality of primary sensorimotor cortex activation during unaffected hand movement was relatively stable. [Jang et al. \(2003a\)](#) similarly found that good motor recovery (from approximately 5 to 15 months post-stroke) in a group of patients was paralleled by a shift in the laterality of primary sensorimotor cortex activation during paretic hand movement from nearly bilateral to strongly

ipsilesional, whereas primary sensorimotor cortex activation during unaffected hand movement was stably lateralized to the contralateral hemisphere. Cumulatively, these studies suggest that normalization of sensorimotor cortex laterality is linked to good recovery of motor function after stroke.

However, some functional neuroimaging studies suggest that normalization of brain activation after stroke may be more linked to the integrity of ipsilesional sensorimotor cortex than to motor recovery. In a serial study, Feydy et al. (2002) observed that during the first 6 months after stroke when patients exhibited some degree of motor recovery, those with a lesion that included primary motor cortex tended to exhibit persistent activation in bilateral sensorimotor cortices, whereas those with a lesion that spared primary motor cortex tended to return to the normal laterality of sensorimotor cortex activation. The degree of motor recovery among these patients was not related to whether the pattern of sensorimotor cortex activation was lateralized or remained bilateral over the 6-month period. Rather, the degree of motor recovery was related to the extent of loss of the corticospinal tract, as measured by the degree of Wallerian degeneration observed on magnetic resonance images of the cerebral peduncle.

A study by Fujii and Nakada (2003) similarly suggested that the integrity of the ipsilesional sensorimotor cortex and its corticospinal tract is an important factor mediating the neural substrate of motor recovery. They found that the rate of motor recovery, and not the absolute level of motor function, related to the pattern of brain activation observed late (3–6 months) after subcortical stroke. In patients who experienced good recovery rapidly (within 1 month post-stroke), the pattern of brain activation during affected hand movement was similar to that observed in normal control subjects. In patients who made good recovery but slowly (by end of the third month post-stroke), an increased frequency of activation in contralesional sensorimotor cortex and supplementary motor area was observed. Patients who experienced poor recovery exhibited an increased frequency of activation in contralesional sensorimotor cortex and supplementary motor area, but to a lesser degree than those who experienced good recovery slowly. These data suggest that in patients with sufficient integrity of the ipsilesional sensorimotor cortex and its corticospinal tract, motor recovery may occur rapidly after stroke and be mediated by reacquisition of the normal dominance by the contralateral (ipsilesional) sensorimotor cortex. In patients in whom the integrity of this corticospinal tract is insufficient to support good recovery, increased recruitment of contralesional sensorimotor cortices may be utilized to achieve motor recovery. This later strategy for achieving motor recovery is consistent with prior studies in well-recovered chronic stroke patients that reported increased activation in ipsilateral (contralesional) sensorimotor cortex during affected hand movement as compared to that in normal control subjects (Chollet et al., 1991; Weiller et al., 1993; Cramer et al., 1997; Cao et al., 1998).

A key question raised by these human brain mapping studies is the degree to which contralesional sensorimotor cortex can compensate for lesions to the motor cortex and its corticospinal tract. Several lines of evidence suggest that activity of contralesional sensorimotor cortex cannot fully replace that of ipsilesional motor cortex. TMS studies suggest that the excitability of ipsilesional motor cortex is closely related to motor outcome (Bastings et al., 1997; Hendricks et al., 2003). As described above, Feydy et al. (2002) found that the degree of Wallerian degeneration of the corticospinal tract measured at the cerebral peduncles was correlated with the extent of motor recovery. Warabi et al. (1990) found that degeneration of the cerebral peduncles in chronic stroke patients could be no greater than 40% to achieve good recovery of motor function. Fujii and Nakada (2003) found that even among patients who recovered well but slowly, the frequency of ipsilesional sensorimotor cortex activation was greater than the elevated frequency of activation in contralesional sensorimotor cortex.

However, contralesional sensorimotor cortex appears to have some capacity to promote motor recovery. As mentioned above, Fujii and Nakada (2003) found that among slowly recovering patients, the frequency of contralesional sensorimotor cortex activation was greater in those who recovered well as compared to those who recovered poorly. Johansen-Berg et al. (2002a) found that patients with greater motor impairment showed relatively greater fMRI activation in contralesional premotor cortex during paretic hand movement. However, TMS-induced disruption of contralesional premotor cortex in these patients caused motor performance of the paretic hand to slow, and greater slowing was observed in those with greater activation in contralesional premotor cortex. In healthy normal adults, Strens et al. (2003) found that increased excitability of motor cortex functionally compensated for TMS-induced disruption of motor cortex in the opposite hemisphere. Cumulatively, these studies suggest that increased activity in contralesional sensorimotor cortices is an available mechanism for compensating, at least partially, for stroke-induced motor impairments.

