Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke?

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Background **Motor impairment resulting from chronic stroke can have extensive physical, psychological, financial, and social implications despite available neurorehabilitative treatments. Recent studies in animals showed that direct epidural stimulation of the primary motor cortex surrounding a small infarct in the lesioned hemisphere ($M1_{lesioned\ hemisphere}$) elicits improvements in motor function.**

Recent developments **In human beings, proof of principle studies from different laboratories showed that non-invasive transcranial magnetic stimulation and direct current stimulation that upregulate excitability within $M1_{lesioned\ hemisphere}$ or downregulate excitability in the intact hemisphere ($M1_{intact\ hemisphere}$) results in improvement in motor function in patients with stroke. Possible mechanisms mediating these effects can include the correction of abnormally persistent interhemispheric inhibitory drive from $M1_{intact\ hemisphere}$ to $M1_{lesioned\ hemisphere}$ in the process of generation of voluntary movements by the paretic hand, a disorder correlated with the magnitude of impairment. In this paper we review these mechanistically oriented interventional approaches.**

What next? **These findings suggest that transcranial magnetic stimulation and transcranial direct current stimulation could develop into useful adjuvant strategies in neurorehabilitation but have to be further assessed in multicentre clinical trials.**

Introduction

Recovery of motor function after stroke is typically incomplete.[1] 6 months after the episode, two-thirds of stroke survivors are unable to take part in activities of daily living with their paretic hand to the extent they were before[2] and only a few are able to carry out professional work.[3] It remains a desirable goal to develop strategies to improve the beneficial effects of neurorehabilitative treatments.

Neuroimaging studies showed increased activity of $M1_{intact\ hemisphere}$ with movements of the paretic hand in patients with motor impairment.[4,5] The role of activity in the intact hemisphere on motor control, presently under investigation, varies depending on lesion site, time from stroke, and magnitude of impairment.[6,7] Patients with stroke experience changes in motor cortical excitability[8–11] and an abnormally high interhemispheric inhibition from $M1_{intact\ hemisphere}$ to $M1_{lesioned\ hemisphere}$ with movements of the paretic hand that is more prominent in cases with more substantial motor impairment.[1] These findings, consistent with interhemispheric competition models of sensory and motor processing,[12–15] raised the hypothesis that purposeful modulation of excitability in motor regions of the intact and affected hemisphere may contribute to improvements in motor function.[16]

Recent studies in animals showed that motor recovery after focal lesions in the hand motor representation can improve with direct epidural cortical stimulation.[17–19] The feasibility and safety of this invasive approach in patients is under investigation;[20] an alternative approach is the use of non-invasive cortical stimulation.

Non-invasive brain stimulation is a powerful method to modulate human brain function.[21–23] Transcranial magnetic stimulation is a painless procedure that modulates cortical excitability and has contributed to the understanding of mechanisms underlying cognitive processes.[21,24] The procedure involves a short strong electrical current that is delivered through an insulated coil of wire placed over the scalp (magnetic coil). The induced electrical currents modulate neuronal excitability at the stimulated sites. Depending on stimulation parameters, transcranial magnetic stimulation can upregulate or downregulate excitability to different extents[25] in the neural structures under the stimulating coil.[26] Transcranial direct-current stimulation is a procedure used to polarise brain regions through the non-invasive application of weak direct currents.[23,27,28] The procedure elicits focal reversible shifts in cortical excitability depending on the polarity, strength, and duration of stimulation.[28] Both techniques can purposefully modulate brain function, are painless and non-invasive, and can be used in double-blind, experimental designs[27,29–34]—although the mechanisms underlying these features may differ (panel[22,23,27,35–38]).

Interhemispheric competition models[16] suggest possible strategies to influence function in the paretic hand (figure): upregulation of excitability in $M1_{lesioned\ hemisphere}$ and downregulation of excitability in $M1_{intact\ hemisphere}$. In this paper we describe recent studies that report the effects of both transcranial magnetic stimulation and transcranial direct current stimulation on cortical excitability and motor function in the paretic hand after chronic stroke. Additional options under investigation include modulation of excitability in non-primary motor regions like the dorsal[39,40] and ventral[41] premotor cortices or the supplementary motor area.

Recent developments

Upregulation of excitability in the affected hemisphere

Two non-invasive strategies have been used to increase excitability in the affected hemisphere: anodal transcranial direct current stimulation and rapid-rate transcranial magnetic stimulation (panel[24,26,28,35]). Anodal transcranial direct current stimulation delivered to $M1_{lesioned\ hemisphere}$ was studied in patients with chronic stroke in sham-controlled double-blind crossover experimental designs.[29–31] These studies showed improvements in performance of motor tasks that mimic activities of daily living (eg, Jebsen Taylor hand function test)[42] with treatment but not with sham stimulation that lasted for more than 30 min after the end of the stimulation period.[29] Performance of less complex motor tasks, such as simple force generation and reaction time tasks, is improved in similar ways (Hummel and colleagues, unpublished data). Behavioural gains were accompanied by enhanced cortical excitability and reduced intracortical inhibition[29,30] within $M1_{lesioned\ hemisphere}$, suggesting the involvement of glutamatergic and GABAergic neurotransmission as possible operating mechanisms.

