Translational Studies in Neurorehabilitation: From Bench to Bedside
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Abstract: Stroke is the leading cause of adult disability in the western world. Consensus has built over the last few years regarding the usefulness of training to improve motor disability resulting from stroke. Until recently, there were no accepted strategies to enhance the beneficial effects of training. However, the combination of basic and clinical science data over the last few years is changing this picture, and is highly relevant to the field of neurorehabilitation. Human studies in both healthy individuals and patients after brain damage demonstrate as a proof of principle that somatosensory input, cortical stimulation, interhemispheric interactions, and pharmacologic interventions can modulate cortical plasticity in neurorehabilitation after stroke. These findings strongly suggest directions in the development of novel strategies to enhance training effects on motor recovery. The intent of this review is to describe these strategies, the basic science principles on which they are based, and the clinical applications that have emerged so far.

Key Words: neuroplasticity, stroke, somatosensory stimulation, transcranial magnetic stimulation, direct current stimulation, dopamine, amphetamine

(Cog Behav Neurol 2006;19:1–10)

PLASTICITY OF THE CENTRAL NERVOUS SYSTEM

In healthy subjects, cortical representations can be modified by training and during acquisition of motor skills. This property of the nervous system to adapt in response to environmental changes is referred to as plasticity.1,2 Plasticity can also be elicited by lesions in the central and peripheral nervous systems and may occur in cortical and subcortical structures.3–7 Cortical reorganization can, depending on the settings, contribute to desirable behavioral developments, such as improved performance and learning (Refs. 2, 4, 6), or can be linked with outcomes such as phantom limb pain in some patients with amputations.8

IMPACT OF BASIC SCIENCE STUDIES ON HUMAN NEUROREHABILITATION

The primary vehicle to understand mechanisms underlying plasticity in the human central nervous system (CNS) has been animal research, from in vitro studies of single cells to the study of complex behaviors in whole organisms. Beginning in the 1970s, research from different laboratories9–11 showed that the adult mammalian CNS can reorganize after injuries. Animal work has provided us with an enhanced understanding of the mechanisms underlying recovery of brain injury, and identified strategies to purposefully modulate these mechanisms.12–14 These studies led to formulating hypotheses of potential relevance in clinical settings.

STATEMENT OF THE PROBLEM

So far, relatively few efforts have been invested in research that translates advances in the basic science domain to the formulation of new, rational strategies for promoting recovery of function in humans. To accomplish this goal, it is important to demonstrate that principles similar to those described in animal models apply to the human cerebral cortex in relevant behavioral settings. Testing these exciting hypotheses clinically, for example with multicenter clinical trials, would be very costly.15–17 In many cases, there is insufficient preliminary information to justify the expenses of a full-fledged multicenter trial. Additionally, strategies that have shown beneficial effects in animals may not be effective in humans.18 For example, the high-affinity glutamate antagonist MK-108 diminishes the size of an ischemic lesion in animal models, but has undesirable psychomimetic effects in humans.19 Other examples are the most effective calcium-channel antagonists, which diminish lesion size in animals, but would probably result in death in humans.20 These considerations have often delayed testing potentially useful interventions in neurorehabilitation. These problems emphasize the need to stimulate research that bridges basic and clinical science, creating the body of experimental evidence required to justify the expense incurred in the design of costly clinical trials. The urgency to develop this type of research is further strengthened by the contrast between the advances in basic science studies and the paucity of clinically effective treatments.

One example illustrates the problem. In the 1950s and 1960s, it was shown that d-amphetamine applied in

Received for publication November 17, 2005; accepted November 20, 2005.
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Cog Behav Neurol • Volume 19, Number 1, March 2006

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combination with motor training accelerated recovery of motor function in rodents after lesions of the motor cortex. Subsequent studies in rodents confirmed these results. Small clinical trials in the 1980s and 1990s showed similar beneficial effects in human patients after brain lesions secondary to stroke. It was only in 2002 that NINDS approved the first multicenter clinical trial testing the hypothesis that D-amphetamine, together with customary rehabilitative training, would be beneficial for motor recovery. Thus, it took 40 to 50 years to generate the body of preliminary evidence required to justify a multicenter clinical trial presently under way (PI Dr. Goldstein).