3.3. Brain plasticity associated with motor rehabilitation after stroke

A PubMed (National Library of Medicine; <http://www.ncbi.nlm.nih.gov/PubMed>) literature search was conducted to identify studies that evaluated the effects of a motor therapy on motor and brain function in hemiparetic stroke patients. The literature search covered the period from 1966 to March 2004 and used the following keywords: stroke; therapy; motor; transcranial magnetic stimulation or motor evoked potentials; functional magnetic resonance imaging; positron emission tomography; near infrared spectroscopy; electroencephalography. Seventeen primary studies were identified, all of which were included in the descriptive review below since this field is in its infancy (Table 1). We classified the experimental design of these studies as

Table 1
Studies examining effects of motor therapy on motor and brain function in stroke patients

Study	Stroke patients (number recovery phase, impairment level)	Brain mapping method	Intervention	Comparison	Study design
Brouwer and Ambury (1994)	10 Subacute-chronic mild-moderate-severe	TMS	Weight-bearing	Normal control subjects	Quasi-experimental
Carey et al. (2002)	10 Chronic mild-moderate	fMRI	Index finger tracking	Randomized, cross-over patient and normal control groups	Experimental
Hummelsheim et al. (1994)	15 Subacute-chronic, severe	TMS	Manual stretching	Retrospective normal control subject	Non-experimental
Hummelsheim et al. (1995)	30 Subacute-chronic, mild-moderate-severe	TMS	5 Facilitation approaches	Normal control subjects	Quasi-experimental
Jang et al. (2003b)	4 Chronic, mild-moderate	fMRI	Functional upper limb training	Patient unaffected upper limb	Quasi-experimental
Johansen-Berg et al. (2002b)	7 Chronic, mild-moderate	fMRI	Modified constraint-induced movement therapy	Baseline period; patient unaffected upper limb	Quasi-experimental
Kopp et al. (1999)	4 Chronic, mild-moderate	EEG	Constraint-induced movement therapy	Patient unaffected upper limb	Quasi-experimental
Levy et al. (2001)	2 Subacute-chronic, mild-moderate	fMRI	Constraint-induced movement therapy	None	Non-experimental
Liepert et al. (1998)	6 Chronic, mild-moderate	TMS	Constraint-induced movement therapy	Patient unaffected motor cortex	Quasi-experimental
Liepert et al. (2000a)	9 Subacute, mild-moderate	TMS	Dexterity training	Baseline period	Quasi-experimental
Liepert et al. (2000b)	13 Chronic, mild-moderate	TMS	Constraint-induced movement therapy	Baseline period; patient unaffected motor cortex	Quasi-experimental
Liepert et al. (2001)	9 Subacute, mild-moderate	TMS	Constraint-induced movement therapy	Baseline period; patient unaffected motor cortex	Quasi-experimental
Miyai et al. (2002)	6 Subacute, severe	TMS	Facilitation	Control technique	Quasi-experimental
Muellbacher et al. (2002)	7 Chronic, mild-moderate	TMS	Upper arm anesthesia	Baseline period	Quasi-experimental
Nelles et al. (2001)	10 Subacute, severe	PET	Functional upper limb training	Control patient group; normal control subjects	Experimental
Schaechter et al. (2002)	4 Chronic, mild-moderate	fMRI	Constraint-induced movement therapy	Baseline period; patient unaffected upper limb; normal control subjects	Quasi-experimental
Wittenberg et al. (2003)	16 Chronic, mild-moderate	TMS, PET	Constraint-induced movement therapy	Control patient group; retrospective normal control group	Experimental

experimental (i.e. random assignment to experimental and control conditions), quasi-experimental (i.e. no randomization, but included a control condition), or non-experimental (i.e. no randomization or control condition) (Trochim, 2001). Note that the majority of these studies were not conducted as true experiments, which weakens their internal validity. Also note that the majority of the studies were conducted in stroke patients with chronic (greater than 6 months) motor impairments. This study design element strengthens its internal validity because motor function of chronic patients is typically stable at this time. Therefore, changes in brain function in chronic stroke patients associated with therapy-induced gains in motor function would be more likely due to the effects of the therapy than to spontaneous recovery. However, the results of studies that enrolled chronic stroke patients may have limited external validity because therapy-induced brain plasticity in patients late after stroke may not generalize to patients early after stroke. This review considers, in turn, the effect of neurofacilitation, task-specific, or task-oriented therapies on motor and brain function in stroke patients.

