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Transcranial Magnetic Stimulation (TMS): Potential Progress for Language Improvement in Aphasia

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Abstract

Aphasia researchers and clinicians share some basic beliefs about language recovery post stroke. Most agree there is a spontaneous recovery period and language recovery may be enhanced by participation in a behavioral therapy program. The application of biological interventions in the form of pharmaceutical treatments or brain stimulation is less well understood in the community of people who work with individuals having aphasia. The purpose of this article is to review the literature on electrical brain stimulation as an intervention to improve aphasia recovery. The article will emphasize emerging research on the use of transcranial magnetic stimulation (TMS) to accelerate stroke recovery. We will profile the current US Food and Drug Administration (FDA)–approved application to depression to introduce its potential for future application to other syndromes such as aphasia.

Keywords

aphasia; stroke; transcranial magnetic stimulation (TMS)

Research-clinical interventions for stroke survivors with aphasia intend to activate dysfunctional brain networks supporting linguistic processing and communicative intent. These interventions may generally fall into 3 broad categories: speech-language rehabilitation treatment; pharmaceutical treatment; and direct brain-stimulation therapies, such as transcranial magnetic stimulation (TMS). Aphasia researchers and clinicians agree that there is a spontaneous language recovery period post stroke and that language recovery may be enhanced by participation in a behavioral rehabilitation therapy program.¹ How biological interventions such as pharmaceutical treatments or brain stimulation can enhance function in the recovering brain is generally less well understood among clinicians working therapeutically with individuals having aphasia. Biological interventions in the form of pharmaceuticals are currently administered to stroke survivors with aphasia to treat co-morbid diagnoses, such as anxiety or depression, rather than directly administered for the clinical application to treat language recovery. Many practitioners accept that medication treatment (antidepressants) for depression post stroke may have a secondary positive effect on poststroke recovery.² Moreover, experimental research for the use of pharmaceuticals for

direct language recovery has also suggested that pharmaceutical treatment can improve communication.³ These approaches are not yet used in the clinical treatment of aphasia perhaps due to obstacles to the knowledge transfer to clinical care secondary to basic science researchers having little interface with clinicians. This is less of an issue with another relatively recent research treatment for language recovery, TMS, a new biological treatment with current promise in language-rehabilitation research. The purpose of this article is to review the literature on brain-stimulation therapies for aphasia. Specifically, TMS will be described, with its current US Food and Drug Administration (FDA)–approved application to depression suggested as a possible model for the potential for future application of TMS to other areas such as aphasia.

General History of Aphasia Research

Much research on intervention for aphasia over the past several decades focused on the development of behavioral therapies for the recovery of language impairment due to acquired brain damage. A comprehensive history of how the effects of behavioral intervention compared to spontaneous language recovery post stroke has been debated between and among clinicians and researchers and is beyond the scope of this article (see review on behavioral interventions for aphasia).⁴ Briefly, behavioral treatments moved from an initial generalized, gestalt approach to language therapy to specific behavioral approaches focused on training specific aspects of communication (eg, naming, grammar). Early behavioral language treatments from the 1940s to 1970s have been described as being pedagogical in nature, with a focus on re-teaching and re-learning, whereas relatively recent behavioral treatments shifted to more specific and more functional behavioral approaches.⁵ However, it was not until the 1990s that approaches to aphasia intervention considered whether increasing brain activation electrophysiologically might complement behavioral intervention for aphasia.⁶

Background on TMS

TMS is a tool used to electrically stimulate brain tissue. It is a noninvasive procedure that creates electrical currents in specific brain regions. An insulated copper coil in the shape of a figure eight is placed over the scalp. A strong, brief electrical current flows through the coil, and the current induces a rapid transient magnetic field in the brain tissue directly below the placement of the coil. The induced magnetic field secondarily induces electric current flow in the cortex in the region parallel to the coil, at a depth of approximately 1 cm, which causes a depolarization or spiking of neurons in the brain.⁷ The participant hears a brief clicking noise and may feel a slight scalp sensation. Typically, participants report the procedure is painless.⁸ However, stimulation can be painful, and headaches, and very rarely seizures, have been reported post TMS.⁹ TMS is a focal, nonsystemic approach with much potential for the treatment of neuropsychological conditions. A TMS-induced change in neural firing may lead to behavior changes; this allows researchers to infer that brain areas that are stimulated may play a necessary role in supporting the studied cognitive functions. This procedure has been used for diagnostic and therapeutic purposes, with an approved therapeutic application for a subset of people with depression.¹⁰