This paper describes experimental studies in humans that are intended to bridge basic science data and clinical applications, by providing the body of human experimental data required to design larger clinical trials. The overall hypothesis is that small, well-controlled human studies can provide important information regarding (a) mechanisms of human plasticity and (b) feasibility of proposals generated in the basic science domain for clinical application. These studies could provide the preliminary data required to design more effective clinical trials.

**EXPERIMENTAL PARADIGMS OF NEUROPLASTICITY IN HUMANS**

This section describes some of the paradigms most frequently employed in human experimental studies of cortical plasticity. With the help of these paradigms, it has been possible to evaluate changes in brain motor function and motor performance in healthy volunteers and patients with brain lesions. The following section is then devoted to strategies employed to modulate cortical plasticity.

**Motor Cortical Excitability**

Transcranial magnetic stimulation (TMS): TMS is a noninvasive tool used to deliver electrical stimulation to neural tissue, including the cerebral cortex. TMS can be applied as single pulses, pairs of stimuli separated by variable interstimulus intervals, or as trains of repetitive stimuli at various frequencies (repetitive TMS, rTMS). In rTMS, a train of pulses of the same intensity is applied to a single brain area at a given frequency that can range from 1 stimulus per second to 20 or more. The effect on cortical excitability can range from inhibition to facilitation, depending on the stimulation variables (especially frequency of stimulation). The suppression of excitability by low-frequency rTMS (in the 1 Hz range) is robust and outlasts the stimulation period. TMS can be applied to the motor cortex and to other brain regions to study brain-behavior relationships; for example, the contribution of ipsilesional premotor areas or contralesional motor and premotor areas in the recovery of motor function in patients with brain lesions such as chronic stroke. The technique of single-pulse TMS is also used for motor mapping and studies on cortical plasticity.

Direct current stimulation: Transcranial application of weak direct currents (transcranial direct current stimulation, tDCS) to the human primary motor cortex is capable of inducing cortical excitability changes. The direction of these modulations depends on stimulus polarity: anodal stimulation increases excitability, whereas cathodal stimulation diminishes it and may outlast the stimulation period for variable periods of time.

Paired-associative stimulation: Enduring changes in motor cortical output can be induced by paired-stimulation protocols that take advantage of the influence of somatosensory afferent input on intracortical motor cortical circuits. In this protocol, a peripheral nerve stimulus is paired with a single TMS pulse applied to the contralateral motor cortex to elicit a motor response. Ninety pairs of stimuli are delivered over a 3-minute period. This intervention results in a well-characterized increase in motor cortical excitability that evolves rapidly, is persistent, yet reversible, and topographically specific. The mechanisms underlying this particular effect are NMDA-receptor dependent. It has been proposed that this phenomenon is mediated by long-term potentiation (LTP)-like and long-term depression (LTD)-like mechanisms that may operate in human motor learning. However, direct experimental evidence in humans is lacking so far.

**Motor Memory Formation**

Motor memory formation (MMF) of thumb-movement representation: MMF can be studied with a variety of training protocols. A paradigm that has been extensively used to evaluate mechanisms of training-dependent plasticity in the human motor cortex and to evaluate the effectiveness of interventional strategies was first introduced by Classen et al in 1998. It uses a short period of training, consisting of simple, voluntary, repetitive thumb movements in a specific direction, to elicit reorganization within the cortical representation of the thumb that encodes the kinematic details of the practiced movement. In short, focal TMS of the motor cortex is used to evoke isolated and directionally consistent thumb movements. Thumb movements are then practiced in a direction different from the baseline direction for a total of 30 minutes. In most subjects, TMS subsequently evokes movements in or near the recently practiced movement direction for several minutes. To initiate a change of the TMS-evoked movement direction, 15 to 30 minutes of continuous training are required in most subjects.