Khedr and colleagues[32] applied repetitive transcranial magnetic stimulation daily (ten 10 s trains of 3 Hz stimulation with 50 s between each train) combined with customary rehabilitative treatment for 10 days within the first 2 weeks after stroke. The researchers reported motor improvements with repetitive transcranial magnetic stimulation relative to sham lasting for at least 10 days after the end of the treatment.[32] There were no complications with either interventions and the researchers proposed that repetitive stimulation sessions could elicit longer-lasting effects than single applications.

Downregulation of excitability in the intact hemisphere

An alternative approach that could theoretically improve motor function in the paretic hand is downregulation of excitability in $M1_{intact\ hemisphere}$, possibly through modulation of inappropriate interhemispheric inhibition.[1] Previous studies in healthy volunteers showed that downregulation of excitability in one motor cortex results in increased excitability in the opposite motor cortex[43,44] and performance improvements in motor functions of the ipsilateral hand,[45] a mechanism proposed to rely on modulation of interhemispheric inhibition between both primary motor cortices.[14,46] Two studies recently tested this hypothesis applying low-frequency repetitive transcranial magnetic stimulation to $M1_{intact\ hemisphere}$ after chronic stroke in double-blind sham-controlled experimental designs.[33,34] Mansur and colleagues[33] used a crossover design in their study, whereas Takeuchi and colleagues[34] applied real repetitive transcranial magnetic stimulation in one group of patients and sham stimulation in another group. Both studies reported improvements in motor functions in the paretic hand, characterised by improved reaction times and pegboard task performance[33] and improved acceleration of force production[34] compared with sham in the absence of effects on maximum force and finger tapping. Studies with cathodal transcranial direct current stimulation, a

Panel: Non-invasive cortical stimulation

Transcranial magnetic stimulation (TMS) and transcranial direct-current stimulation (tCDS) modulate cortical activity and influence motor, sensory, and cognitive functions

TMS

Delivered to the brain by passing a strong brief electrical current through an insulated wired coil placed on the skull

Current generates a transient magnetic field in the brain inducing electric currents in the cortex that flow parallel to the coil and depolarise neurons

Depending on the frequency, duration of the stimulation, the shape of the coil, and the strength of the magnetic field TMS can activate or suppress activity in cortical regions

Effects of repetitive TMS can outlast the stimulation period for up to 1–2 h.[24,25]

tDCS (1–2 mA)

Applied through two surface electrodes placed on the skull—eg, for the primary motor cortex (M1), one electrode is placed over M1 and one other over the contralateral supraorbital region

Depending on duration and polarity of stimulation, tDCS enhances or depresses excitability in the stimulated region for minutes to 1–2 h

Does not seem to induce direct neuronal depolarisation like TMS but modulates the activation of sodium and calcium-dependent channels and NMDA-receptor activity, promoting long-term-potentiation/long-term-depression-like mechanisms

Similarities

Similar duration of effects (up to hours), non-invasive, and under presently used parameters and guidelines safe

Differences

Possible mechanisms underlying their effects; TMS equipment is more expensive, allows more focal stimulation, protocols are better established; TMS applied with millisecond-level accuracy whereas tDCS is applied over minutes

tDCS is easier to use in double-blind or sham-controlled studies, and more easily applied simultaneous to cognitive and motor training protocols

Safety

rTMS can cause seizures, but strict rules of use and training protocols have made them rare[36]

Patients with a history of seizures should be excluded from studies using this technique

Safety studies are needed for tDCS; brief tingling sensations are common, rarely accompanied by redness under the electrodes[27,35,38]

Transient headaches have been described for both interventions

Remote effects

Application of both of these techniques to one cortical region will probably influence distant cortical or subcortical sites through trans-synaptic effects

In patients with brain lesions, expected models of current flow elicited by both of these techniques may differ from those in healthy brains[37]

Non-specific effects on attention, fatigue, discomfort, or mood

Specificity of both of these techniques on cognitive or motor measures may be influenced by possible concomitant effects on attention, fatigue, discomfort, or mood

Study design and experimental hypotheses

Given these characteristics, similarities, and differences the choice of technique to modulate cortical function is highly dependent on study design and experimental hypotheses

