Repetitive Transcranial Magnetic Stimulation as a Complementary Treatment for Post-stroke Aphasia

a report by

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Aphasia is an acquired language disorder affecting more than 20% of stroke patients.[1–3] Six months post-stroke, 12% of survivors still suffer significantly from this severely incapacitating deficit,[1] the prognosis depending mainly on the extent and localisation of the infarction. A Cochrane review could not determine whether speech and language therapy is more effective than informal support.[4] Thus, novel therapy options are needed.

Transcranial magnetic stimulation (TMS) is a non-invasive method of inducing the depolarisation of cortical neuronal assemblies by delivering short magnetic pulses penetrating the skull. The excitability of the cortex can be either inhibited or facilitated depending on stimulation parameters. High-frequency repetitive TMS (rTMS) (>5Hz) increases cortical excitability, whereas stimulation with frequencies of 4Hz or lower decreases excitability (see *Figure 1*).[5,6] With this in mind, many studies have been conducted in order to determine whether rTMS might be used as a therapeutic option in stroke rehabilitation[7–11] and other disorders such as depression[12–14] or tinnitus.[15–17]

Spontaneous Recovery of Post-stroke Aphasia

In most adults language function is extremely lateralised to the left hemisphere.[18] Functional studies in healthy subjects suggest that these specialised areas inhibit adjacent cortical areas, as well as more remote regions connected by fibre pathways.[19–22] A simultaneous rTMS and positron emission tomography (PET) activation study directly demonstrated collateral (i.e. in adjacent regions) and transcallosal (i.e. in contralateral homotopic regions) inhibition in healthy subjects.[23] Suppression of cortical excitability with low–frequent rTMS in the Broca area led to a prolongation of reaction time latencies during a verb-generation task. In addition, during rTMS the cerebral blood flow was decreased in those regions under the coil but increased in neighbouring regions and in contralateral homologous areas (see *Figure 2*).

After a stroke damaging specialised regions, the functional and structural networks involved in the affected function have to be modified, which is facilitated by the adaptive plasticity of the cerebral cortex. One prominent finding is that excitability in peri-lesional but also in more remote cortical areas is increased.[24] Also in aphasia patients, functional imaging revealed language-related cortical activations in peri-lesional regions, as well as contralateral homologous areas,[25–29] suggesting overactivation.[30] As it could be shown that unilateral ischaemic lesions led to transcallosal disinhibition,[31] the increased activations may be seen as a result of reduced inhibition by the lesioned structures.[18,32,33]

Several studies demonstrate that aphasic patients with favourable outcomes predominantly activate in regions ipsilateral to the lesion,[34–38] although contralateral activations were also observed. Thus, (re-) integration of ipsilesional areas seems to be the most effective reorganisation pattern. Several studies report beneficial effects of the recruitment of peri-lesional regions.[32,37–41] In contrast, increased activation in the contralesional hemisphere might represent an inferior strategy,[42,43] e.g. in the sense of maladaptive plasticity.[44] In a longitudinal study by Richter et al., activation of right hemispheric areas decreased in aphasic patients with better therapy response, whereas activation increased in patients with less clinical improvement.[29]

The function of contralateral regions for language performance in aphasic patients was directly investigated by decreasing the excitability of the right hemispheric inferior frontal gyrus (IFG) (i.e. Broca's homologue) with rTMS.[45] In most of these patients, the right IFG was activated during PET, and low-frequency rTMS resulted in increased error rate or reaction time latency in a word-generation task. This indicates an essential function of the right IFG for language performance in aphasic patients. However, in a verbal fluency task patients with a bilateral activation pattern revealed a lower performance compared with patients with left hemispheric activations only, suggesting a less effective compensatory potential of contralesional areas. These findings were reinforced by another study in which the laterality index as a marker of interhemispheric balance correlated significantly with verbal fluency.[27]

Thus, a hierarchy of regions in recovery of post-stroke aphasia was proposed.[18] According to this assumption, restoration of original activation patterns within the dominant hemisphere seems to be most effective. Increased activation of regions surrounding the lesion due to collateral disinhibition is supposed to be beneficial, whereas an interhemispheric compensation with activation of contralateral homotopic

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Figure 1: Inducing Virtual Brain Lesions with Repetitive Transcranial Magnetic Stimulation