This form of MMF may underlie the initial stages in acquisition of motor skills such as performance of complex motor sequences or playing the piano. The capacity of the motor cortex to store kinematic information in the short term, induced by motor training, may be important in longer-term procedural learning, which is
thought to involve the basal ganglia, cerebellum, and cortical networks such as the primary motor cortex. Movement repetition is likely to reinforce particular connections in the cortical neuronal network that weaken when practice stops. By analogy with the declarative memory system, storage and rehearsal of procedural information in short-term memory may then promote formation and consolidation of information in the longer term.

Recovery of function after brain damage requires extensive skills relearning. Thus, MMF may be one of the crucial functions that mediate recovery of motor function after stroke. This task has been used to study mechanisms underlying human neuroplasticity and interventions that could potentially enhance the effects of motor training, such as pairing amphetamines with motor training (Fig. 1).

Behavioral Paradigms Used to Study Motor Function

Finger tapping: Rapid finger tapping is a task that relies predominantly on activity originating in the primary motor cortex and that is conducted through fast corticospinal projections. Finger tapping correlates well with achievement of functional goals in patients with brain lesions undergoing neurorehabilitation. This task has also been used in studies assessing cortical reorganization and the effects of interventions on motor function in patients with stroke.

Pinch force: Pinch force has been used to assess motor performance and motor learning. In some paradigms, briefly practicing ballistic pinches improves peak pinch force and peak pinch acceleration and is accompanied by changes in motor cortical excitability. Measurements are carried out by having the subject hold the arm of the dynamometer between the lateral aspect of the middle phalanx of the index finger and the thumb pad to squeeze as hard as he/she can. Maximal peak pinch muscle strength [in newton (N)] is the primary outcome measure.

Jebsen-Taylor Test (JTT) of hand function: The JTT is widely used to assess a broad range of hand functions required for activities of daily living since 1969. The test has been validated and normal scores have been reported for different age and gender groups. The test evaluates both the dominant and nondominant hands using a series of 7 subtests related to activities of daily living (writing, simulation of turning pages, lifting small common objects, simulation of feeding, stacking checkers or lifting large, light, or heavy objects). The time required to complete gross motor, fine motor, weighted, and nonweighted activities is measured with a stopwatch. Time to complete the entire test (with a subanalysis of gross motor, fine motor, weighted, and nonweighted activities) is the primary outcome measure (Fig. 2). Complex force adaptation: Acquisition of motor skills such as accurate reaching or manipulating a tool
involves learning internal models of the dynamics of the task. The human brain designs motor commands based on a prediction of forces that will be experienced in the upcoming movement, such that the motor commands counter the effects of the predicted forces. An experimental motor learning paradigm has been developed to formally address this learning process. Participants are asked to execute reaching movements while holding a robotic arm with changing forces. Subjects have to learn how to move in different force fields. Accuracy and speed in adjusting to the changes in the force field, reflecting the acquired motor memories, are assessed as the primary outcome measure.

The above-mentioned protocols represent a few examples of strategies to evaluate behavioral gains in the motor domain.

MODULATION OF HUMAN PLASTICITY BY PHARMACOLOGIC MEANS

Drugs that promote LTP, neural sprouting, and synaptogenesis include enhancers of noradrenergic neurotransmission and dopaminergic agents, which influence plastic changes in the CNS. These drugs may benefit learning processes and functional recovery after brain damage. Consistent with this information, drugs that antagonize LTP-like mechanisms may delay recovery of function after brain injury.

Pharmacologic interventions can influence functional recovery in different ways. Clinical trials of pharmacologic agents in stroke have predominantly focused on events shortly after the acute insult, such as restoration of blood flow with thrombolytic therapy or reducing the effects of ischemia with neuroprotective therapy. However, thrombolytic therapy is only effective within the first few hours after the ictal event. So far, no neuroprotective therapy has proven to be useful within the first few hours after the ictal event.

