Assessing and Inducing Neuroplasticity With Transcranial Magnetic Stimulation and Robotics for Motor Function

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ABSTRACT. O’Malley MK, Ro T, Levin HS. Assessing and inducing neuroplasticity with transcranial magnetic stimulation (TMS) and robotics—and to investigate and promote the recovery of motor function after brain damage.

OBJECTIVES: To describe 2 new ways of assessing and inducing neuroplasticity in the human brain—transcranial magnetic stimulation (TMS) and robotics—and to investigate and promote the recovery of motor function after brain damage.

DATA SOURCES: We identified recent articles and books directly bearing on TMS and robotics. Articles using these tools for purposes other than rehabilitation were excluded. From these studies, we emphasize the methodologic and technical details of these tools as applicable for assessing and inducing neuroplasticity.

STUDY SELECTION: Because both tools have only recently been used for rehabilitation, the majority of the articles selected for this review have been published only within the last 10 years.

DATA EXTRACTION: We used the PubMed and Compendex databases to find relevant peer-reviewed studies for this review. The studies were required to be relevant to rehabilitation and to use TMS or robotics methodologies. Guidelines were applied via independent extraction by multiple observers.

DATA SYNTHESIS: Despite the limited amount of research using these procedures for assessing and inducing neuroplasticity, there is growing evidence that both TMS and robotics can be very effective, inexpensive, and convenient ways for assessing and inducing rehabilitation. Although TMS has primarily been used as an assessment tool for motor function, an increasing number of studies are using TMS as a tool to directly induce plasticity and improve motor function. Similarly, robotic devices have been used for rehabilitation because of their suitability for delivery of highly repeatable training. New directions in robotics-assisted rehabilitation are taking advantage of novel measurements that can be acquired via the devices, enabling unique methods of assessment of motor recovery.

CONCLUSIONS: As refinements in technology and advances in our knowledge continue, TMS and robotics should play an increasing role in assessing and promoting the recovery of function. Ongoing and future studies combining TMS and robotics within the same populations may prove fruitful for a more detailed and comprehensive assessment of the central and peripheral changes in the nervous system during precisely induced recovery.

Key Words: Brain; Motor cortex; Neuronal plasticity; Rehabilitation; Robotics.

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The adult brain’s potential for reorganization of function has been supported by experiments using animal models to study use-dependent neuroplasticity,1,2 by functional brain imaging studies of patients undergoing training after sustaining focal brain lesions,3,4 and by imaging of changes in cortical representation associated with acquisition of skills in healthy human subjects.5 Extrapolation of neuroplasticity principles from research laboratories to rehabilitation settings is ongoing, but several obstacles continue to impede progress. In the case of recovery and reorganization of motor function, one limitation of functional magnetic resonance imaging (fMRI), at least in typical paradigms, is the requirement that the subject execute a movement. During early stages of recovery from stroke, many patients are unable to move their more affected limb sufficiently for motor mapping by fMRI. Another limitation of fMRI is the inability of some patients to tolerate confinement in the scanner, and the logistics of scheduling and transportation can be problematic, especially when repeated measurement is specified by the study design. As described below, transcranial magnetic stimulation (TMS) mitigates these problems because no motor response is required, the procedure can be performed on the rehabilitation unit, and the patient can be seated comfortably during mapping. TMS also offers the capability of inducing neuroplasticity via repetitive stimulation, thus facilitating intervention studies.

Clinical trials that apply principles of neuroplasticity, as in novel therapies such as constraint-induced movement therapy (CIMT), have also been challenged by logistics and treatment fidelity. These limitations include, among many others, the extensive human resources needed to provide several hours of daily treatment with an individual therapist, and the potential variation in treatment technique across different therapists. Robotics, although perhaps introducing other limitations for providing therapy including an initial investment of resources and time for equipment acquisition and training, could overcome or at least mitigate these limitations by economically, efficiently, and precisely providing repetition of guided movement while preserving oversight by a therapist. Manipulation of the parameters of motor training, including repetition, timing, stimulus displays, and the distance and resistance required for the patient’s movement can all be better controlled by robotics than with a therapist. Feedback systems, which use algorithms for changing response requirements depending on the patient’s performance, can also be more consistently implemented and flexibly changed through robotics. Similarly, data generated by the patient’s movement can be more reliably recorded by the device than through human interaction. Depending on the goals and design of a study, some combination of robotics and therapist interaction may be specified. In any
case, the initial studies reviewed below lend support to the expectation that both TMS and robotics will increasingly be used in translational and clinical intervention studies designed to enhance neuroplasticity and improve patient outcomes.

