Non-invasive Repeated Therapeutic Stimulation for Aphasia Recovery: A Multilingual, Multicenter Aphasia Trial

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Noninvasive brain stimulation such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) has been used in case series and small randomized controlled trials to improve recovery from poststroke aphasia in combination with speech and language therapy. Results of these studies suggest possible clinical efficacy and an excellent safety profile. Therefore, a larger international multicenter proof-of-concept trial was launched, to directly compare the safety and efficacy of rTMS, tDCS, and sham stimulation as adjuvant therapy to speech and language therapy in subacute poststroke aphasia. In the 4 participating centers, subacute stroke patients with aphasia are randomized between 5 and 30 days after ischemic stroke to either receive rTMS, tDCS, or sham stimulation in combination with a daily 45 minutes speech and language therapy session for 10 days. Efficacy is evaluated at 1 and 30 days after the last of the 10 treatment sessions using 3 outcome measures, validated in all participating languages: Boston naming test, Token test, and verbal fluency test. Additionally, adverse events are recorded to prove safety. In this study, a total of 90 patients will be recruited, and data analysis will be completed in 2016. This is the first multilingual and multinational randomized and controlled trial in poststroke aphasia and if positive, will add an effective new strategy for early stage poststroke aphasia rehabilitation. **Key Words:** Aphasia—clinical trial—noninvasive brain stimulation—ischemic stroke—rehabilitation—speech and language therapy.

In the brain of healthy right handers and most left handers, language function is a faculty of the left, dominant hemisphere. This asymmetry is established during language acquisition[1] and actively maintained in the adult brain by fiber bundles, connecting both hemispheres across the corpus callosum (so called

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transcallosal pathways). These fibers are glutamatergic and are connected to inhibitory interneurons in the nondominant hemisphere[2] such that language areas active in the dominant hemisphere (eg, Broca area) actively suppress activity in homologous areas of the nondominant hemisphere (transcallosal inhibition). The existence of these inhibitory mechanisms has been directly demonstrated in normal subjects using imaging guided repetitive transcranial magnetic stimulation (rTMS).[3] A unilateral and focal brain lesion (such as a stroke) to language areas of the dominant hemisphere does not only reduce activity in the affected hemisphere thus causing aphasia, but also releases activity in the unaffected hemisphere, via interruption of those transcallosal fibers.[2] This increased activity of brain regions in the nondominant hemisphere in the first days and weeks after a stroke has repeatedly been demonstrated in sequential brain imaging studies.[4,5] In the following weeks and months of recovery, brain activation may shift back to the dominant hemisphere. The extent of this shift back to the dominant hemisphere varies from patient to patient and is associated with a more successful recovery of language function[6] in the acute and subacute phase. Re-establishing functional networks of the affected dominant hemisphere early in the course of recovery seems to be the superior strategy over recruiting homologous brain regions in the unaffected nondominant hemisphere to achieve good rehabilitation results.[7] Based on this evidence, a reasonable strategy for improvement of language function would be to actively suppress right hemisphere and to enhance left hemisphere activity in the early phase after stroke.

Most approaches to aphasia rehabilitation aim at generally activating all available networks, paying little attention to the fact that activation of brain regions in the nondominant hemisphere may actually be counterproductive.[8-10] It has thus been suggested that the lack of inhibition of the intact right hemisphere is likely to interfere with early aphasia recovery because SLT may facilitate establishing networks in the right hemisphere rather than training residual left hemisphere networks.[11] Thus, downregulating this increased activity in the nondominant hemisphere using noninvasive brain stimulation could render language areas in the affected hemisphere more susceptible to conventional speech and language therapy (SLT) and may even facilitate base-dependent repair mechanisms such as axonal outgrowth if there is salvageable tissue in the ischemic penumbra.[12,13] To achieve this modulation of brain activity, 2 methods have been used: rTMS, which uses rapidly changing magnetic fields at low frequency to induce currents in the cortex, and transcranial direct current stimulation (tDCS), which applies cathodal or anodal low intensity direct currents.

Evidence from single case studies and case series in chronic stroke indeed demonstrates the rehabilitation potential of these brain stimulation techniques for regaining language function[11,14] and the feasibility of such an approach was demonstrated in small RCTs.[15,16] Inhibitory[11] rTMS over the right homologue to Broca area (BA45) immediately preceding conventional SLT indeed prevented a shift of activity to the nondominant hemisphere and improved language function compared with patients receiving sham stimulation. A similar recent pilot study employing cathodal tDCS over the nondominant hemisphere also yielded significant treatment effects.[17,18]

Based on this evidence, Non-invasive Repeated Therapeutic Stimulation for Aphasia Recovery (NORTHSTAR) was designed as a blinded sham-controlled proof-of-concept study to directly compare the effect of inhibitory rTMS, inhibitory tDCS, and sham stimulation as adjunctive therapy for recovery of language function in the subacute phase after stroke in a larger patient sample representative of a typical clinical poststroke aphasia population. Another novel aspect of this proof-of-concept project is that it is the first multilingual aphasia trial. Experience gained from NORTHSTAR will be invaluable for the future design of larger multilingual studies on recovery from poststroke aphasia in general.

Methods

Design

NORTHSTAR is a 3-armed sham-controlled blinded prospective proof-of-concept study. Patients will be randomized to either sham or rTMS or tDCS treatment. Patients randomized to rTMS treatment will in addition receive sham tDCS, and patients with tDCS treatment will be receiving sham rTMS. Patients randomized to the sham group will receive both sham conditions. All patients will receive 45 minutes of model-oriented individualized aphasia therapy administered by a certified therapist and according to SLT best practice guidelines.[19] The study timeline and major events are summarized in Figure 1. Outcome measures will be assessed 1 and 30 days after the last therapy sessions.

Patient Population

Ninety right-handed participants between 50 and 85 years of age with first left hemisphere stroke will be recruited from the 4 participating centers in Canada and Germany between 5 and 30 days after stroke onset. Inclusion criteria and exclusion criteria are listed in Table 1.

Baseline Measurements

The following procedures, listed in Table 2, will be performed during the initial testing (baseline)—before treatment. All tests (except demographics and magnetic resonance imaging [MRI]) will be repeated 1 and 30 days after the last treatment session. Adverse event