In healthy humans, intake of a single oral dose of D-amphetamine can enhance MMF. Motor training 1 hour after receiving a single oral dose of 10mg D-amphetamine resulted in increased magnitude, faster development, and longer-lasting duration of MMF relative to placebo. It was also determined that D-amphetamine combined with motor training could elicit MMF in individuals poorly responsive to training alone.

In patients with stroke, clinical trials showed encouraging results indicating the usefulness of this drug in combination with rehabilitative treatment on motor and language function. At present, a multicenter, NINDS-funded clinical trial is under way testing this hypothesis. One concern about the use of drugs of this type is the possibility of potentially dangerous cardiovascular side effects, especially in elderly patients with frequently multimorbid conditions. Furthermore, physical and psychologic dependence cannot be excluded, which restricts its use.

Levodopa: It is well documented that endogenous dopamine modulates corticostral activity by enhancing transmission at active synapses while suppressing it at inactive ones. Dopamine seems to be a key regulator in specific synaptic changes observed during certain stages of learning and memory. Although most animal studies using indirect catecholamine-releasing drugs such as amphetamine favor a mainly noradrenergic mechanism of action for amphetamine (for a review see Refs. 70, 77), there is now accumulating data suggesting that dopaminergic function may also be effective. For example, Grondin et al found that dopaminergic therapy can improve upper limb motor function in elderly nonhuman primates. Moreover, dopamine agonists can reduce the severity of experimentally induced neglect whereas dopamine receptor antagonists re-instate neglect in recovered animals. One of the advantages of using dopaminergic agents relative to D-amphetamine is that it exhibits less side effects. Clinical trials on the effects of dopaminergic agents showed, similar to the ones on amphetamines, somewhat mixed results: in language rehabilitation, preliminary uncontrolled studies suggested that the administration of bromocriptine, a dopamine agonist, improved fluency in certain patients with aphasia. However, 2 small controlled studies found no differences. The lack of effect of dopaminergic agonists in patients with stroke might be due to the subtypes of the stimulated receptors; that is, whereas most of the orally available dopaminergic drugs stimulate mostly D2 and D3 receptors, levodopa has a wide action also stimulating D1 receptors. In motor rehabilitation, a small but randomized and placebo-controlled study demonstrated beneficial effects of levodopa premedication. However, the authors themselves ascribe the beneficial effects of their levodopa premedication to its conversion (rate of only 5%) in the brain to noradrenaline. At the same time, a randomized, double-blind study testing the effectiveness of ropinirole, a dopamine receptor agonist, in enhancing motor rehabilitation in chronic stroke patients, is under way, but still needs several years to be completed (Fig. 3).

Cholinergic agents: Central cholinergic neurotransmission through muscarinic receptor activation contributes to learning and memory formation and influences LTP. In humans, deficits in cholinergic transmission have been documented in conditions associated with memory loss such as Alzheimer disease and dementia whereas anticholinesterases seem to have a beneficial effect on cognitive performance. Additionally, acetylcholine and cholinergic agents enhance the relative
amplitude of LTP in neocortical structures, most likely by enhancing NMDA currents. Cholinergic agents such as the acetylcholinesterase inhibitors are already widely used to treat memory impairments due to Alzheimer disease (for a recent review see Ref. 101). They are safe but have potentially troublesome cholinergic side effects, including nausea, anorexia, diarrhea, vomiting, and weight loss. These adverse events are often self-limited and can be minimized by slow drug titration. In fact, a study by Sawaki et al. has recently demonstrated the influence of cholinergic neurotransmission on MMF in the human motor system, by using a cholinergic antagonist. Given the beneficial effects of these drugs on training-dependent plasticity, an exciting possibility in neurorehabilitation would be to pair these agents with rehabilitative treatments.

