TRANS-CRANIAL DIRECT CURRENT STIMULATION (tDCS): A PROMISING NEW TOOL TO FACILITATE REHABILITATION OF MANUAL DEXTERITY AFTER STROKE

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ABSTRACT

A major cause of disability after stroke is impaired contralateral manual dexterity. Recently it has been suggested that this may be at least partly due to a maladaptive increase in inhibition from the unaffected primary motor cortex (M1). Transcranial direct current stimulation (tDCS) is a non-invasive potential therapy that modulations M1 excitability via a weak electrical direct current applied to the scalp. Immediate improvement of affected hand function was obtained by anodal (excitatory) tDCS over the affected M1 or by cathodal (inhibitory) tDCS over the unaffected M1. Although the tDCS "after-effects" can last for hours to days following a 20-minute stimulation session, they are inherently transitory. There is hope that repeated tDCS sessions applied early after stroke could reduce the maladaptive neuroplasiticy and aid hand dexterity rehabilitation.

Key words: stroke, inter-hemispheric imbalance, manual dexterity, rehabilitation, trans-cranial direct current stimulation

INTER-HEMISPHERIC IMBALANCE IMPAIRS MANUAL DEXTERITY IN STROKE PATIENTS

A major cause of disability after stroke is impaired contralateral manual dexterity that affects more than 50% of stroke survivors. Functional imaging studies have revealed that poor recovery of hand function is associated with an increased activity in the unaffected primary motor cortex (M1) (1), whereas a more contralateral activation pattern, similar to that of healthy individuals, is associated with a good recovery (2). In healthy individuals inter-hemispheric inhibition is balanced between the two M1s via the trans-callosal pathways. Following stroke, a common hypothesis would suggest a maladaptive increase in inhibition from the unaffected M1 which is thought to increase functional impairment of the affected M1 so that the greater the level of inter-hemispheric inhibition, the poorer the recovery (3).

This understanding of inter-hemispheric imbalance in stroke has raised the hypothesis that methods that aim to rebalance excitability between the two M1s, either by increasing the excitability of the affected M1 or by reducing the excitability of the unaffected M1, could be a strategy for rehabilitation of manual dexterity. The M1 imbalance after stroke cannot be satisfactorily compensated by pharmacologic modulation of the excitatory/inhibitory neurotransmission at the whole brain level as these are nonspecific and often have moderate or severe ad-

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verse effects. Several therapeutic interventions for regional modulation of M1 excitability are currently under investigation, such as constraint induced therapy (4), peripheral nerve stimulation (5) and direct brain stimulation (6).

TRANSCRANIAL DIRECT CURRENT STIMULATION

Transcranial direct current stimulation (tDCS) of the brain is a "rediscovered" therapeutic approach for regional modulation of neocortical excitability (7).

In the clinical setting, tDCS can be applied non-invasively using simple neurophysiological equipment. tDCS implies the delivery of a weak direct current (DC) via 2 non-polarizable (e.g. Ag/AgCl or conductive rubber) large patch electrodes attached to the head: an "active electrode" placed just above the cortical region of interest and a "reference electrode" placed as much as possible away from the brain – typically above the contralateral supraorbital ridge or the mastoids. The preference for a cephalic instead of a distant extra-cephalic reference (that would be electrically inert in respect to the brain), is imposed by theoretical safety concerns to avoid the current passing through the heart or through the brainstem and increase the risks of a respiratory arrest.

Commonly, tDCS is carried out by using constant DC currents ("slow oscillating" current waveforms e.g. (8) will not be covered by this review). From the injected current, as much as 50% is "shunted" through the low resistance pathway between the electrodes, given by the scalp. The remaining "residual" current density is maximal at the brain-skull interface and then decreases with the depth of the volume conductor represented by the brain (9). Experimental and mathematical modeling has indicated that a stimulating surface current density around 0.04 mA/cm^2 (e.g. a current of 1 mA delivered over a 5 cm x 5 cm electrode) is necessary to induce biological effects within the whole thickness of the neocortex under the active electrode. It should be clarified that the intended biological effect of tDCS is a shift in neuronal excitability and not direct stimulation of neuronal firing. Thus, tDCS is a subthreshold stimulation technique and, as such, is very well tolerated and has virtually no side-effects (10-12). The only absolute tDCS contraindications are metal implants inside the skull or eye and severe scalp skin lesions. Relative contra-indications are represented by known history of previous seizures or predisposing factors that might increase seizure risk such as neuromodulatory medication. Furthermore, it should be considered that the effects of tDCS have not yet been tested on pregnant or breast-feeding women and should be temporarily avoided in these situations.