There are 3 basic types of TMS: single-pulse, paired pulse, or repetitive TMS (rTMS). In single-pulse TMS, one pulse is applied no faster than once every few seconds. In paired pulse, there are 2 pulses applied out of phase to inhibit or excite neurons within the same hemisphere or to inhibit neurons in one hemisphere while exciting them in the other hemisphere. In rTMS, magnetic pulses are delivered in a rapid series or “train.” When rTMS is used, multiple single-pulse stimuli are presented at a specific frequency, intensity, and time duration. This facilitates an excitation or inhibition of activity in the affected cortical

area. An example of slow rTMS at 1 Hz (inhibitory) means that one magnetic pulse is applied every second (one cycle per second). An example of fast rTMS at 10 Hz (excitatory) means that 10 magnetic pulses are administered every second (10 cycles per second).

The intensity of the signal administered is participant specific and is based on a percentage of each individual's resting motor threshold (RMT) at any given point in time. The resting motor threshold (RMT) is defined as the minimal stimulation intensity needed to produce motor-evoked potentials (activating muscle fibers in a target muscle such as in the hand). Use of TMS to activate muscles and determine the threshold for activation takes place before TMS is applied to brain areas to study cognitive function such as language (since motor cortex may not critically support language-related cognition). Intensity is determined for each individual just prior to each TMS application. Duration of the TMS pulse is usually fixed within experiments and is not participant dependent.⁸

TMS Treatment for Depression

Effects of TMS on cortical activity vary. Slow trains of rTMS and fast trains of rTMS affect the cortex differently. As noted previously, a slow train of rTMS (eg, 5 Hz) decreases excitability of the targeted cortical region, whereas fast rTMS (10 or 20 Hz) fosters an increase in cortical excitability.^{6,11} Due to the noninvasive nature of TMS, there have been many small-scale studies that looked at the application of TMS for many neurological and neuropsychological conditions. Depression has been the most commonly studied condition both in Europe¹²⁻¹⁴ and the United States.¹⁵⁻¹⁷ Currently, 3 large multisite trials on TMS for depression have been published.¹⁸⁻²⁰ The study that resulted in FDA approval for the application of TMS to the improvement of major depression used TMS in a subset of people with depression who failed initial medication treatment.¹⁹ This trial involved randomization of 301 patients with depression to TMS or sham treatment. The treatment lasted 4-6 weeks. There were some methodological problems with this research that negatively affected the initial analysis of the results. Specifically, the depression scale used to enroll participants (the Hamilton Depression Rating Scale) was different from the scale used for their primary outcome measure (the Montgomery-Asberg Depression Rating Scale [MADRS]). The initial analysis of the results using this outcome measure did not demonstrate reduced depression in the experimental group, yet the researchers successfully published their results after re-analyzing the data after extracting 6 participants. These individuals were deemed outliers due to their initial scores on the depression scale that was used to enroll participants. Due to the large effect size for people who were less treatment resistant, the FDA approved the use of TMS for depression in adults who demonstrate major depression and have failed to respond to a first attempt at medication management. The actual approval states that the medication must be administered during the current episode of major depression at or above the minimal effective dose and duration. If this pharmacological treatment does not have a positive effect on the depressive disorder, then clinical application of TMS for this specific population of adults with major depression is approved. In this group of people, a greater response was reported for younger adult participants without psychoses and those who demonstrated a lack of refractoriness to antidepressants.²¹ Although the clinical application of TMS for depression is gaining acceptance, it is FDA approved for only a subgroup of depressed individuals – those who are severely depressed. This FDA-approved clinical application to depression is the beginning of utilization of this technique to treat this disorder; continued research is underway to develop standards for the treatment of depression at various levels. Debates regarding the effective use of TMS to treat depression have moved from asking whether it works to establishing multicenter collaborations to determine the best methods of use to maximize its effects.