TRANSCRANIAL MAGNETIC STIMULATION

TMS is a relatively new, noninvasive technique that produces transient disruptions in brain activity. Although its roots date back to over a century ago when several scientists attempted to stimulate the brain with a magnetic pulse, these early attempts of magnetic stimulation generated through various different types of devices were for the most part unsuccessful. In 1980 and 1985, however, the first reports of successful cortical stimulation using TMS were published. Today, TMS is being routinely used to investigate human brain function and also particularly for assessing as well as inducing neuroplasticity noninvasively.

The technique of TMS complements other neuroscientific techniques for examining plasticity, such as fMRI, by providing high temporal as well as spatial precision for studying, assessing, and altering brain function. Furthermore, like traditional patient lesion studies in neurology and neuropsychology, and unlike functional imaging studies that measure correlations between brain activation and function, TMS allows for examination of whether a particular brain area is necessary for a given function. In this regard, TMS frequently has been referred to as producing “virtual lesions,” inducing similar behavioral manifestations as naturally occurring lesions. (For a comparison of natural vs TMS-induced lesions on visual function, see Ro and Rafal.) Unlike naturally occurring lesions, however, TMS can only influence surface brain structures that are close to the scalp because the strength of the magnetic flux drops off rapidly with increases in distance from the stimulating coil. In addition, TMS can be safely applied to humans in ways similar to the direct stimulation of cortical neurons often conducted in presurgical mapping procedures and in nonhuman primate neurophysiology studies, albeit with far less spatial resolution. This allows for a more direct comparative approach with previous neurophysiologic studies investigating brain-behavior relations. It therefore provides one of the strongest new tools for human neuroscience investigation and affords many potential ways for assessing and inducing neuroplasticity.

The physical principles and technologic requirements of TMS are reasonably simple and straightforward. In brief, TMS uses a small but strong and focused magnetic pulse that is administered through a stimulating coil, usually composed of copper strips with a plastic casing, held on the surface of the head (fig 1). The magnetic flux is generated by passing a very brief electric current through the stimulating coil. This magnetic pulse, which travels through the scalp and skull, consequently induces current into the brain. Thus, the size and extent of the magnetic pulse is highly dependent on the spatial configuration of the stimulating coil and the position in which it is held. Many commercially available coils in different sizes and configurations are available, but most studies typically use a focal figure-8 coil with 45- or 70-mm circular components or a larger, less focal circular coil. In terms of cortical volume affected by these coils, some estimates have suggested that the focal figure-8 coils can stimulate as little as approximately 1cm³, but the true extent and depth of stimulation from induced current spread remains unknown. Nonetheless, we have shown that subcentimeter resolution can be obtained by systematically moving the focus of the figure-8 coils in 1-cm steps to demarcate borders of cortical regions. Furthermore, when stimulating with 45-mm figure-8 coils, twitches restricted to an individual finger can frequently be evoked, further suggesting a fairly restricted site of action of the TMS on cortex.

TMS can also be administered with repetitive trains of TMS pulses at varying intensities and frequencies. Because the effects on neuronal activity are short lived with single-pulse TMS, the on and off of tens to only a few hundred milliseconds, repetitive transcranial magnetic stimulation (rTMS) ensures that the neuronal disruptions occur for longer periods of time. It has also been shown that rTMS at certain frequencies for extended periods of time can induce longer-lasting changes in cortical function. For example, with rTMS delivered at approximately 1Hz for 15 minutes, it has been shown that cortical excitability decreases for at least 15 minutes after the rTMS, but curiously it has no effect on motor behavior as assessed with finger tapping speed measurements. Conversely, rTMS delivered at higher frequencies (eg, 10Hz) can increase cortical excitability for up to 3 or 4 minutes. These frequencies relate well to the known neurophysiologic properties for inducing long-term potentiation and long-term depression. Whether rTMS is used during a task or to induce lasting changes in cortical function, the temporal resolution is sacrificed because the precise timing of when neural events might be occurring cannot be determined. Thus, high temporal resolution can be obtained only when using single-pulse TMS.