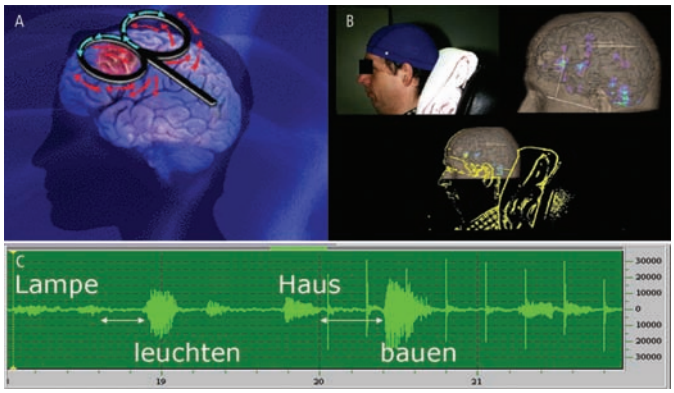


Figure 1A illustrates the electric currents flowing through the coil (blue arrows) and inducing a rapidly fluctuating magnetic field, thus leading to depolarisation of underlying neurons (light red area). Figure 1B: The target sites on the head surface are ideally localised depending on the individual cortical and functional anatomy. One way to measure the interference of language functions by transcranial magnetic stimulation (TMS) is the recording of verb-generation latencies, as demonstrated in Figure 1C.

Figure 2: Effect of Repetitive Transcranial Magnetic Stimulation on the Activation Pattern in a Healthy Subject[23]

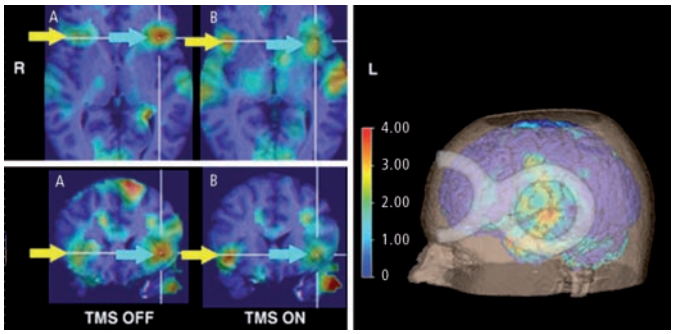


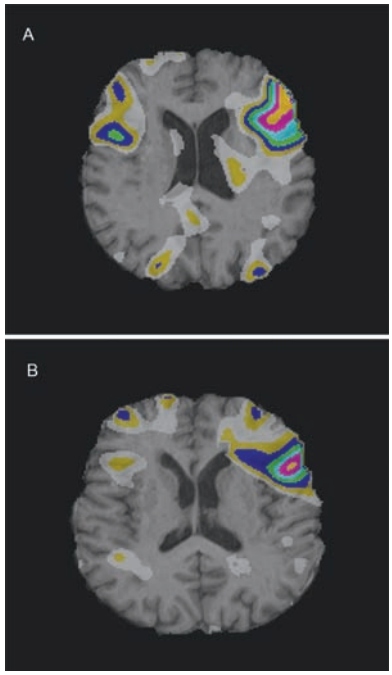
Figure 2A shows the activation of the inferior frontal gyrus (IFG) during verb generation. Figure 2B illustrates the decreased left-hemispheric and increased right-hemispheric activation during transcranial magnetic stimulation with 4Hz. The position of the figure-of-eight transcranial magnetic stimulation (TMS) coil over the left IFG can be seen on the 3D rendering.

areas might even be maladaptive. However, it must be considered that the proposed model is not necessarily valid for all language functions in all types of aphasia,[18,46,47] e.g. aphasia due to slowly developing brain lesions.[27,28] Many factors seem to influence the functionality of the right hemisphere in aphasia recovery, such as time since stroke onset,[48] lesion size and localisation[38,49] and therapeutic interventions,[29,35,42,50–55] and maybe also the cognitive effort made by the subjects.[56,57]

Concerning the latter, a recent study compared the PET activation patterns of 10 aphasic patients with those of 20 healthy subjects re-learning words of a long-acquired but forgotten foreign language.[56] Interestingly, both groups exhibited comparably increased activation in inferior frontal regions, thus suggesting that enhanced activity of right-sided areas might represent lexical learning rather than only the result of disinhibition. The discrepancy of these results from those of previous studies might be partly due to the fact that in this case the control subjects had to make a considerable cognitive effort during the activation paradigm.

