Neuromuscular electrical stimulation and voluntary wrist extension movements elicit similar sensorimotor cortex activation: a continuous-wave fNIRS study

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Abstract— **Our previous study [1] using a high-cost time-domain (TD) functional near-infrared spectroscopy (fNIRS) prototype instrument showed that unilateral neuromuscular electrical stimulation (NMES) evoked wrist extension movements (50% of maximal tolerated current intensity-50%MTI) activated (increase in oxy-hemoglobin-O_2Hb and concomitant decrease in deoxy-hemoglobin-HHb) a similar region of the contralateral sensorimotor cortex (SMC) as that of voluntary (VOL) movements. The aim of this study was to use a continuous-wave (CW) relatively low-cost commercial fNIRS instrument to measure contralateral (left) and ipsilateral (right) SMC activation (O_2Hb and HHb time course, integral [O_2Hb_{INT} and HHb_{INT}] and peak levels [O_2Hb_{max} and HHb_{min}]) during NMES (50%MTI) and VOL wrist extension movements of the right arm in 7 healthy male volunteers. Both NMES and VOL wrist extension movements activated the contralateral (left) and ipsilateral (right) SMC, however, the level of contralateral SMC activation was significantly greater than the ipsilateral SMC. Although the HHb parameters (HHb_{INT}, HHb_{min}) indicated that there was no significant difference between conditions, the O_2Hb parameters (O_2Hb_{INT} and O_2Hb_{max}) indicated a significantly greater contralateral SMC activation during VOL than NMES. Since HHb is less influenced by skin blood flow changes than O_2Hb, we consider that HHb parameters provide a more accurate estimation of task-related cortical activation. In conclusion, these CW-fNIRS findings using HHb parameters indicate that NMES at moderate current intensity (50%MTI) and VOL wrist extension movements elicit a similar contralateral SMC activation, which confirms our previous study using a TD-fNIRS instrument.**

I. Introduction

Neuromuscular electrical stimulation (NMES) improves movements of clinical populations unable to activate their muscles independently, such as post-stroke and incomplete spinal cord injury [2]. During NMES, repeated electrical currents are applied to the peripheral motoneuronal axonal branches overlying the muscle of interest at a stimulation current intensity that elicits muscle contractions. Although less well characterized, the NMES electrical field also activates peripheral sensory neuronal axons that send proprioceptive (and nociceptive) signals from the stimulated/moving muscles and joints to the central nervous system (CNS) leading to improvements in voluntary activation [3, 4]. In this regard, NMES current intensities above the motor threshold have been shown to increase corticospinal excitability [3, 5]. Thus, NMES current intensity above motor threshold is an important factor in determining cortical excitability and activation.

Functional near-infrared spectroscopy (fNIRS) is a non-invasive neuroimaging modality that measures oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin concentration changes in cortical microcirculation blood vessels by means of the characteristic absorption spectra of hemoglobin in the near-infrared range (for review see Ferrari and Quaresima [6]). fNIRS relies on the neurovascular coupling mechanism to infer changes in neural activity that is mirrored by changes in blood oxygenation in the region of the activated cortical area (i.e., the increase in O_2Hb and the decrease in HHb) [7]. Thus when a specific brain region is activated, cerebral blood flow increases in a temporally and spatially coordinated manner tightly linked to changes in neural activity through a complex sequence of coordinated events involving neurons, glia, arteries/arterioles, and signaling molecules [8]. Given that fNIRS does not require stringent physical and head constraints, and moreover the optical measurements are not affected by the electrical or magnetic fields, fNIRS represents a suitable cortical imaging monitoring tool during NMES.

In our previous study [1], we utilized a prototype time-domain (TD) fNIRS instrument to determine the absolute O_2Hb and HHb concentration changes in a cortical sensorimotor network induced by unilateral NMES-evoked wrist extension movements at increasing current intensities relative to the individual maximal tolerated current intensity (MTI), and with reference to those obtained in response to voluntary (VOL) wrist extension movements. The unilateral VOL wrist extension movements were characterized by activation of regions of the contralateral sensorimotor network centred on the sensorimotor cortex (SMC), which is well known to be activated to perform hand motor tasks [9-11]. NMES-evoked wrist extension movements also activated the contralateral SMC. However, the regions and levels of activation were greater for NMES than VOL, which we consider was due to greater discomfort/pain induced by the higher stimulation currents of the MTI conditions. Since we found a relatively similar SMC activation pattern between the 50%MTI and MTI conditions but with minimal discomfort/pain compared to the MTI conditions, we consider that the 50%MTI condition is a more suitable current intensity (13-25mA) to compare to VOL wrist extension movements.