3.3.1. Neurofacilitation techniques

Neurofacilitation techniques are commonly used to increase recruitment of centrally paretic muscles, and thereby promote normal movement. Hummelsheim et al. (1995) used TMS to test the immediate effect of various facilitation approaches (cutaneous/proprioceptive; weight-bearing; proximal pre-innervation; contralateral pre-innervation; pre-innervation of target muscle) on MEP in the affected hand of subacute to chronic stroke patients classified by their level of upper limb motor impairment. They found that with the exception of the cutaneous/proprioceptive facilitation approach (i.e. tapping and rubbing the skin overlying the paretic target muscle), each approach improved parameters of the MEP (increased frequency, increased amplitude, reduced latency) in all patient groups and normal control subjects. Pre-innervation of the paretic target muscle (i.e. direct voluntary contraction) produced the most marked improvements in MEP. However, it was not tested whether the effects on MEP were mediated by changes in excitability at the level of the spinal cord or motor cortex, or both.

Neurofacilitation techniques include methods to inhibit abnormal muscle tone. The tone-reducing technique of weight-bearing through the affected upper limb (Brouwer and Ambury, 1994) and applying a sustained stretch to affected muscles (Hummelsheim et al., 1994) have been shown to favorably reduce muscle tone and improve the characteristics of TMS-induced MEP in affected muscles toward those observed in normal control subjects.

A study by Miyai et al. (2002) provides preliminary evidence that neurofacilitation techniques improve motor function in stroke patients by normalizing activity in the sensorimotor network. Using NIRS, they compared the effect on brain activation of a facilitation technique (i.e. manual facilitation at the pelvis) versus a control technique (i.e. manual assistance at the paretic foot or thigh) during treadmill-assisted gait with partial body weight support in subacute stroke patients. They found that the facilitation technique produced greater gains in gait performance. Activation in sensorimotor cortex (primary sensorimotor cortex, premotor cortex, supplementary motor area) during the control technique was weighted toward the contralesional hemisphere. In contrast, sensorimotor cortex activation during the facilitation technique was more symmetric, toward that previously observed in normal adults. One confound of this result, however, is that the two interventions applied somatosensory stimulations that differed in intensity and location on the body. It is therefore not clear whether the observed laterality shift in sensorimotor cortex activation during the facilitation technique relative to the control technique was simply due to differences in brain activity produced by the somatosensory stimulations or to changes in the neural control of gait, or both.

While these studies provide limited evidence that neurofacilitation techniques applied to stroke patients tend to normalize central, and possibly peripheral, components of movement, it is untested whether these neural effects are retained for any period of time after application of the neurofacilitation technique.

3.3.2. Motor task-specific training

A few studies have tested the effect of task-specific training on motor performance and brain function in chronic stroke patients. Carey et al. (2002), using a randomized cross-over design, intensively trained stroke patients with mild to moderate impairment to track waveforms with their paretic index finger. After the training period, and not after a control period of equal duration, the patients exhibited improved tracking accuracy as well as improved hand grasp and release function. These motor gains were associated with a shift in the laterality of activation in sensorimotor cortex (primary motor cortex, primary somatosensory cortex, premotor cortex) from largely contralesional to largely ipsilesional, detected using fMRI during paretic index finger tracking. Normal control subjects who received the same intensive training did not improve in tracking accu-

racy nor exhibit a change in the predominantly contralateral sensorimotor cortex activation. In healthy adults, increasing the amplitude (Waldvogel et al., 1999) and frequency (Rao et al., 1996) of finger movements has been shown to increase activation in contralateral sensorimotor cortex. Therefore, better matching of waveform amplitude and frequency may have contributed to the increased activation in ipsilesional (contralateral) sensorimotor cortex observed after training in patients. Nonetheless, this study suggests that motor gains produced by task-specific rehabilitation in chronic stroke patients are associated with normalization of sensorimotor cortex laterality.