POLARITY-DEPENDENT EFFECTS

It was established experimentally that the balance between excitation and inhibition within the cortical region of interest can be modulated by tDCS in a polarity-specific manner (7,13). When the active electrode is held at a positive potential as compared to the reference electrode ("anodal stimulation"), the net result is an increase of network excitability. Conversely, a net decrease in excitability can be induced by "cathodal stimulation" (7).

At first, the directionality of the polarity-dependent effects of tDCS seems to contradict the golden rule of extracellular neurophysiology that excitation arises under the cathode. Indeed, neurons have a membrane potential that is negative in respect to their surroundings and, as such, an extracellular cathode should cause a depolarizing shift in membrane potential (reduces the potential difference across the membrane) hence an increase and not a decrease in excitability. A possible explanation for this discrepancy is that the surface current flow could setup a "virtual electrode" of opposite polarity deeper within the cortex. Furthermore, it should be considered that similar changes in membrane potential, albeit not necessarily of the same magnitude, affect both excitatory and inhibitory neurons that are densely packed within the electric field induced by tDCS. How these neuron-level effects converge into network effects remains poorly understood. It should, however, be emphasized that in healthy brains this relationship between tDCS polarity and excitability changes appeared consistent over different regions strongly suggesting that it depends on the anatomical rather than the functional neocortical organization. This raises the clinically relevant concern whether the same effects will be maintained in pathologic brains with profound alterations in cortical architecture.

AFTER-EFFECTS

The magnitude of the biological effects of tDCS depends on the stimulating current density. However, increasing the stimulation intensity above 0.08 mA/cm^2 increases safety concerns that changes in excitability will reach threshold in the upper cortical layers and, more importantly, that they will

alter excitability of deeper brain structures with unpredictable results (11). During the last decade, attempts to overcome these limitations leaded to experiments with increasing duration rather than the intensity of stimulation. These experiments arise to the unexpected observation that excitability changes induced by tDCS recovered slowly after the stimulation has stopped with a time-course dependent on the duration of stimulation.

The after-effects of tDCS are negligible following stimulation lasting a minute; however, they can outlast a 10-minute tDCS session by more than an hour (14). Even increasing the duration of tDCS sessions up to 20 minutes is typically not associated with electrolytic scalp injury under the active electrode (the occasional mild redness/itching may be left by the electrode, but this is transient and not a sign of skin damage). One should note that current density under the stimulating patch is non-uniform, being maximal at the edges. As a precaution, it is recommended that the intensity of the current applied should not exceed 2 mA and that the electrode should be covered with conductive electrode gel on its whole surface or with sponges immersed in a standard saline solution (NaCl 9%). For a good stability on the scalp, rubber bands or a cap can be used to strap down the electrodes (10-12). Furthermore, it should be considered that the contact impedance changes during prolonged tDCS sessions; so, it is a challenging task for the stimulator to compensate the potential difference to maintain constant the stimulation current. Fortunately, a wide range of relative inexpensive stimulators meet the safety requirements for the task such as those specifically produced by NeuroConn (Ilmenau, Germany). Furthermore, stimulators adequate for nerve excitability testing, such as the DS5 produced by Digitimer (Hertfordshire, England) can also be used, especially in research settings where online monitoring of contact impedance is required.

Although the prompt excitability changes during tDCS – referred to as "online" effects (15) - can reasonably be explained by changes in membrane potential, such potential shifts would also promptly recover at the offset of stimulation and could not account for the after-effects. Thus, other changes must be induced apart from acute changes in membrane potential, which can explain these changes. A number of studies have suggested that prolonged tDCS can also induce long-term regional changes in synaptic activity (16-18), similar to the long-term potentiation (LTP) and long-term depression (LTD) observed with prolonged stimulation of hippocampal synapses in animal experiments (19). This view has generated a fruitful line of research indicating a facilitatory effect of tDCS on learning and memory, especially related to implicit (20,21) or explicit (22,23) acquisition of new motor skills by healthy brains.

tDCS OF THE PRIMARY MOTOR CORTEX (M1) IN STROKE

A number of proof-of-principle studies have been carried out to investigate the improvement of manual dexterity by tDCS of M1, mostly concerning single, unilateral stroke patients without a major direct ischemic injury to M1 (6,24,25). In line with the interhemispheric imbalance paradigm, these studies clearly demonstrate that the affected hand function can be directly facilitated by anodal (excitatory) tDCS over the affected M1 or, indirectly, by cathodal (inhibitory) tDCS over the unaffected M1 (Figure 1).