Therefore, the aim of this study was to utilize a commercial continuous wave (CW) fNIRS instrument to measure the relative O_2Hb and HHb concentration changes from left and right SMC during unilateral NMES (50%MTI) and VOL wrist extension movements. We hypothesize that both NMES and VOL wrist extension movements will activate the contralateral (left) SMC greater than the

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ipsilateral (right) SMC. Since our previous study [1] showed that HHb is less influenced by changes in skin blood flow, it will provide a more accurate measure of cortical activation.

II. Materials and Methods

A. Subjects

Seven healthy male volunteers (26.3 ± 4.3y) participated in this study. All subjects were right handed as determined by the Edinburgh handedness questionnaire [12], and all subjects had no known health problems or any upper extremity muscle or joint injuries. The study conformed to the recommendations of the local Human Research Ethics Committee in accordance with the Declaration of Helsinki.

B. Neuromuscular Electrical Stimulation

NMES was carried out with the portable CEFAR Physio 5 system (DJO France SAS, France). A pair of self-adhesive electrodes of 25cm^2 (5cm x 5cm) were placed on the motor point of the right wrist extensor muscles (i.e., extensor carpi radialis longus, extensor carpi radialis brevis, extensor digitorum communi, and extensor carpi ulnaris) and the distal end of the muscle near the wrist.

C. Functional Near-infrared Spectroscopy

A CW fNIRS system (Oxymon Mk III, Artinis Medical Systems, The Netherlands) was used to measure the relative changes of O_2Hb and HHb concentrations in the bilateral SMC regions during NMES and VOL conditions. This device measures changes in light attenuation at two wavelengths, 765nm and 856 nm. Two optical fiber bundle receivers (avalanche photodiode detector) and 8 optical fiber bundle transmitters were placed in a specially designed cap to obtain 8 measurement points (which are defined as the midpoint of the corresponding detector-transmitter pairs separated by ~3 cm) primarily covering the left (4 channels) and right (4 channels) SMC regions (see Fig. 1 for locations of the 8 channels). The cap was positioned according to the International 10-20 system for the electroencephalography electrode placement. The O_2Hb/HHb data from the 8 measurement points were acquired at 10 Hz.

D. Experimental Protocol

Initially, each subject's MTI was determined by using a series of 6-8 brief (3-5s) electrically stimulated contractions (biphasic symmetrical rectangular pulses at 30 Hz frequency and 200 μs pulse width) with increasing current intensity. After each increase in current intensity, the subject was asked to report their tolerance to further increases in current intensity. Then, MTI was defined as the intensity of stimulation received when the subject was unable to tolerate an increase in current intensity. Three MTI attempts were made at an individual level in order to ensure a consistent MTI determination. The group-range of MTIs was between 30-50 mA with a group-average MTI of 41 ± 7 mA. The fNIRS experimental session started at least 10 min after determining the individual MTI.

Subjects first performed the VOL condition, which consisted of 10 blocks of 10 wrist extension contractions (70° wrist extension, 1-s duration interleaved with 1-s rest, 0° wrist extension). Consecutive blocks were separated by a 20-s rest interval. Five min after the end of the VOL contractions, the subjects underwent the NMES condition at 50%MTI (30 Hz; 200μs). The NMES condition consisted of 10 blocks of 10 evoked wrist extension contractions (1-s stimulation, 1-s rest) with a 20-s interval between blocks. During the data collection procedure, the time course of changes in O_2Hb and HHb concentration values were displayed in real time, and the signal quality and absence of movement artifacts were verified.

At the end of each experimental condition subjective pain was measured using a pain rating scale (PRS) and discomfort ratings using a visual analogue scale (VAS)[1]. Participants were asked to verbally rate the level of pain on the PRS from 0 (no pain) to 12 (extremely painful), and to manually mark the level of discomfort on the VAS, consisting of a 10-cm line with "no discomfort" on one end and "intolerable sensation" on the other end.

E. Data Analysis

The changes in O_2Hb and HHb concentrations (expressed in μM) were calculated by the fNIRS system according to a modified Beer-Lambert Law that included an age-dependent constant differential pathlength factor ($4.99+0.067*Age^{0.814}$) [13].

