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Brain state-dependent peripheral nerve stimulation for plasticity induction in stroke patients

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***Abstract*—Artificial activation of peripheral afferent fibers, with the resulting sensory feedback timed to arrive at the peak negativity of the movement-related cortical potential, induces significant increases in the excitability of cortical projections to the target muscle in healthy individuals and chronic stroke patients. In the currently ongoing study, we applied this associative brain-computer interface paradigm to sub-acute stroke patients. Compared to a sham group, where the peripheral electrical stimulation intensity was below the activation threshold of the sensory afferents, the associative intervention group displayed substantial increases in corticospinal excitability to the target muscle (tibialis anterior).**

I. Introduction

In a typical paired associative stimulation (PAS) protocol, repetitive couplings of peripheral nerve stimulation and cortical stimulation delivered at a specific inter-stimulus interval elicit lasting increases in the excitability of cortical projections to the target muscle [1]. PAS interventions directly follow the principle of Hebbian learning, which hypothesizes that neural assemblies activated in a correlated manner will strengthen synaptic connections [2].

While the cortical stimulation in PAS is typically applied using transcranial magnetic stimulation (TMS), our group has developed a novel PAS-like approach in recent years that replaces TMS with a naturally occurring cortical brain signal associated with actual and imagined movements, the movement-related cortical potential (MRCP) [3], [4]. The MRCP is a negative potential measured by electroencephalography (EEG), detectable up to two seconds prior to the onset of a movement and reaches its peak negative phase (PN) at movement execution, followed by a rebound phase [5].

In our protocol, participants are asked to either imagine or actually perform a ballistic dorsiflexion, hold the contraction for two seconds, and then relax. On each repetition, a single peripheral electrical stimulus of the common peroneal nerve is delivered at motor threshold and timed so that the resultant afferent signal arrives to the cortex at PN of the MRCP. As little as 30 pairings are required to significantly increase the amplitude of TMS-elicited motor evoked potentials (MEPs), a measure of corticospinal excitability, in the tibialis anterior (TA) muscle for at least 30 minutes following the training in both healthy volunteers [3] and chronic stroke patients [4]. Furthermore, in non-associative control groups, where the artificially generated afferent feedback was randomly applied in relation to the different phases of the MRCP and not at PN, there were no such increases in MEPs [3], [4].

The current study was designed to investigate the effect of this intervention on the excitability of cortical projections to the TA muscle of the affected limb in sub-acute stroke patients.

II. Methods

To date in this ongoing study, twelve sub-acute stroke patients have been recruited from the Neurorehabilitation Center in Brønderslev, Denmark. Patients were randomized into either intervention (five men and one woman; age: 59.5 ± 5.2 years; time after stroke: 48.8 ± 33.1 days) or sham (four men and two women; age: 60.3 ± 7.1 years; time after stroke: 59.5 ± 44.8 days) groups.

A. *Movement-related cortical potentials (MRCPs)*

Monopolar EEG signals were recorded using an active EEG electrode system and g.USBamp amplifier (gTec, GmbH, Austria) from FP1, Fz, FC1, FC2, C3, Cz, C4, CP1, CP2, and Pz according to the standard international 10–20 system. Ground and reference electrodes were placed on Fz and the left earlobe, respectively. EEG data were sampled at 256 Hz and filtered between 0-100 Hz. Patients were shown a visual cue including five stages: focus, preparation, execution, hold and rest. After a random duration to focus, a drawing of a ramp appeared on the screen. A cursor moved along the ramp and when it reached the upward turn, the movement period commenced and patients had to perform (or attempt to perform) and sustain a ballistic ankle

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dorsiflexion for 2 seconds, followed by a rest period. During the training phase of the intervention, a total of 30 dorsiflexion trials were completed and the MRCPs and the time of PN were extracted offline.

B. Recording and stimulation

Surface electrodes (20 mm Blue Sensor Ag/AgCl, AMBU A/S, Denmark) were used to record the electromyographic (EMG) activity of the TA muscle of the affected leg at a frequency of 2 kHz. EMG data were amplified and band pass filtered between 10 Hz to 1 kHz.