TMS for Assessing Neuroplasticity

Single-pulse TMS has been shown to reliably and efficiently localize the hand area of the motor cortex, as well as to detect changes in cortical motor representation. When stimulating over the hand area of the motor cortex, in addition to observable twitches that are induced in the contralateral hand, motor-evoked potentials can be reliably recorded, and several criteria have been established to determine the motor threshold intensity for a given subject. Because there is tremendous variability in the effective TMS intensities (ie, motor thresholds) across subjects, it is essential that the motor threshold intensity be established in each subject. Using these and other measures for examining motor function, several recent studies have taken advantage of the noninvasive, effi-
cient, and highly effective technique of TMS for assessing motor neuroplasticity after extensive practice or brain damage. In one of the first studies showing rapidly induced changes in motor representations with TMS, it was elegantly shown in neurologically normal participants that the implicit learning of a motor sequence can enlarge the cortical output representations for movement of the hand that is performing the movement sequence. Classen et al. have further shown that practice and performance of a given movement can transiently alter subsequent motor representations as assessed with TMS.

It has also been shown that single-pulse TMS can be used effectively and safely to map changes in motor representations in patients with motor deficits consequent to stroke. For example, several studies have shown that CIMT is effective for inducing central nervous system (CNS) reorganization and motor recovery, as assessed by changes in motor representations of the more affected limb with single-pulse TMS. Furthermore, in a recent study done in collaboration with several other investigators from the Texas Medical Center, we examined the effectiveness of CIMT in acute stroke patients by measuring motor performance as well as motor reorganization using single-pulse TMS.

Our CIMT protocol involved constraining the less affected upper extremity of the hemiparetic stroke patients for about 2 weeks while they underwent extensive motor training. Motor performance and CNS reorganization were assessed with TMS at baseline, after 2 weeks of CIMT, and at a 3-month follow-up. For the TMS mapping, an abbreviated version of the criteria defined by Rossini et al. was used to determine whether a given cortical site was involved with or recruited for motor function. We found that motor recovery at 3 months poststroke, as assessed through several functional outcome measures, was highly correlated with CNS reorganization as measured with TMS over the motor cortex (fig 2). Importantly, whereas some of the earlier patients in our study could not complete fMRI scanning to assess motor recovery, all of the

Fig 2. Motor recovery at 3 months poststroke, as assessed through several functional outcome measures, correlated highly with CNS reorganization as measured with TMS over the motor cortex. For this figure, following systematic mapping of motor-evoked responses from TMS over a grid centered on motor cortex, the region of cortex from each patient that induced movement of the contralateral hand was overlaid on the Montreal Neurological Institute template brain in Matlab. Adapted from Ro et al.
patients tolerated TMS well and could be conveniently tested, even at bedside in some cases. These results highlight that TMS can provide a very effective, low-cost means for assessing the effects of rehabilitation and neuroplasticity over time. Furthermore, with the portability of some of the available TMS systems, repetitive testing can easily be done even at bedside and therefore it may be more feasible than many other techniques at assessing plasticity.

TMS for Inducing Neuroplasticity

Several investigators have also taken advantage of the potential short- and long-term changes associated with the application of TMS of the cerebral cortex. Thus, in addition to being able to map changes in brain organization with TMS, recent studies have been showing that it may be possible to induce plasticity or recovery of function by selective stimulation of the cerebral cortex. A series of studies conducted in patients with hemispatial neglect after parietal cortex damage have shown that either single-pulse or low-frequency repetitive TMS of the unimpaired, contralesional hemisphere may restore perceptual imbalances can effectively be restored.

