Transcranial Stimulation as a Potential Therapeutic Intervention in Chronic Stroke

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Background

There are records of electrical currents being used for the relief of various neurological and psychiatric disorders for approximately two millennia. Techniques have developed from the use of torpedo electric fish in the days of Galen and Pliny the Elder to the transcranial stimulation techniques in use today: Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS).

TMS elicits excitability changes in the underlying cortex via production of large, rapidly modulating magnetic pulses within a coil placed on the scalp to induce current in the underlying tissue. tDCS involves passing very small currents in the order of a few milliamps through the skull via two large electrodes placed on the scalp. Typically, tDCS currents are passed continuously for between 10 and 20 minutes. Although both techniques have an important potential role in clinical studies, tDCS has a number of practical advantages as a prospective rehabilitation tool in that it is well tolerated, relatively easy to administer and portable. In addition, although the neurophysiological effects of tDCS and TMS are similar, their mechanisms of action are at a cortical level, and therefore their potential effects in patients, are likely to be distinct. For these reasons this review will concentrate mainly on tDCS; for a wider review of the potential of TMS in the stroke population see Hummel & Cohen (2006).[1]

The effects of tDCS are polarity dependent. Anodal stimulation, when the current is flowing from the active electrode over the motor cortex to the reference, is facilitatory whereas cathodal stimulation, where the current flow is in the other direction, is inhibitory.[2] The effects on cortical excitability outlast the stimulation period by up to 90 minutes, dependent on the duration of the stimulation applied. Because of the potential of tDCS to robustly modulate cortical excitability the technique is attracting interest as a potential tool for neurorehabilitation, particularly in the context of chronic stroke.

Neuroimaging studies suggest that patients with impairments of their hand function after stroke demonstrate increased activity in the motor areas within the intact hemisphere when moving their paretic hand compared with controls.[3] This contralesional activity is greatest in patients who have made a poor recovery; patients who have made a good recovery show a more lateralised activity pattern closer to that of healthy controls.[4] In addition, poorly recovered patients exhibit abnormally high levels of inter-hemispheric inhibition between the two motor cortices,[5] suggesting that the intact hemisphere may be exerting a pathological level of inhibition on the stroke-damaged hemisphere. This idea of an "inter-hemispheric imbalance" between the two motor cortices has prompted the use of transcranial stimulation in these patients to try and "rebalance" the hemispheres, either by facilitating the affected hemisphere, or inhibiting or down-regulating the unaffected hemisphere.

Both these approaches have been shown to improve motor function in the affected hand in a clinically relevant task,[6,7] and a recent study has demonstrated that tDCS is capable of shifting the inter-hemispheric balance of motor-related activation in healthy controls,[8] suggesting this "rebalancing" as a putative mechanism for observed behavioural improvements. However, the functional improvements in patients were short-lived, lasting less than one hour before the patients' performance returned to baseline.

For this reason, there remain a number of questions to be answered before transcranial stimulation paradigms can be used as adjuncts to rehabilitation in clinical practice: in particular whether the duration of effects of stimulation can be increased; whether this model of inter-hemispheric imbalance holds true for the wider clinical population and whether the magnitude of the effects would be increased if stimulation was applied in the acute or sub-acute period.

Duration of after-effects

An increasing body of evidence suggests that tDCS modulates both the GABA and glutamatergic systems.[9,10,11] This observation raises the possibility that synaptic modulation occurs with tDCS, and as a result that longer-term modifications in cortical excitability, and consequently behaviour, may be possible if the correct stimulation parameters are used. There is evidence from the animal literature to suggest that in neocortical slice preparations, repeated stimulation sessions are often required to elicit long-lasting excitability changes.[12] Although the stimulation parameters used in these studies are clearly far-removed from those used in humans, a recent study in healthy controls has suggested that the use of repeated stimulation sessions may be a powerful approach. Reis and colleagues investigated the effects of five daily sessions of tDCS paired with a visuo-motor learning task, and demonstrated residual improvements in task performance with tDCS which outlasted the stimulation period by more than 90 days.[13] Similar effects have yet to be established in the chronic stroke population, but this study suggests the potential of such an approach.

Inter-hemispheric Imbalance

A number of studies have demonstrated that down-regulating the unaffected hemisphere using either tDCS or TMS leads to improvements in motor function in patients.[1] However, it is important to note that the patients included in these studies were highly selected for their relatively good recovery and small, sub-cortical strokes. In patients with more extensive or cortical strokes, or in those who have not made such a good recovery, there is increasing evidence that the activity within the unaffected hemisphere may be playing a helpful, rather than a pathological, role.[14,15,16] If transcranial stimulation is to be used as an aid to rehabilitation, then the question of how best to target stimulation must be addressed for the wider population of patients. An algorithm has been proposed based on baseline MRI and neurophysiological characteristics to differentiate between patients who might benefit from therapy targeted to their affected hemisphere and those who might benefit from approaches designed to increase activity in the unaffected hemisphere.[17] This differentiation will become of primary importance if transcranial stimulation approaches become more widely used.

Acute and sub-acute settings

It seems an attractive idea that, if transcranial stimulation can modulate behaviour in the chronic phase of stroke recovery, then it may have even more powerful effects in improving behaviour in the days or weeks following the stroke, when the brain is undergoing massive adaptation and reorganisation. Caution has been applied in this approach for two major reasons: a concern over potential behavioural effects and fears over the safety of the intervention.

In healthy controls the effects of tDCS depend on the background activity of the cortex. If anodal, facilitatory tDCS is applied synchronously with a motor task subjects' performance of that task improves.[18] However, if the stimulation is applied before the task, performance is unchanged.[19] The concept of the effects of a stimulation paradigm being dependent on prior activity within the cortex is in line with the theory of homeostatic plasticity, a regulatory mechanism postulated to stabilise neuronal activity within a useful dynamic range.[20,21] Homeostatic theory might therefore suggest that the effects of transcranial stimulation will differ between patients with concurrent cortical reorganisation and chronic patients. However, in contrast, a therapeutic trial of facilitatory, 3Hz rTMS for 10 days in the acute period, combined with rehabilitation, led to improvements over and above the control condition for a year after stimulation,[22,23] suggesting that beneficial effects can be achieved with stimulation in the acute phase. Similar effects of tDCS in the acute phase have not been demonstrated, but a large, multi-centre trial is currently underway to investigate the potential of the technique in this setting (http://clinicaltrials.gov/ct2/show/NCT00909714).

As with the use of transcranial stimulation in any setting, potential safety has been a concern. Both tDCS and TMS have the potential to induce seizures, although they are now extremely rare as subjects at an increased risk of seizures are excluded from studies.[24] However, in a population where cortical excitability is already increased, seizure risk may also be increased, especially if repeated sessions or high doses of stimulation are used. A number of TMS studies have been performed in the acute and sub-acute phases of stroke, none of which reported any adverse events,[24] suggesting that, for selected patients at least, the procedure is safe. However, as with any novel intervention, adverse event reporting must continue to occur and it will be some time before a full safety profile can be determined.

Summary & Conclusions

Transcranial stimulation paradigms are well-tolerated by patients and induce clinically relevant, albeit short-lived, behavioural improvements. Because of these promising effects in proof-of-principle studies the full potential of transcranial stimulation as a rehabilitation intervention is currently being actively explored by research groups world-wide. It is to be hoped that the results from these studies will allow a more complete understanding of the possible role of transcranial stimulation in stroke rehabilitation. ◆

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