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Transcranial direct current stimulation reduces secondary white-matter degradation after stroke

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LETTER TO THE EDITOR

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Motor recovery during the first 3 to 6 months after stroke shows a striking dichotomy. For the upper-extremity, most patients recover ≈70% of the difference between their baseline Upper Extremity Fugl–Meyer (UE-FM) score and the maximum UE-FM score (proportional recovery, PROP) [1]. However, patients with severe initial impairment often show poor recovery (POOR). POOR patients do not sufficiently benefit from current treatment approaches and it would be important to identify new treatment targets that might enable better outcome for this group of patients. Previous studies have shown that POOR patients are characterized by a large lesion load to the cortico-spinal tract and diffuse secondary white matter (WM) degeneration in the affected hemisphere in the subacute period [2, 3]. A reduction of secondary WM degeneration is therefore an interesting treatment goal for patients with POOR.

One treatment strategy that might be able to influence WM tracts is non-invasive brain stimulation (NIBS) [4, 5]. However, the effect in patients with POOR is largely unknown. Here, we analyzed diffusion tensor imaging (DTI) data reflecting WM integrity and Fugl–Meyer (UE-FM) scores of upper extremity motor function from a previous randomized controlled trial [6].

Forty-one stroke inpatients from the Division of Neurorehabilitation, Geneva University Hospitals, Switzerland, with unilateral hemispheric stroke and impaired upper limb motor function (mean age 65 years; mean Fugl-Meyer score 14) participated in the study. The inclusion and exclusion criteria are indicated in the *Supplemental Material*.

This was a randomized controlled study. Participants were assigned to neuronavigated, paired theta burst stimulation (cTBS, a form of rTMS, N=14), cathodal transcranial direct current stimulation (ca-tDCS, N=14), or sham stimulation (N=13) over the contralesional primary motor cortex. Subjects included in the sham group received either sham ca-tDCS or sham cTBS in alternate order. Patients participated in 9 stimulation sessions over 3 weeks combined with 30 minutes of active motor training (see *Supplemental Material* for stimulation details).

The motor deficit was assessed by an occupational therapist using the UE-FM before NIBS and 30-days after. Thirty-four patients underwent DTI and were tested for changes in fractional anisotropy (FA) using tract based spatial statistics before and after NIBS (see *Supplemental Material*). The remaining patients refused because of intolerance such as claustrophobia.

A hierarchical cluster analysis reliably segregated patients into two different recovery groups (cophenetic correlation 0.89). A first cluster of patients improved an average of 68.7% of maximum possible recovery (PROP, N=21) and the second cluster improved 7.1% of maximum (POOR, N=20) (Figure 1A).

Patients with POOR presented significant longitudinal reduction of FA during the treatment period in the affected hemisphere, in particular in the corona radiata, the internal capsule, the corpus callosum, and the superior longitudinal fascicule ($p<0.05$, TFCE corrected, Figure 1B), in accordance with a previous study [3]. This was not the case in patients with PROP.

Tracts with significant degradation in patients with POOR were then defined as region of interest and the mean FA value was extracted for all patients. A two-way ANOVA with stimulation type (cTBS, tDCS, sham) and recovery pattern (PROP, POOR) as

between factors showed a significant main effect of stimulation type ($F_{31,2}$=7, p=0.003) and recovery pattern ($F_{31,2}$=26.2 p<0.0001) on FA decrease within the ROI. Post-hoc comparisons (Tukey-Kramer HSD) revealed that, among patients with POOR, cTBS and sham stimulation groups showed more FA decrease than ca-tDCS patients (p<0.05). Furthermore, FA decreases were significantly lower in the POOR group than in the PROP group only in patients that were treated with cTBS or sham stimulation (p<0.05) but not in patients treated with ca-tDCS (Figure 1C). Therefore, ca-tDCS was associated with a reduction of white-matter degradation in the affected hemisphere, which occurred in patients with POOR in comparison with the other treatment groups.

Furthermore, we observed a significant correlation between FA change in the ipsilesional hemisphere and clinical recovery (r=0.61, p=0.0001) such that more white-matter degradation went along with proportionally less motor improvement (*Supplementary* Figure S1).

Our results provide first evidence that ca-tDCS can reduce secondary WM degeneration in patients with severe motor impairment. Furthermore, the observed correlation with clinical improvement suggests that recovery of motor function might be partly influenced by structural preservation of WM of the lesioned hemisphere.

At this stage, the neuroprotective effects on neural axons following ca-tDCS remains conjectural. However, we can speculate that the reduction of degradation might be due, at least in part, by brain-derived neurotrophic factor (BDNF) and oligodendrocyte precursors were previously reported to go in parallel with tDCS [7, 8]. These factors may promote the survival of neurons and regenerative processes.

The second important result of our study is that ca-tDCS and cTBS have differing effects on WM tracts in subacute phase of stroke. One explanation for this difference

could be the mode of action of each NIBS technique. The first direct consequence of tDCS is the modification of the resting membrane potential during motor relearning. In contrast, cTBS is thought to actively initiate action potentials in neurons and/or alter the level of neural excitability and is applied before the motor therapy [9, 10]. We can speculate that the moment of NIBS coupling is critical. Indeed, tDCS delivered simultaneously with the task may foster specific neuronal networks in the cortex voluntary activated by the patients. tDCS may therefore promote the survival of connections and decrease the likelihood of developing maladaptive changes.

Some caveats have to be taken into consideration. First, our study was limited by the small sample size of POOR patients included. This emphasizes the need to improve patient stratification to include more homogenous study populations. Second, our study design did not include an excitatory stimulation protocol. We can therefore not generalize our findings to the application of excitatory NIBS directly over the ipsilesional hemisphere.

In conclusion, adding ca-tDCS to physical therapy in patients with POOR may interfere with early WM degeneration and lead to better motor outcome. Future studies in a larger population of POOR patients are needed to confirm these results.

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Figure Caption

Figure 1 **Patients with POOR showed significantly reduced white matter degradation after ca-tDCS**.

A histogram of the proportion of motor recovery after stroke demonstrates a separation into two recovery groups (**A**). Patients with poor motor recovery (Fugl-Meyer < 40% of maximum improvement) presented significant degradation of white matter tracts in the affected hemisphere (shown in blue, TFCE corrected $p<.05$, **B**). Green lines indicate examined tracts, red/yellow colors significant differences between groups. This degradation could be reduced by ca-tDCS (**C**). Black horizontal brackets indicate significant differences between groups in post-hoc tests (Tukey-Kramer HSD, $p<.05$).