Stroke patients reported the tingling sensation associated with tDCS less frequently compared to healthy subjects, but more often report a minor headache (12). Particular safety concerns for the use of tDCS in stroke patients are related to the increased risks of seizures and the disruption of gross anatomy of the affected M1. In an attempt to minimize these risks, cathodal stimulation of the unaffected M1 may be preferable to anodal stimulation of the affected M1 especially for patients with damage to the non-dominant than to the dominant hemisphere (26,27). However, it should be noted that the inhibition of the unaffected M1 may not be appropriate in patients with large M1 neuronal loss, whose motor function improvement relies mostly on activity within the unaffected hemisphere.

Optimal placement of the M1 electrode can be defined based on transcranial magnetic stimulation (TMS) localization of the motor hotspot for the hand. Giving the relative large electrode size in respect to the motor hotspot, in routine clinical setting, an anatomical localization based on scalp coordinates is preferred (24,25), being a significantly easier and less time-consuming. In relation to the 10-20 electroencephalographic electrode placing convention, the active electrode is centered over C3/C4, which corresponds approximately to the hand region of M1 (28), while the reference electrode is placed over the contralateral supraorbital ridge (Figure 1).

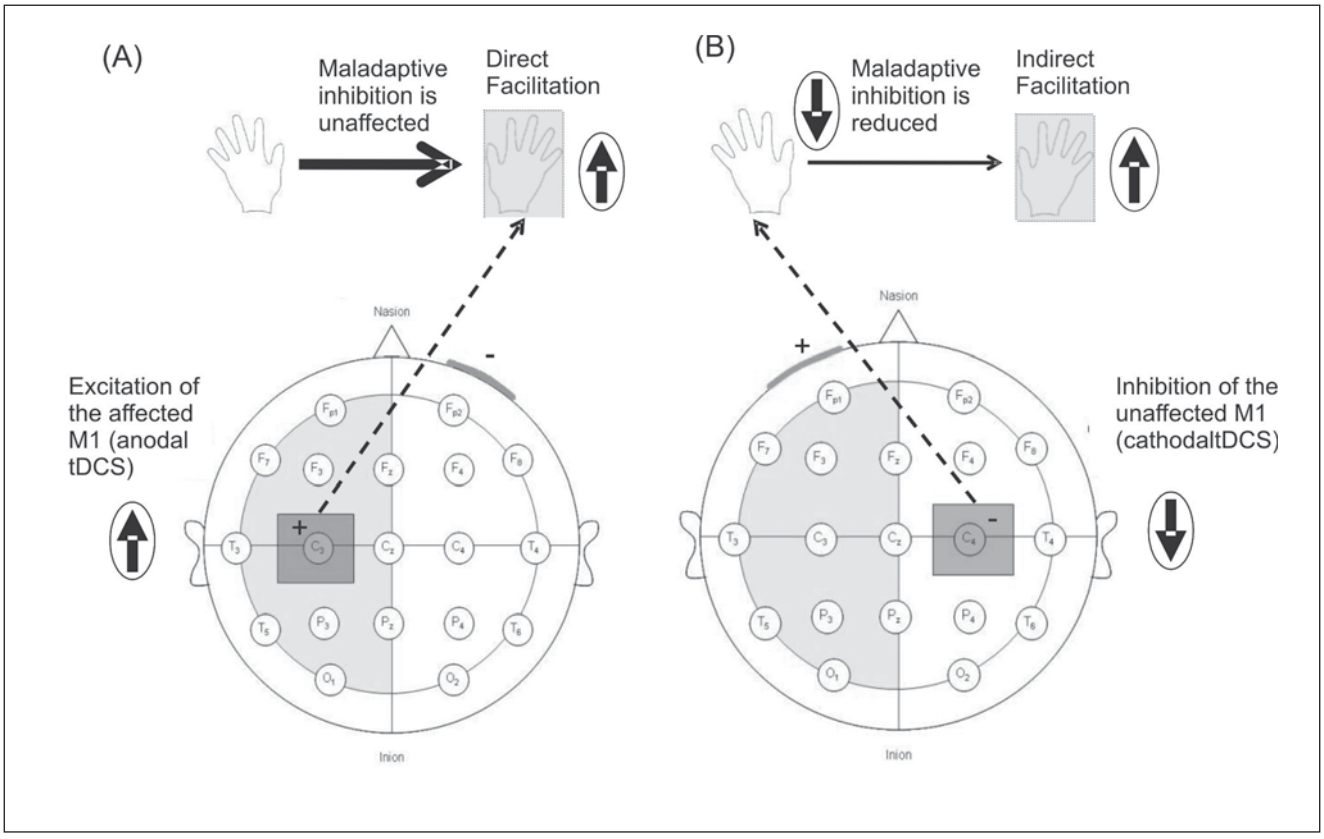

Figure 1. *Transcranial direct current stimulation (tDCS) montages used for rebalancing the interhemispheric inhibition in stroke patients. The active electrode is centered over the representation area of the hand in the M1 (C3/C4 according to the 10-20 electroencephalographic electrode system) and the reference electrode is placed on the contralateral supraorbital ridge. Immediate facilitation of the affected hand function was obtained by anodal (excitatory) tDCS over the affected M1 (A) or by cathodal (inhibitory) tDCS over the unaffected M1 (B).*

To minimize itching, the current should be ramped up gradually over 10 seconds and the contact impedance should be kept below 10 kΩ. A typical tDCS session (either anodal or cathodal) consists in the stimulation of M1 with 1 mA for 20 minutes using 7 cm x 5 cm electrodes.

The immediate tDCS effects can be evaluated by standardized measures such as Upper Extremity Fugl-Meyer-Assessment (UEFMA), Jebsen-Taylor Test (JTT), Action Research Arm Test (ARAT) or Nine Hole Peg Test (NHPT). Although these clinical measures are relevant because they mimic activities of daily living, e.g. ARAT involves grasping, gripping, pinching and gross arm movements, the scoring procedure is subjective and the performance is complex, thus not being appropriate for highly impaired patients. Consequently, these measures can be combined with simpler motor tasks, e. g. objective measurements of the force in the paretic hand by squeezing a dynamometer (maximum grip force task) or the speed of reaction in bending the wrist (reaction time task).