A monophasic transcranial magnetic stimulator (Magstim 200, Magstim Company, UK) with a focal figure-of-eight double coned coil was used to apply single pulses to elicit a MEP in the TA muscle. Once the hotspot was identified, the resting motor threshold (RMT) was determined. Ten stimuli were applied at 90, 100, 110, 120, 130 and 140% of RMT prior to, immediately following and 30 min after the intervention. The peak-to-peak amplitude of the MEPs was extracted as the dependent variable and expressed as a fraction of the maximum MEP amplitude from the pre-intervention measures.

The deep branch of the CPN of the affected leg was stimulated during the intervention using an external stimulator (Noxitest IES 230, Aalborg, Denmark) with the cathode proximal.

C. The associative and sham interventions

During the testing phase of the intervention, patients were asked to attempt a total of 30 dorsiflexion movements as fast and as powerfully as possible in time to the visual cue. A single electrical stimulation of the CPN was delivered at motor threshold (associative intervention) or below perceptual threshold (sham group) timed to arrive at the cortex at PN of the MRCP.

III. Results

The mean peak-to-peak TA MEP amplitudes prior to, immediately following, and 30 minutes after the intervention for the associative and sham intervention groups can be seen in Fig. 1A and Fig. 1B, respectively. Note the increase in MEP amplitude for the associative but not the sham intervention group at both time points after the intervention compared to pre-intervention values.

IV. Discussion

Based on these results, one single session of the associative BCI intervention appears to lead to substantial increases in corticospinal excitability in sub-acute stroke patients in the associative compared to the sham intervention group. However, due to the relatively low sample size in this ongoing study, statistical analyses have not been employed on these data.

V. Conclusion

The precise temporal association between the patients' own brain commands and the artificially induced afferent feedback is critical in our BCI paradigm and this can be individually tailored to the patients' current brain state.

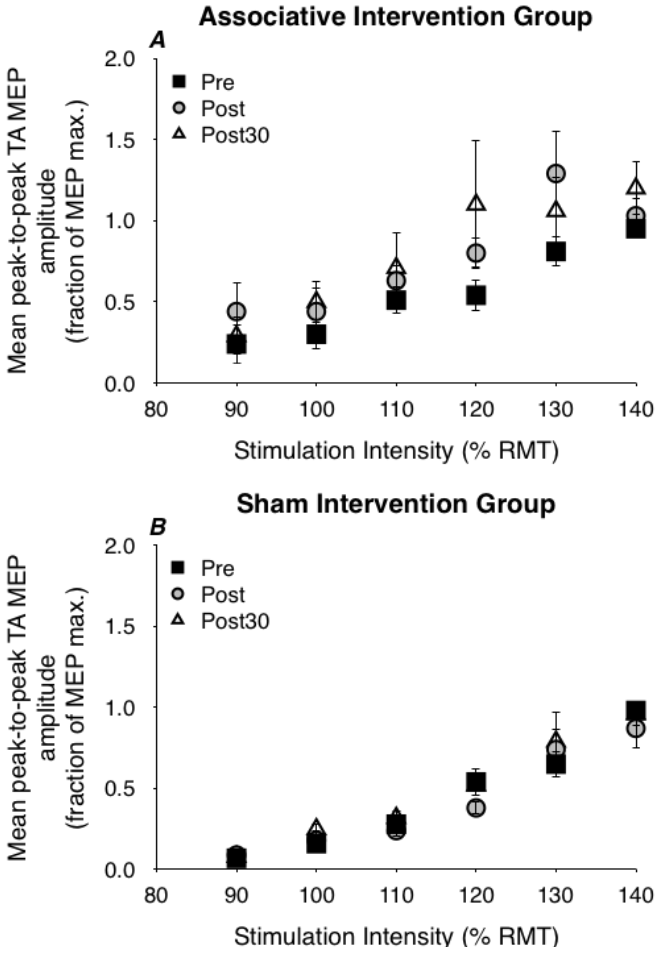

Fig. 1. Changes in motor output after the associative (A) or sham (B) interventions during session 1. Mean (± SEM) TA MEP recruitment curves prior to (pre), immediately following (post) and 30 minutes after (post30) the interventions. TA MEP size is expressed as the peak-to-peak amplitude as a fraction of MEP max. and the TMS intensity as a percentage of RMT.

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