Application of TMS to Aphasia

As trials look at the application of TMS for subgroups of depressed populations (eg, depression in pregnancy, postpartum, and in Parkinson's disease), perhaps these explorations can support initial evaluations regarding the application of TMS to aphasia. The TMS application for depression may serve as a model for TMS utilization for the improvement of speech and language. There is currently no FDA approval for the application of TMS to people with poststroke aphasia or for any neurologic or neuropsychological condition other than severe depression.

Much of the research in the area of impaired language has used rTMS to modulate interhemispheric interaction so as to support language recovery. It is used to inhibit what is thought to be overactivation of the right hemisphere homologue after a left hemisphere stroke.⁸ Although it may seem surprising that the use of rTMS to inhibit the right hemisphere could actually improve language, there have been animal studies and some case reports in humans that suggest that neural damage to specific areas in the brain (in the case of aphasia, contralateral to the lesion) may promote improved behavior or function of certain conditions. Support for this use of rTMS to inhibit overactivation of the unimpaired hemisphere is also derived from studies that have demonstrated increased right hemisphere blood flow after left hemisphere stroke utilizing functional magnetic resonance imaging (fMRI),^{22,23} suggesting that the right hemisphere may change (ie, become overactivated) by the brain damage that occurred in the left hemisphere. Moreover, case studies that documented improved behavioral function after a lesion in the presumed contralateral hemisphere also supported a theory that overactivation of the right hemisphere may interfere with language recovery post stroke. For example, Helm-Estabrooks reported improved speech fluency in an individual with a history of chronic perseverative stuttering after a head injury, suggesting that the acquired brain injury had a positive effect on speech.²⁴ In summary, documented overactivation in the right hemisphere post stroke and case reports noting changes in function after brain damage led to the idea that a reduction in right brain activation may improve stroke recovery (paradoxical functional facilitation).²⁵ However, other researchers suggested that right brain activation may improve recovery when interhemispheric interaction is optimized.^{26, 27}

Devlin and Watkins review the existing literature on TMS use for language.²⁸ Research that investigated the impact of TMS on normal speech production and for the recovery of speech and language post stroke is described. Both studies that implement single-pulse TMS and rTMS are reported, with the rTMS used to inhibit pathologic overactivation of the right hemisphere Broca's area homologue region. According to Naeser et al, improved picture naming after rTMS for 4 patients even 2 months after the treatment had stopped is encouraging.²⁹ Moreover, a recent case report by Hamilton and colleagues indicated that use of rTMS had a positive effect on discourse (a picture description task) as well as naming, which suggests that the use of rTMS in conjunction with behavioral therapy may promote a positive prognosis for language recovery post stroke for some people.³⁰

Future Research on TMS Use and Aphasia

Current research on TMS use with aphasia is still at the small-scale study or “proof of principle” stage. Only relatively few research groups are investigating its application by intensive examination of a relatively small set of individuals with no control groups (eg, Naeser et al²⁹), because many studies used within-subjects comparisons. Randomized trials with between-subject comparisons need to be completed to provide the necessary parameters for the use of TMS to enhance language recovery post stroke. Establishing multi-center collaborations to determine the best methods for maximizing the impact of the effect of

TMS on language recovery is a future goal that will bring us closer to an FDA-approved clinical application. Because people with poststroke aphasia may be a heterogeneous group, even when carefully classified by psycholinguistic characteristics, newer longitudinal statistical procedures may be preferred to analyze results from treatment studies in which subjects undergo multiple outcome assessment sessions.³¹ Higher intercorrelation of data within subjects as compared with intercorrelation of data between subjects (clustering at the subject level) greatly reduces the power to detect treatment effects (increases the likelihood of Type II error) when data are analyzed using techniques based on linear regression (eg, analysis of variance [ANOVA]). Thus, studies that use ANOVA rather than longitudinal analytic methods (eg, random effects modeling) may incorrectly fail to detect an effect of the experimental treatment.

In this review, we introduced noninvasive brain stimulation as a method being developed to research and support poststroke recovery of aphasia. Although we have described the initial steps that have been taken to promote the future clinical use of TMS for aphasia, there is still much work to be done. If this method moves forward toward clinical application, we hope future studies will uncover feasibility obstacles, subject characteristics important to treatment response, and ideal combinations of behavioral and noninvasive stimulation.

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