The potentially restorative effects from repetitive TMS have also been tested in patients with motor cortex damage. As in the previous studies that were attempting to restore function and induce plasticity in patients with neglect, a recent study has focused on repetitively stimulating the contralesional hemisphere in attempts to restore interhemispheric inhibitory balances and consequently motor function and behavior. In this study, Mansur et al showed that repetitively stimulating the contralesional motor cortex with low frequencies leads to subsequently improved motor functions. Importantly, this rTMS-induced improvement occurred only when stimulating over the contralesional motor cortex and not with premotor cortex or sham stimulation. Research establishing the optimal parameters for the most effectively and efficiently induced neuroplasticity remains to be completed.

Khedr et al at the Assiut University Hospital in Egypt have further shown that higher frequency rTMS over the more affected motor cortex itself can also lead to improved motor function compared with sham rTMS. Thus, motor plasticity and improved outcome with rTMS can be induced either by low-frequency rTMS over the less affected hemisphere or high-frequency rTMS over the more affected hemisphere. Taken together, these findings using TMS show the vast potential that this relatively new technology has on assessing and promoting neuroplasticity and rehabilitation. With modifications and extensions of its applications, the use of TMS has progressed from an assessment and diagnostic tool to one that can also be used to directly induce changes within the CNS.

ROBOTICS FOR REHABILITATION

Concurrent with development of TMS as a technology for assessment and intervention in rehabilitation-related research, the potential of robotics for training motor skills and studying the effects of novel treatment protocols has been recognized. Recent developments in rehabilitation engineering suggest that it is timely to investigate the use of robotics as a means to reduce the resources required to implement intensive motor training of impaired limbs in stroke patients and to facilitate home-based treatment.

Robotics-Assisted Rehabilitation

Clinical studies have shown that the injured motor system is capable of reorganization in the setting of motor practice. Indeed, stroke recovery may continue for months after initial onset because of cortical plasticity. In light of such implications, therapeutic exercise has become the cornerstone of rehabilitation efforts after stroke. The goals of classical arm therapy in neurorehabilitation include recovery of motor function, improvement of movement coordination, training of new motion strategies, and prevention of secondary complications including, but not limited to, spasticity. In order to deliver therapy, physical treatment strategies have taken several approaches. Examples include repetitive training of isolated movements, CIMT to overcome learned nonuse of the paretic limb, bilateral practice to facilitate movement of the paretic extremity, and robot-aided rehabilitation to increase intensity and/or duration of therapy.

Although several studies have shown improved motor outcome with short and distributed therapy schedules, clinical findings also indicate that increases in either training intensity or training duration can yield moderate positive effects on neuromuscular function and the patient’s execution of activities of daily living (ADLs). Because treatment duration and intensity can have such a profound effect on motor recovery, the use of robotics is well suited to improve rehabilitation outcomes. Robotics, as an assistive technology, can be used to support and enhance the productivity of clinicians and facilitate recovery of patients because of the controllable, repetitive delivery and variable intensity (via assistive or resistive action) of the devices. Other potential benefits of the introduction of robotics include new sensing capabilities for monitoring progress of the patient, increased accessibility to therapy for patients, and increased therapy efficiency with the possibility of group therapy. Robotics for rehabilitation has the potential to automate labor-intensive therapy procedures, bringing therapy to new venues including rehabilitation hospitals and clinics, subacute skilled nursing facilities, acute care hospitals with outpatient services, and even the home. Furthermore, with continued research and a better understanding of neuroplasticity and rehabilitation, more optimal and efficient robotic therapy procedures may be introduced and further developed. This capability comes at an opportune time, given the pressures on the health care systems of the United States and other nations that have resulted in a decrease in the amount of therapy delivered to patients due primarily to decreases in length of stay after medical rehabilitation.