The influence of time since stroke onset on language-related activation patterns in aphasic patients was examined by Saur et al. in a longitudinal study.[48] Their data suggested a reorganisation in three phases. In the

Figure 3: The Effect of Repetitive Transcranial Magnetic Stimulation on Language-related Activations in an Aphasic Patient



This figure illustrates the activation patterns before and after a two-week course of daily repetitive transcranial magnetic stimulation (rTMS) over the right-hemispheric homologue inferior frontal gyrus (IFG) in combination with speech therapy. Before the first TMS session there is a generalised upregulation with recruitment of homologue right hemispheric language areas (Figure 3A). Figure 3B shows language-related activations in the same patient after 10 TMS sessions with a similar pattern to healthy subjects (see Figure 2A for comparison). This indicates that rTMS over right-hemispheric areas might normalise persistent contralesional activations. Whether this normalisation leads to clinical improvement is still to be ascertained.

acute phase, group analysis of functional magnetic resonance imaging data showed generally little activation in peri-lesional regions and in the contralateral hemisphere compared with controls. In the subacute phase, activation in Broca's homologue increased strongly, yielding a right hemispheric peak activation. In the chronic stage, language-related activation decreased in the right hemisphere, and activations in the dominant hemisphere normalised. All of these processes were associated with clinical improvement of language functions, thus representing an effective reorganisation. Despite these results, in accordance with earlier studies one may assume that in some aphasia patients activation of right hemispheric regions persists in the chronic stage.[58]

A recent study showed a positive correlation between persisting contralesional language-related activations in chronic aphasia patients and the subsequent success of speech therapy.[29] Thus, the existence of increased right hemispheric activation might predict the potential for further clinical improvement. These results support the aforementioned assumptions, as they imply that the reorganisation pattern in patients with contralesional overactivation is suboptimal and thus might be improvable.

Repetitive Transcranial Magnetic Stimulation as a Novel Therapy Approach

The objective of utilising rTMS in neurorehabilitation is mainly to decrease the cortical excitability in a specific region that is presumed to hinder optimal recovery.[30] If activation of right hemispheric regions in aphasia patients represents an inferior adaptive strategy, suppression using rTMS might result in clinical improvement.[30,59,60] As the impact of a single rTMS session is short-lasting, multiple sessions are assumed to prolong the

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response and thus carry into effect a continuing clinical benefit.[60] In fact, an open-protocol study by Naeser et al. reported improved picture-naming ability after application of 1Hz rTMS to an anterior portion of right Broca's homologue daily for 10 days in four aphasia patients who were five to 11 years post-stroke.[59] In three patients, positive effects could still be observed eight months after the previous TMS session. Another case report supports these findings.[44] These results strongly endorse the concept that interhemispheric compensation is not necessarily beneficial for the recovery process.[18,42,43]

Current studies further explore the influence of rTMS on activation patterns and the clinical course in the subacute phase of aphasic stroke patients. It is assumed that in this stage of recovery the benefit from therapy might be greater than in the chronic phase.[61] In current studies, rTMS is mostly combined with speech therapy. This conforms to the interaction model, after which rTMS might be unlikely to specifically restore functions, but rather "increases the ability of the brain to undergo compensatory changes that improve behaviours."[62] In addition, current projects emphasise methodological issues such as larger sample sizes, blinding, randomisation, control groups receiving sham therapy and longitudinal design. Some preliminary results are illustrated in *Figure 3*.

Future Prospects

In healthy subjects, rTMS was shown to have effects ranging from facilitation of naming to speech arrest, depending on the stimulated target and other rTMS parameters.[59,63–66] Also, when applying magnetic stimulation as a complementary aphasia therapy, it is crucial to choose appropriate stimulation parameters[67] such as optimal frequency and duration and intensity of the magnetic stimuli. Future studies may refine these specifications and show which cortical regions should be targeted.[30]

In order to explore the long-term efficacy of rTMS as an aphasia therapy, large clinical trials including patients in different phases after stroke and with different lesion patterns are necessary. Another important question will be the identification of those patients who benefit most from magnetic stimulation, thus drafting criteria for indications. In addition, although rTMS of non-motor cortical areas under the existing guidelines appears to be safe, adverse effects should be systematically reported in future studies.[68] To evaluate its clinical relevance, rTMS should be compared with other methods of non-invasive brain stimulation (e.g. transcranial direct current stimulation[69–71]) concerning safety, applicability and effectiveness.

Conclusions

Recovery of post-stroke aphasia seems to be most effective when ipsilesional regions can be functionally (re-)integrated. It remains to be clarified whether increased contralateral activation is beneficial or maladaptive. If persistence of right hemispheric activations represents an inferior reorganisation strategy, rTMS might provide a novel treatment approach for aphasia. ■

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