The time course of changes in O_2Hb and HHb concentrations for each of the 8 channels were first low-pass filtered at 0.1 Hz to attenuate cardiac signal, respiration, and Mayer-wave systemic oscillations [13], and then each of the 10 task blocks (20-s duration) were normalized using the mean of the O_2Hb and HHb values measured during the last 5s of the 20-s rest period preceding each block. The filtered and normalized O_2Hb and HHb time course data of all 8 channels were then sample-to-sample averaged (i.e., 10 samples/s) over the 10 blocks, yielding one average O_2Hb and HHb time course for each subject. A number of O_2Hb and HHb parameters were then computed from the individual average O_2Hb/HHb time course:

i) The group average time course of changes in O_2Hb and HHb concentrations during the VOL and NMES condition were calculated from the 5s average data covering the 5s before (baseline time point), 20-s task period (4 time points), and 10-s after (2 time points), resulting in 7 time points for each of the 8 channels and subject, which was then averaged at a group level.

ii) The integral values of the changes in O_2Hb (O_2Hb_{INT}) and HHb (HHb_{INT}) concentrations during the 20-s task period were calculated as the area under the curve from the beginning (at 0s) until the end of the task period for each of the 8 channels and subject, and were then group averaged.

iii) The peak changes in O_2Hb and HHb concentrations during the 20-s task period were computed as the O_2Hb maximum (O_2Hb_{max}) and the HHb minimum (HHb_{min}) values for each of the 8 channels and subject, and then group averaged.

F. Statistical Analysis

For statistical analysis of the O_2Hb and HHb time course for each of the 8 channels, a Condition (NMES, VOL) x Hemisphere (Left SMC, Right SMC) repeated measures ANOVA over time (baseline, 5s, 10s, 15s, 20s, 25s, 30s) was

used. For statistical analysis of the O_2Hb_{INT}, HHb_{INT}, O_2Hb_{max}, and HHb_{min} parameters during the task period, a Condition (NMES, VOL) x Hemisphere (Left SMC, Right SMC) x Channel (8 channels) ANOVA was used. If a significant main or interaction effect was evident, then post-hoc Tukey's tests were performed. Significance was set at $P \leq 0.05$. Data are presented as mean ± SD.

III. Results and Discussion

The VOL wrist extension movements induced no subjective indications of pain or discomfort. The NMES condition at moderate current intensities (20.6±3.5 mA) produced overt wrist extension movements as those produced during VOL. However, the stimulations were considered mildly painful (PRS: 2.1±2.0; Scale 0-12) and discomforting (VAS: 3.3±1.4; Scale 0-10).

Fig. 1 shows the group mean time course of changes in O_2Hb and HHb concentrations for each of the 8 channels during the VOL and NMES conditions. As shown in Fig. 1, for both the VOL and NMES conditions, significant increases in O_2Hb and concomitant decreases in HHb from baseline were observed in all left SMC channels; while only 1 channel on the right SMC (Ch 6) showed this effect.

Table 1 shows the group mean changes in O_2Hb and HHb parameters during the NMES and VOL conditions. The HHb parameters (HHb_{INT}, HHb_{min}) indicated that there was no significant difference between NMES and VOL conditions for either the left or right SMC; however, the O_2Hb parameters (O_2Hb_{INT} and O_2Hb_{max}) indicated a significantly greater left SMC activation during VOL than NMES. Since our previous study [1] and that of others [14] have shown that HHb signal responses are less influenced by superficial layer changes, HHb might be a more appropriate fNIRS signal to determine real cortical activation changes. In the present study, since there were no significant differences between the NMES and VOL conditions for any of the HHb parameters we are confident that this represents the true cortical activation, and that O_2Hb parameters are in some way contaminated by skin blood flow changes, which were more affected in the VOL than NMES condition.