Muellbacher et al. (2002) examined the effect of a novel strategy for improving paretic hand motor function in chronic stroke patients. Task-specific motor practice was coupled with modulation of ipsilesional motor cortex excitability. Previous studies in healthy adults have suggested that there is a competitive interaction between neuronal representations of the hand and upper arm in contralateral sensorimotor cortex (Kaas, 1991). Accordingly, Muellbacher et al. (2002) hypothesized that motor function of the paretic hand in stroke patients would be improved if the ipsilesional sensorimotor cortex representation of the paretic upper arm is inhibited, thus permitting increased neuronal activity of the paretic hand representation. To test this hypothesis, the paretic upper arm was transiently anesthetized so that its skin lost tactile sensation and its muscles lost strength. Under regional anesthesia, or unanesthetized, the paretic hand practiced a thumb-to-index-finger pinch grip. They found that paretic hand pinch strength and acceleration were increased after practice, more so under anesthesia than unanesthetized. Further, the gains in paretic hand pinch strength under anesthesia were correlated with increases in the amplitude of MEP recorded from the paretic hand with TMS to the ipsilesional motor cortex. The anesthesia-induced gains in pinch force were retained 2 weeks later. These findings suggest that the excitability of the representation of the paretic hand in ipsilesional motor cortex is affected by the sensorimotor status of body parts that neighbor the hand, and thereby the efficacy of motor training of a paretic hand.

3.3.3. Task-oriented training

The functional gains produced in stroke patients by task-oriented training, like those produced by neurofacilitation approaches and task-specific training, may be due to reestablishing control exerted by ipsilesional sensorimotor cortex.

Liepert et al. (2000a) examined the effects on dexterity and motor cortex function of a single task-oriented session focused on improving dexterity of the mildly to moderately paretic hand in patients early (4–8 weeks) after stroke. Using TMS, they observed that prior to training, the size of the representation in contralateral motor cortex was smaller for the paretic hand than the unaffected hand. Just after

training, most of the patients (seven of nine) exhibited improved dexterity. Paralleling this motor gain, the size of the representation in contralateral motor cortex of the paretic hand enlarged, whereas that of the unaffected hand was unchanged. Neither the behavioral nor the contralateral (ipsilesional) motor cortex change was retained 1 day after training.

Functional neuroimaging studies suggest that the functional gains produced in stroke patients by task-oriented training are associated with increased activity in ipsilesional primary sensorimotor cortex and redistribution of activity in several areas of the sensorimotor network. Nelles et al. (2001) compared the motor outcome of subacute, severely impaired stroke patients after random assignment to 3 weeks of intensive task-oriented training directed at improving affected upper limb function or standard rehabilitation. The experimental patients showed trends toward better motor recovery of the affected upper limb as compared to the control patients. Further, after therapy the experimental patients exhibited greater increases in activation in ipsilesional primary sensorimotor cortex and secondary sensorimotor cortices (bilateral inferior parietal cortex, bilateral premotor cortex), as measured by PET during passive movement of the affected elbow, relative to the control patients. Normal control subjects did not exhibit changes in brain activation when scanned twice over the same time period. Jang et al. (2003b) provided a home-based, task-oriented program designed to improve affected upper limb function in chronic stroke patients. After training, the paretic hand of patients showed greater gains in dexterity and grip strength than the unaffected hand. In parallel, they showed using fMRI that the laterality of activation in primary sensorimotor cortex, and in some cases secondary motor areas (premotor cortex, supplementary motor area), shifted from largely ipsilateral (contralesional) to largely contralateral (ipsilesional) during paretic finger movement, yet was stably contralateral during unaffected hand movement.

3.3.4. *Constraint-induced movement therapy*

Constraint-induced movement therapy is a task-oriented approach that has gained much attention in the rehabilitation community because of findings of significant functional gains of the paretic upper limb of chronic stroke patients (Taub et al., 1993; Kunkel et al., 1999; Miltner et al., 1999; van der Lee et al., 1999). The therapy combines intensive practice using the affected upper limb to achieve functional goals with restricted use of the unaffected upper limb (usually by means of wearing a sling) to prevent its habitual compensatory use. This combination of strategies is believed to be necessary to overcome the learned-nonuse that develops early after stroke from repeated failed attempts to use the affected upper limb (Taub, 1980). After constraint-induced movement therapy applied to patients with mild to moderate motor impairment, the most marked behavioral gain has been in self-reported use of the affected upper limb in activities-of-daily-living; less marked gains in motor control

parameters have also been found (Taub et al., 1993; Kunkel et al., 1999; Miltner et al., 1999; van der Lee et al., 1999).