Drugs That Possibly Decrease Cortical Plasticity

Interest in this issue began with reports that stroke patients who received α-adrenergic blockers in the early stages after a stroke experienced poor functional recovery relative to those who did not. These observations are consistent with results from basic science studies that documented the deleterious effects of α-adrenergic antagonists on recovery of motor function. Altogether, these reports called for caution in administering drugs with α-adrenergic antagonistic action in patients recovering from brain damage. Studies in healthy humans showed that MMF in the motor cortex is similarly affected by drugs that interfere predominantly with α but also to some extent with β-receptor function. Using the paradigm of thumb-movement training, the authors found that α blockers (prazosin) led to substantially reduced training-induced plasticity. Therefore, caution should be exercised in the use of α and β blockers in neurorehabilitative settings.

In rehabilitative settings, experimental human studies may demonstrate potential differences between the effects of certain agents on animal models and on human patients. For example, traxodone is an antidepressant drug that impairs recovery from hemiplegia in rodents but may reduce disability in patients with poststroke depression. Therefore, similar to β blockers, the effects of antidepressants on functional recovery in humans seem to be different from the effects predicted based only on animal studies. In a recent review Goldstein points out that “...determining whether the detrimental effects of drugs anticipated from laboratory studies also occur in humans is difficult but important...” (p. 456).

MODULATION OF HUMAN PLASTICITY BY CORTICAL STIMULATION

TMS allows noninvasive focal stimulation of the human brain and may, in particular settings, enhance cortical reorganization and information processing. According to Hebbian principles, the potentiation of synaptic efficacy (LTP) occurs when its presynaptic and postsynaptic elements are simultaneously active. When inputs converge onto a target neural structure in temporal synchrony, they can enhance cortical plasticity. Application of TMS, at a time when the motor cortex is engaged in generating a training motion, may enhance plasticity in the motor cortex. Previous work demonstrated that TMS can increase the excitability of the primary motor cortex, enhance deafferentation-induced plasticity in humans, and induce LTP-like and LTD-like changes in slice preparations of cortical tissue. Butefisch et al. applied TMS to the motor cortex synchronously with individual voluntary training motions, in a paradigm similar to in vitro experiments in which stimulation of cortical afferents is paired with depolarization of the synaptic target neuron in a specific temporal relationship. The authors found that application of TMS in synchrony with the execution of the training movements led to a longer-lasting plastic change, compared with training alone or with asynchronous delivery of the stimulation. TMS can similarly enhance deafferentation-induced disinhibition in the
human sensorimotor cortex: Ziemann et al\textsuperscript{105} studied excitability changes of the biceps brachii muscles induced by low-frequency rTMS, with and without concomitant deafferentation of the ipsilateral hand muscles, and found enhanced and prolonged deafferentation-induced plasticity in healthy humans. This study not only suggests similar mechanisms for synaptic plasticity in animals and the intact human brain, but also carries significant clinical implications. They raise the possibility that noninvasive cortical stimulation could contribute to rehabilitative treatments in patients with brain lesions. One recent study using tDCS in the motor domain\textsuperscript{108} and one using TMS in the language domain\textsuperscript{109} are consistent with this view.

**SOMATOSENSORY INPUT**

Somatosensory input is required for accurate motor performance\textsuperscript{110} and skill acquisition.\textsuperscript{111} Reduction of such input by local anesthesia impairs motor control,\textsuperscript{112,113} as shown in patients with large-fiber sensory neuropathy who display characteristically abnormal motor behavior.\textsuperscript{114,115} In stroke patients, somatosensory deficits are associated with slower recovery of motor function.\textsuperscript{116}

**Prolonged Somatosensory Stimulation**

It has been proposed that somatosensory stimulation could operate as an adjuvant to rehabilitative treatments.\textsuperscript{117–119} Somatosensory stimulation leads to increased corticomotoneuronal excitability targeting the stimulated body site in humans. This functional change outlasts the duration of stimulation and seems to occur cortically.\textsuperscript{120,121} In the latter study, the authors explored the mechanisms underlying this phenomenon, and found evidence for the involvement of GABAergic receptor function within the motor cortex.