This section will discuss the state of the art in rehabilitation robotics for stroke, focusing on therapeutic robotics and the upper extremity. The technical requirements for therapeutic robotics will be discussed, along with the control approaches and clinical outcomes (where applicable) of various devices. It should be noted that, unlike TMS, robotic technologies were originally developed as intervention tools, delivering therapy at potentially higher intensities than could be delivered by a therapist with traditional techniques. It was only after such devices were used in clinical trials as intervention tools that researchers began to investigate uses of robotics for patient evaluation. Indeed, many systems were developed to assess patient progress and adapt the intervention protocols online. Therefore, robotic systems will be discussed without specifically separating those intended for assessment from those designed to deliver therapy.
The design of robotic devices for therapy inherently defines the potential applications of a particular system. For example, the degrees of freedom of the robotic device will dictate the ranges and types of movement therapies that can be delivered. Often, robotic devices are designed with particular movement strategies in mind, for example, reaching movements with the arm involving primarily the shoulder and elbow, or devices designed specifically for repetitive grasping of real or virtual objects. The control methodology for the robotic device will also affect its design and implementation.

The reader is referred to extensive reviews of robotic therapy for the upper and lower extremity for a more complete discussion of the state of the field. To date, 3 randomized controlled studies of robotic therapy for the upper extremity after stroke have been published. Several studies of robotic therapy used chronic stroke or spinal cord injury patients as the baseline control. The reader is directed to these articles for a more thorough presentation of clinical results from these publicized trials.

Control Methodologies for Robotic Therapy

A review of control algorithms for robotic therapy is presented by Reinkensmeyer et al. Specifically, for the upper extremity, a variety of control techniques have been presented in the literature, including passive, active-constrained, counterpoise, resistive, error-amplifying, bimanual, and active assistance. The active assistance approach is by far the most used in robotic therapy, in which the patient attempts a movement and the robot assists with the completion of the movement through its sensing and actuation. The active assistance methodology is derived from traditional clinical settings where the therapist assists the patient to complete a motion if the patient attempts the movement but is unable. The approach may improve recovery by enhancing proprioceptive input, reducing spasticity, restoring soft-tissue suppleness, improving self-confidence, or making exercise psychologically more tolerable because the therapist manually helps to complete the movement if the patient is unable to do so. The drawbacks of active assistance in the traditional clinical sense are that it is labor intensive and that the approach has not been validated in clinical trials. Therefore, a logical solution for active assistance, specifically for weak patients, is to deliver therapy with force-generating robots. Robots offer several advantages over traditional devices that have been used to provide assistance therapy (eg, mobile arm supports, arm skateboards, or overhead slings) in that they can provide programmable levels of assistance, the robotic device can do work against gravity because of its actuation, and the algorithms can be designed so that the output of the robotic device is automatically modified based on sensing of the patient’s progress and abilities.

Summary of Clinical Findings

The first robotic therapy device to be used in clinical trials for stroke therapy was the MIT-MANUS, a 2 degree-of-freedom back-driveable device that allows planar pointing and drawing movements, targeting the elbow and shoulder joints. The robot uses an impedance controller so that a programmable compliance is maintained between the patient’s arm location and the desired position along a programmed trajectory. The study concluded that supplemental robot therapy, in addition to traditional physical and/or occupational therapy, can improve recovery in acute and chronic (shown in later studies) stroke patients. However, this work failed to address what features or unique advantages robotic therapy may provide when compared with traditional clinical intervention techniques.

The mirror image motion enabler (MIME) took a different approach by using a 6 degree-of-freedom industrial robot (PUMA 560) to provide 4 interaction paradigms for shoulder and elbow reaching motions and orientations. The robot provides passive, active assist, active constrained, and bimanual modes of interaction for the patient. The study found that robotic therapy, delivered via MIME, resulted in greater improvements in Fugl-Meyer Assessment (FMA) score, strength, and reach extent at the conclusion of the trials as compared with conventional therapy. Six months after the trial, the robot group still had greater improvements in functional independence in ADLs, although the FMA scores were equal for the robot and conventional therapy groups. The results suggest that robotic therapy is at least as effective, possibly more so, than conventional therapy.