Several small studies have applied human brain mapping technologies in an attempt to reveal changes in brain function that underlie the efficacy of constraint-induced movement therapy. The results of these studies have variously pointed to changes in activity in ipsilesional sensorimotor cortex, contralesional motor cortex, and perilesional cortex as related to the therapy-induced gains in motor function.

TMS studies suggest that normalization of activity in ipsilesional motor cortex underlies the functional gains in stroke patients after constraint-induced movement therapy. Liepert et al. (1998, 2000b, 2001) found that before therapy, the size of the representation in contralateral motor cortex was smaller for the paretic hand than the unaffected hand. After therapy, when functional use of the paretic upper limb had improved, the size of the paretic hand representation in contralateral motor cortex was enlarged, whereas that of the unaffected hand was not different, representing a return to the normal balance of excitability of the two hemispheres. Wittenberg et al. (2003) found that chronic stroke patients who received constraint-induced movement therapy made greater gains in function of the paretic upper limb than patients who received a less intense control therapy. TMS revealed a trend toward an increased ratio in the size of the contralateral motor cortex representation of the paretic hand relative to the unaffected hand in the experimental patients as compared to the control patients.

In the Wittenberg et al. (2003) study, the patients underwent PET scanning in addition to TMS. PET showed that before constraint-induced movement therapy, activation in contralateral primary sensorimotor cortex was greater during paretic hand movement than during hand movement of normal control subjects. After therapy, the experimental patients exhibited greater decreases in activation in contralateral primary sensorimotor cortex during paretic hand movement as compared to the control patients, toward the level observed in normal control subjects. In parallel, the TMS and PET results may appear paradoxical, yet might reflect differences in the physiologic basis of these brain mapping methods. Therapy that effectively improves paretic limb function might lower the firing threshold of neurons in ipsilesional motor cortex, resulting in MEP elicited from a larger cortical territory. A lower firing threshold might also translate into more efficient recruitment of neurons during performance of the prescribed motor task during PET, resulting in lesser increase in regional cerebral blood flow.

A role of ipsilesional secondary sensorimotor cortices in mediating the efficacy of constraint-induced movement therapy in chronic stroke patients is suggested by the Johansen-Berg et al. (2002b) study. They found that a home-based program modeled on constraint-induced movement therapy yielded greater strength gains of the paretic hand as compared to the unaffected hand of patients. Further, the gains in paretic handgrip strength were positively correlated with increased activation in ipsilesional premotor

cortex and secondary somatosensory cortex, as measured using fMRI during paretic hand movement. This result is particularly appealing because of the graded nature of the observed relationship between motor function and activation increases associated with the paretic hand.

Other brain mapping studies suggest that increased recruitment of contralesional sensorimotor cortices may be involved in the efficacy of constraint-induced movement therapy. Using EEG, Kopp et al. (1999) found that the source location of cortical potentials associated with paretic hand movement shifted anteriorly within the ipsilesional hemisphere immediately after therapy, and into the contralesional hemisphere 3 months later. In contrast, the source location associated with the unaffected hand was unchanged over time. These authors suggested that the delayed source shift into the contralesional hemisphere may reflect the hemisphere's increased contribution to control of paretic upper limb movement in association with progressively greater use of the limb in the real world. In an fMRI study, Levy et al. (2001) evaluated two stroke patients before and after constraint-induced movement therapy. The motor gains exhibited by one of these patients were accompanied by increased activation in both hemispheres, more contralesionally than ipsilesionally, during paretic hand movement. However, since activation patterns associated with the unaffected hand over time were not reported, it is difficult to draw conclusions from this finding. In another fMRI study, Schaechter et al. (2002) found that the motor gains exhibited by the paretic upper limb after therapy were associated with a trend toward a shift in the laterality of activation in motor cortex (primary motor cortex, premotor cortex, supplementary motor area) toward the contralesional hemisphere during paretic hand movement. The motor gains and laterality shift associated with the paretic upper limb were retained 6 months later. In contrast, the laterality of motor cortex activation associated with the unaffected hand of patients was unchanged over time. Cumulatively, these studies raise the possibility that in chronic stroke patients, motor gains of paretic limb produced by constraint-induced movement therapy may be mediated by shifting the balance of activity toward sensorimotor cortices of the contralesional hemisphere. Decreased use of the unaffected limb during constraint-induced movement therapy may contribute to a relative increase in the representation of the paretic limb in contralesional sensorimotor cortices.