Conforto et al\textsuperscript{59} built on these findings to demonstrate the beneficial effects of somatosensory stimulation on motor function in stroke patients. They studied the effects of median nerve stimulation on pinch muscle strength (a function mediated predominantly by median nerve innervated muscles) in the paretic hand of chronic stroke patients. A 2-hour period of median nerve stimulation elicited an increase in pinch strength that outlasted the stimulation period. The improved muscle strength correlated with the intensity of somatosensory stimulation and was identified in the absence of motor training. It was concluded that somatosensory stimulation may be a promising adjuvant to rehabilitation of the motor deficits in stroke patients. However, the improvement in motor function was small and may not be clinically relevant. Subsequently, Wu et al\textsuperscript{112} explored the hypothesis that somatosensory stimulation could influence performance of tasks that mimic activities of daily living (JTT) in patients with chronic stroke. This study demonstrated that stimulation of 3 nerve trunks in the paretic hand, but not the paretic leg, shortened the time required to perform the JTT. Another group studied the effect of somatosensory stimulation on the lower extremity.\textsuperscript{123} Here, 4 weeks of daily dual stimulation (peripheral nerve and motor cortical stimulation) were applied to 9 patients with chronic motor impairment of the leg after hemispheric stroke. Parallel improvements in both neurophysiologic and functional measurements of the paretic leg were found.\textsuperscript{123} Therefore, results from different laboratories support the view that somatosensory stimulation may contribute to motor rehabilitation after a stroke.

**Deafferentation**

Deafferentation of contralateral body parts: Given the existence of physiologically active interhemispheric interactions between motor and sensory cortices,\textsuperscript{124–134} it is not surprising that somatosensory input from one hand could influence motor function in the other hand in the healthy CNS.\textsuperscript{132,133} In a recent study, Floel et al\textsuperscript{17} applied this principle of neuroplasticity, previously demonstrated in healthy volunteers,\textsuperscript{137} to a group of chronic stroke patients, and documented an improvement of approximately 20% in a motor task performed by the paretic hand with anesthesia of the opposite, healthy hand. This finding supports the view that somatosensory input from the healthy hand influences motor control in the paretic hand. It is possible that modulation of somatosensory input originating in the intact hand, in combination with motor training of the paretic hand, could enhance the beneficial effects of training alone, consistent with interhemispheric competition models of sensorimotor processing.\textsuperscript{134}

Deafferentation of adjacent body parts: Functional recovery of the proximal arm is often more prominent than that of the hand after stroke. As there is competition among body part representations for territory in the sensorimotor cortex, even limited activity of the upper arm representation 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.\textsuperscript{105} Muehlbacher et al\textsuperscript{60} explored whether deafferentation of the upper arm, produced by a technique of regional anesthesia during hand motor practice, helps recovery of hand function in patients with long-term stable weakness of their hand after stroke. They found that deafferentation 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 TMS-evoked motor output to the practice hand muscles. This approach may be tested and evolve into a novel therapeutic strategy to improve hand function after stroke.

In summary, motor performance of the paretic hand could theoretically be influenced by different operational strategies (Fig. 4), including reduction of somatosensory input from the intact hand, as in cutaneous anesthesia (Fig. 4, left), increased somatosensory input from the paretic hand\textsuperscript{59,117–119,135,136} (Fig. 4, right bottom), and...
anesthesia of a body part proximal to the paretic hand (upper arm, Fig. 4, right top).

CONCLUSIONS

Basic science findings over the last few years have led to advances in understanding the mechanisms underlying plasticity in the human CNS. However, despite the advances made in the field of basic neuroscience research, there is still a relative dearth of effective interventions in clinical neurorehabilitation. This mismatch could be partly attributable to the gap between the number of promising interventions evolving from basic science studies and the fraction of interventions eventually being tested in clinical trials. Given the medical and societal impact of stroke, bringing the findings from the basic science laboratory to the clinical setting more quickly and efficiently is of utmost importance. In this review, we have described several paradigms used in human neuroscience research and have illustrated in what ways these paradigms may be useful to study mechanisms of neuroplasticity. We also discussed the feasibility of proposals generated in the basic science domain for clinical application. We believe these studies are crucial for developing more rational strategies to promote recovery of function that may, in time, impact patient care.

REFERENCES