TABLE I. Group Mean (± SD) changes in Oxygenated (O_2Hb) and Deoxygenated (HHb) hemoglobin parameters from the left (channels 1,2,3,4) and right (Channels 5,6,7,8) sensorimotor cortex (SMC) during neuromuscular electrical stimulation (NMES) and voluntary (VOL) wrist extension movements

		Condition	
Parameter	**SMC**	***NMES***	***VOL***
O_2Hb_{INT} (µM•s)	Left	3.82 (± 0.56)*+	6.07 (± 0.72)*
	Right	1.08 (± 0.79)+	3.22 (± 1.26)
HHb_{INT} (µM•s)	Left	-1.94 (± 0.17)*	-2.05 (± 0.51)*
	Right	-0.62 (± 0.45)	-0.96 (± 0.56)
O_2Hb_{max} (µM)	Left	0.33 (± 0.04)*+	0.44 (± 0.03)*
	Right	0.21 (± 0.05)	0.28 (± 0.05)
HHb_{min} (µM)	Left	-0.17 (± 0.01)*	-0.16 (± 0.03)*
	Right	0.10 (± 0.02)	0.10 (± 0.03)

*: Significant (P<0.01) difference between Left and Right SMC; +: Significant (P<0.05) difference between NMES and VOL Condition

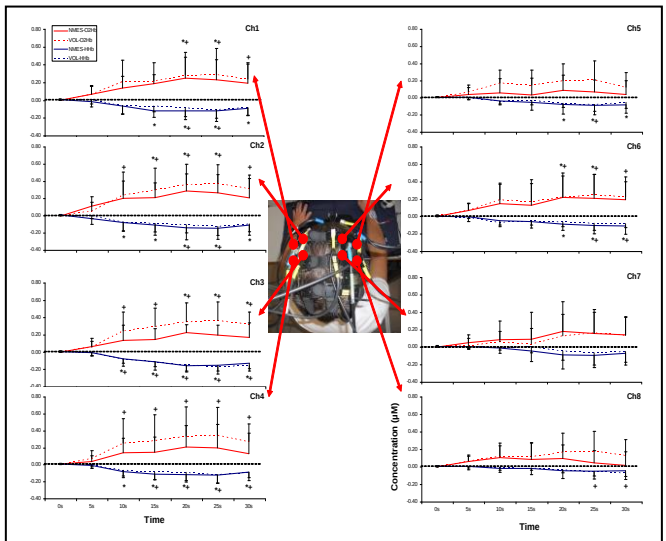

Figure 1. Group mean (±SD) time course of changes in oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin concentrations from the left (Ch 1,2,3,4) and right (Ch 5,6,7,8) sensorimotor cortex during neuromuscular electrical stimulation (NMES) and voluntary (VOL) wrist extension movements.*: NMES significantly ($p<0.05$) different from baseline (0s); +: VOL significantly ($p<0.05$) different from baseline (0s).

As expected, VOL wrist extension movements activated (increase in O_2Hb and concomitant decrease in HHb) the contralateral (left) SMC that is well known to be associated with unilateral motor tasks [11, 15]. NMES-evoked wrist extension movements also increased contralateral SMC activation, which confirms our previous study [1] using TD-fNIRS system, and is also in agreement with fMRI studies that compared the cortical sensorimotor network activation profile between VOL and NMES-evoked movements at current intensities at or above the motor threshold [16, 17].

The clinical benefits of NMES have been proposed to be *via* a sensorimotor integration mechanism; increased proprioceptive signals from NMES-evoked movements activate the sensorimotor network, particularly the SMC, thereby increasing corticospinal excitability, and facilitating greater voluntary activation of the relevant neuronal network [4, 18]. Accordingly, it can be suggested that NMES-evoked wrist extension movements at moderate current intensities (50%MTI) activate brain regions related to sensorimotor integration. This provides evidence for the concept that NMES-evoked somatosensory (and nociceptive) inputs to the CNS lead to changes in SMC excitability [3, 4], which in turn can cause functional improvements, including muscle activation and strength [4]. Note that the detection of bilateral SMC activation (particularly the anterior SMC channels 5 and 6) elicited by unilateral VOL and NMES-evoked wrist extension movements is consistent with the presence of transcallosal interactions between the two hemispheres [19].

IV. Conclusion

The results of the present study performed with a relatively low-cost commercial CW fNIRS instrument, have shown that NMES-evoked wrist extension movements at moderate current intensity (50%MTI) activate a relatively similar contralateral SMC region compared with VOL movements. These findings confirm our previous TD fNIRS study [1] (performed with a high-cost prototype), which also suggested that HHb is a more appropriate parameter for determining the

level of cortical activation. This fNIRS study provides a better understanding of how therapeutic NMES of the peripheral nervous system could interact with the CNS, which may allow for improved neurorehabilitation monitoring.

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