Increased fMRI activation in perilesional cortex has been also reported in some cases after constraint-induced movement therapy. In the Levy et al. (2001) fMRI study mentioned above, the increased ipsilesional activation observed in the two patients after therapy bordered their respective lesion. Similarly, Johansen-Berg et al. (2002b) found that the increased activation in ipsilesional secondary somatosensory cortex detected after therapy bordered the lesion in two of the seven patients. Previous fMRI studies in chronic hemiparetic patients who recovered to varying degrees have also occasionally noted increased activation in perilesional cortex

during affected hand movement (Cao et al., 1994; Cramer et al., 1997). It is possible that integration of this tissue into the sensorimotor network controlling paretic hand movement is a mechanism supporting the motor gains promoted by efficacious rehabilitation.

It is noteworthy that these brain mapping studies provide no consensus of the neural mechanisms underlying the efficacy of rehabilitation, even when applying a single therapeutic approach—constraint-induced movement therapy. This may be due to several factors. One factor is that different technologies are sensitive to different neurophysiologic phenomena, as raised in regard to the Wittenberg et al. (2003) TMS-PET study. TMS is sensitive to the excitability of motor cortex. This is not equivalent to the neurovascular sensitivity of functional neuroimaging methods. While both technologies provide insight into the neural effect of rehabilitation, the neurophysiologic relationship between findings based on these technologies is currently unclear. Another factor may be that the neural and behavioral sensorimotor status of a patient prior to therapy predisposes a particular neural mechanism to mediate recovery induced by therapy. For example, therapy-induced brain plasticity may be influenced by changes in the sensorimotor network that occurred during spontaneous recovery, and the degree of damage to the ipsilesional motor cortex and its corticospinal tract. Accordingly, among a group of study patients, the detected change in brain activity after therapy may reflect the dominant neural and behavioral sensorimotor characteristics among the patients prior to therapy.

4. Speculation on future impact of human brain mapping on rehabilitation

The above review highlights that there is still much to be learned about the neural mechanisms underlying spontaneous and rehabilitation-induced motor recovery in hemiparetic stroke patients. There is evidence that both processes can involve a shift in brain activity toward more normal function. As well, there is evidence that both processes can involve compensatory changes that result in patterns of brain activity that diverge from normality (e.g. greater than normal activity in ipsilateral sensorimotor cortices and contralateral secondary motor cortices). Therefore, it is currently unclear if rehabilitation is efficacious by promoting the same neural processes that underlie spontaneous recovery, or by promoting compensatory changes in brain activity that would not occur spontaneously. The mechanism of rehabilitation efficacy may depend on several variables, including the rehabilitation approach, neural status of the patient, and time post-stroke.

Future studies that clarify the changes in brain activity that mediate efficacious motor rehabilitation will likely lead the way toward brain mapping being used to determine the optimal rehabilitation protocol in a stroke patient. The use of human brain mapping in this clinical capacity rests on

acquiring two sets of information. One set of information is the status of brain activity in the individual stroke patient. This could be accomplished using one or more probe tasks appropriate for the brain mapping technology applied. The resultant brain activity map would be used to identify brain areas for targeting motor rehabilitation. For example, in patients with sufficient sparing of ipsilesional motor cortex and its corticospinal tract, ipsilesional motor cortex might be targeted. In other patients with little sparing of ipsilesional motor cortex and its corticospinal tract, contralesional motor cortex might be targeted. The second set of information is the impact of rehabilitation approaches on activity of brain areas or networks mediating spontaneous and compensatory motor recovery in stroke patients. For example, task-specific training might prove to promote spontaneous motor recovery by normalizing ipsilesional motor cortex activity. In contrast, constraint-induced movement therapy might promote a compensatory increase in recruitment of an attentional network. Given these two sets of information, a prescription would be made by selecting the rehabilitation approach expected to most effectively promote the targeted change in brain activity in the stroke patient. Selection of the most appropriate rehabilitation approach could be fine-tuned by conducting on-line brain map testing, or brain mapping before and after a short trial of therapy. The brain map-based selection process could be repeated periodically, as the targeted change in brain activity and/or brain responsiveness to a rehabilitation approach may change as a function of motor status and time post-stroke.

Acquiring a more complete understanding of brain plasticity mediating spontaneous and rehabilitation-induced motor recovery will also open up the possibility of developing new rational post-stroke therapies. These new therapies would target changes in brain activity that underlie motor recovery. The therapies might be delivered via the peripheral nervous system, such as modifying somatosensory inputs to elicit specific changes in brain function. The new therapies might also be delivered directly to the central nervous system, for example by means of TMS to modify the excitability of a targeted brain area.

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