TIMING OF TDCS IN STROKE AND FUTURE PERSPECTIVES

Although tDCS after-effects can extend over several hours and even days, they are inherently transient. Clinical interest for therapeutic applications of tDCS arises in situations associated with neuroplastic changes of the brain (functional/anatomical adaptation), such as the M1 imbalance after stroke in patients with good preservation of the pyramidal tract (29).

Brain neuroplasticity is the primary mechanism responsible for spontaneous recovery after cerebral stroke and comprises in the functional and anatomical reorganization in response to the ischemic neuronal loss. In the first few days post-stroke, there is an acute phase of recovery consisting of a rapid functional improvement which slows progressively in the subacute phase (up to 6 months after the cortical event) and then plateaus in the chronic phase so that it becomes negligible after 3 years following the ischemic event (30).

There is hope that repeated tDCS sessions applied early in the subacute phase after stroke could reduce the maladaptive neuroplasiticy and aid hand dexterity. Little is known regarding the optimal repetition rate, however, in a preliminary study, repeating tDCS over 5 consecutive days was found to be advantageous as compared to weekly sessions (31). Furthermore, consistent with improvement in motor learning in healthy brains, tDCS was found to enhance the effects of rehabilitative hand therapy (32,33), leading to an ongoing large multicentre clinical trial (http://clinicaltrials.gov/ct2/show/NCT00909714).

A growing body of controlled clinical studies will provide indisputable data over the efficacy and safety of tDCS to facilitate rehabilitation of manual dexterity after stroke, leading to a therapeutic tool currently available for clinical use. Nevertheless, optimization of tDCS protocols relies on further research involving both human and experimental animals. One pivotal question that needs to be clarified in the near future is the relationship between tDCS and neuronal energy metabolism (34-36) which is profoundly affected after stroke. Furthermore, it remains to be clarified whether the regional effects of tDCS could be enhanced by systemic pharmacologic manipulations aimed at increasing functional neuroprotection/neuroplasticity.

CONCLUSION

tDCS has a great clinical potential for recovery of manual dexterity after stroke because it can reestablish the inter-hemispheric imbalance for increased periods of time in a non-invasive, safe, easy to administer and low-cost manner. tDCS might become an important therapy in routine rehabilitation both in early and in chronic stages of stroke.

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