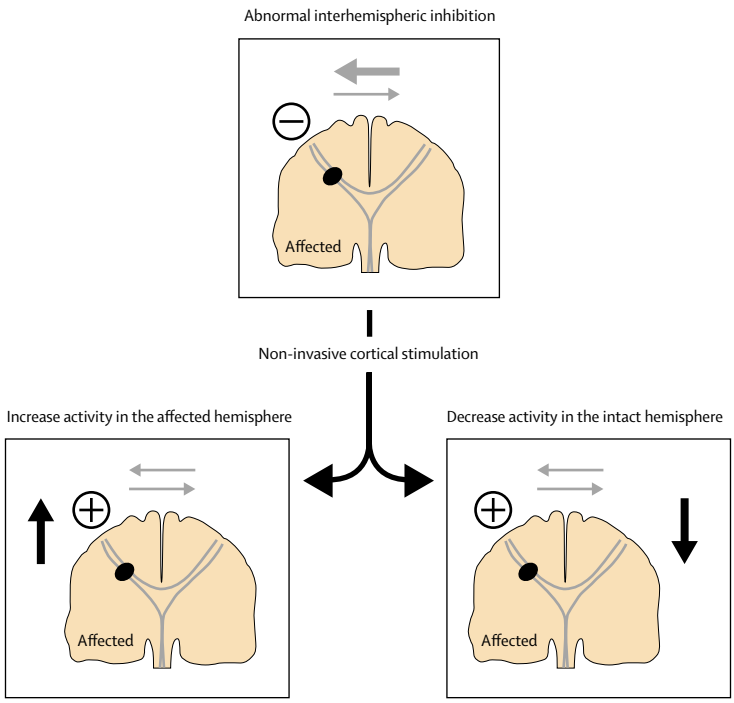

***Figure*: Targets for intervention strategies based on possible pathophysiological mechanisms**
Movements of the paretic hand are associated with unbalanced interhemispheric inhibition targeting the motor cortex of the affected hemisphere in patients with subcortical stroke.[1] Two interventional approaches might normalise this pattern leading to improvements in motor function: upregulation of excitability of the motor cortex of the affected hemisphere[29–31] and downregulation of excitability of the motor cortex in the intact hemisphere.[31,33,34]

form of stimulation that downregulates excitability in the stimulated cerebral cortex, showed results comparable to those achieved with repetitive transcranial magnetic stimulation.[31] These studies reported improvements in tasks that mimic activities of daily living with the paretic hand, which lasted for up to 25 min. One theoretical advantage of this approach over stimulation of the affected hemisphere is its application to healthy neural structures. Direct comparison of the effects of both strategies is inconclusive.

Different mechanisms not mutually exclusive could contribute to the behavioural gains elicited by non-invasive cortical stimulation. Upregulation of excitability in $M1_{lesioned\ hemisphere}$ and downregulation in $M1_{intact\ hemisphere}$ could contribute to correcting abnormalities in interhemispheric inhibition identified after stroke,[1] as proposed in previous reports.[29–31,33,34] This proposal is consistent with the finding that downregulation of excitability in $M1_{intact\ hemisphere}$ may correct abnormally high interhemispheric inhibition from $M1_{intact\ hemisphere}$ to $M1_{lesioned\ hemisphere}$ to an extent proportional to the magnitude of improvements in the paretic hand.[47] These findings are in line with interhemispheric models in other domains such as attention, memory, language and somatosensory processing.[48–52,53] One additional contributing mechanism, proposed by Khedr and colleagues,[32] could be the Hebbian interaction between either form of non-invasive stimulation and rehabilitative training.[32]

These results were obtained mostly in patients with chronic stroke with moderate impairment (group size between six and 20 patients), as the primary outcome measures for these proof of principle studies were relatively complex skilled movements.[29–31,33,34] However, Khedr and colleagues[32] assessed the effects of repetitive transcranial magnetic stimulation in moderately impaired subacute patients (52 patients) starting with the treatment 1–2 weeks after the stroke. It is important to explore in more detail the usefulness of these methods in patients with poor motor recovery, for whom there are virtually no therapeutic alternatives.

Search strategy and selection criteria

References for this review were identified by searches of MEDLINE between 1969 and April 2006 and references from relevant articles. The search terms used were "brain stimulation", "stroke", "recovery", "TMS", "tDCS", "plasticity", "imaging", "interhemispheric inhibition", "intracortical inhibition", "interhemispheric competition". Abstracts and reports from meetings were also included. The final reference list was generated based on originality and relevance to the topics covered in the review.

Where next?

Performance improvements reported so far with transcranial magnetic stimulation and transcranial direct current stimulation have been moderate in magnitude (10–30%) and, depending on the study, relatively transient. Implementation of repetitive stimulation and synchronous application with established rehabilitative treatments may lead to more prominent or longer lasting performance improvements. Areas for future investigation are the optimisation of parameters and sham controls, the role of lesion site, time from stroke, drugs and impairment levels on response magnitude, and duration. The successful implementation of these techniques as interventional strategies for these different patient groups will rely on improved understanding of underlying neuronal correlates of functional recovery.[7,54] Furthermore, from a mechanistic viewpoint, more attention should be paid to possible influences of transcranial magnetic stimulation and transcranial direct current stimulation on subcortical and spinal networks. Additionally, it will be important to determine the extent to which these stimulation techniques influence different types of motor tasks commonly used in neurorehabilitation trials. Despite these limitations, proof of principle studies indicate that non-invasive methods represent powerful approaches to modulate brain function in patients with stroke and could possibly contribute to motor recovery in real-life

neurorehabilitative settings. The data discussed above provide preliminary information, crucial for the design of larger scale, double-blind, sham-controlled clinical trials, which are needed to validate this novel experimental approach.

Contributors

Both authors contributed equally to the preparation of this article.

Conflicts of interest

We have no conflicts of interest.

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