Transcranial Direct Current Stimulation Enhances Recovery From Motor Deficits Following Neonatal HIE Stroke

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Statement of Purpose: Perinatal hypoxic-ischemic encephalopathy (HIE) stroke, resulting from a blockage of blood vessels and oxygen to specific parts of the brain, affects 1 infant per every 1600 born (van der Aa, Benders et al. 2014). Currently there are no therapies for acute or chronic stroke in this population. The National Institute of Child Health and Human Development recently reported an urgent need to develop neuro-rehabilitative therapies to be used after the insult. One alternative could be a form of neurostimulation known as transcranial Direct Current Stimulation (tDCS); the clinically proven method of noninvasively passing weak, direct electrical currents through the intact scalp and head. The current generates a DC electric field that alters the resting membrane potential of neurons that are under stimulation. It is a safe and unobtrusive way to alter regional cerebral processes and elicit changes in physical and cognitive functioning. Studies have shown that adult patients with chronic stroke had significant improvement of motor function after tDCS of bilateral motor cortices when compared to a sham group (Lindenberg, Renga et al. 2010). This pilot study was aimed to test the efficacy of noninvasive tDCS on the expected behavior a neonatal rat model of HIE.

Methods: Using the Rice-Vannucci model for neonatal HI, 32 P7 rat pups had the left common carotid artery (LCCA) ligated and then were placed in a hypoxic chamber and exposed to 8% oxygen and 92% nitrogen gas for 150 min . The sham group (n=8) had the same incision made on the neck but was sealed without manipulation of the LCCA instead exposed to room air. At P20, Bipolar electrodes were then transplanted onto the left frontal epidural space, corresponding to the ischemic injury on the cortical surface of the cortex. At P21 each animal was anesthetized and the electrode connected to an electronic stimulator with a pulse generator. A corresponding surface electrode was attached to the rat pups chest using a small vest. HI pups were separated into two groups: Non-stimulated (n=13) and Stimulated (n=19). For the Stimulated group, a specific current protocol of short interstimulation intervals of 13 minutes on, 3 off, 13 on at 200 μA was used. Each experiment was performed every day for 1 week with behavior tests occurring beforehand. The Non-stimulated and Sham (n=8) groups were connected to the stimulator for the same duration, but no current was passed. All animals were subjected to multiple neurofunctional tests including negative geotaxis (n=35), grip strength (n=10), and a CatWalk Gait analysis (n=6). Following stimulation and behavior tests, tissue and protein samples were collected and used to measure brain-derived neurotropic factor (BDNF) levels in a small sample group of stimulated and non-stimulated animals (n=3). BDNF has shown to be essential for plasticity and neuronal remodeling (Clarkson, Overman et al. 2011).

Results: The results of the negative geotaxis (Figure 1) The HIE pups in both the Stroke and Stim-Stroke were similar before testing with a marked increase in the time needed to rotate upward when compared with sham operated pups. After stimulation, there was a marked improvement in the negative geotaxic reflex in the Stim group compared with the Stroke group ($p<0.01$ at P25 and continuing for all other time points).

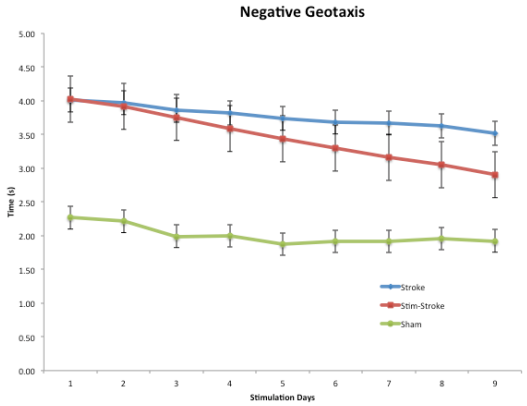

Figure 1. Negative Geotaxis

Grip strength was tested on the contralateral paw to the cortical injury. The Sham group had higher baseline grip strength and there was no difference in the Stroke groups prior to testing. The Stim-Stroke group had an increase in strength compared with the Stroke group after 4 days of treatment ($p<0.01$). The Stim group approached the Sham controlled group at postnatal day 29. Weight was examined prior to and after treatment. Prior to treatment there was no difference between the Stroke group and the Stim-Stroke group. After stimulation, the Stim-Stroke group had a marked increase in weight gain, which differed significantly from the Stroke group at P26 ($p<0.01$) with no significant difference between the Stim-Stroke and sham group at this time point. After analyzing the CatWalk Gait test, the Stimulated stroked pups showed a significant change in right-front to left hind phase dispersion compared to those not stimulated ($p<0.05$), being more comparable to the Sham group, as well as increased paw print area. BDNF showed a 2:1 increase in Stimulated animals compared to a reduction by half in those that were not.

Conclusions: Results of this pre-clinical pilot study suggest that non-invasive tDCS has a positive effect on the motor behavior of young rats following ischemic stroke. These results most likely represent baseline plasticity, which can be seen in neonates and also correlates well to the small sample of BDNF results. We next plan to investigate the changes in BDNF and plasticity in further detail and explore how the current flows through the brain and can be targeted in more specific ways for maximum improvement potential.