There are a few other clinical studies of robotic therapy for the upper extremity, along with numerous other robotic devices that are under development or have not undergone clinical testing. Clearly the potential benefits of robotic-assisted rehabilitation have been recognized by the research community, and future research will address unanswered questions such as the unique contributions of the robotics compared with therapy delivered by humans directly, appropriate dosage level, and treatment protocols for robotic rehabilitation.

Assessment With Therapeutic Robotics

Robotic devices developed to deliver therapy for upper-extremity motor deficit can also be used for assessment. For example, if the device is back-driveable, meaning that the endpoint of the robot can be easily translated through the workspace when no power is supplied to the system, then the device can be used as a motion capture device. This allows for assessment of the smoothness of movements, determined by the kinematic features of the paths tracked through the workspace. Additionally, directional error can be assessed by recording position data from the robotic device and comparing that with the desired paths or trajectories through the workspace. If the device is non–back-driveable, movement properties can also be quantified by tracking reaction force patterns in directions of high impedance, such as lateral forces during reaching. Because the availability of precise evaluation tools to the clinical population has been limited, robotic devices with their suite of sensors (eg, position, velocity, force) offer an opportunity to gain insight into motor processes and the effects of rehabilitation on the recovery of motor function. Additionally, patient progress can be quantified with data from the robotic therapy sessions and associated evaluations, and such data can be used to show the need for continued intervention.

CURRENT AND FUTURE TRENDS

This review has presented 2 recent therapeutic tools for assessment and therapy intervention of stroke patients. TMS has been shown to be a valuable tool for assessment of motor function, and rehabilitation robotics can provide repeatable, controlled motion input for reaching motions of the upper extremity. These tools are slowly transitioning to multifaceted implementation, with TMS being investigated as an intervention tool, and robotics being used for combined rehabilitation delivery and patient assessment.

Current and future trends in stroke rehabilitation include extensions of the techniques mentioned here. For example, some groups are attempting to combine automated delivery of therapy, guided by a computer but not necessarily robotic, with CIMT, in a project dubbed AutoCITE. Other groups are extending upper-extremity robotic-assisted rehabilitation distally, to include movement therapies for wrist and hand.
and fabricated that can provide force assistance for elbow flexion and extension, wrist pronation and supination, and radial and ulnar deviation (fig 3). The RiceWrist is intended to provide robotic therapy via force feedback during range-of-motion (ROM) tasks. Joint ROM and torque output of the electric motor-driven device are matched to human capabilities. Passive, triggered, and active-constrained modes, such as those developed for MIME, allow for therapist control of therapy protocols based on patient capability and progress.

In studies that we are currently conducting, robotic devices are being used to induce neuroplasticity and recovery, and future studies will use TMS to assess it. There is also a significant research thrust toward using virtual reality in rehabilitation applications. Although there are too many individual works to cite, the reader is encouraged to review proceedings from the International Workshop on Virtual Rehabilitation, which has been held annually since 2002 (http://www.iwvr.org). The utilization of virtual reality for rehabilitation has allowed researchers to investigate interesting theories, such as visual feedback distortion assistance forces in virtual reality systems that use haptic feedback (eg, the system shown in figure 4) and home-based telerehabilitation. With such advances in technologies and the combination of highly flexible tools, not only will assessments of neuroplasticity be more feasible, accurate, and cost effective, but so will the magnitude of induced plasticity and recovery of function.

CONCLUSIONS

This review presents a review of TMS and robotics as 2 novel technologies for assessing and inducing neuroplasticity, with a focus on motor recovery. Although TMS has primarily been used as an assessment tool for motor function, an increasing number of studies are using TMS as a tool to directly induce plasticity and improve motor function. Similarly, robotic devices have been used for rehabilitation because of their suitability for the delivery of highly repeatable training. New directions in robotics-assisted rehabilitation are taking advantage of novel measurements that can be acquired via the devices, enabling unique methods of assessment of motor recovery. Although the 2 technologies are presented individually, much could be gained in terms of understanding the mechanisms of robotic-assisted rehabilitation with TMS as an assessment tool, just as coupling TMS and robotics as intervention methodologies may result in improved gains for patients undergoing therapy.

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