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EFFECT OF MRGFUS TREATMENT ON CORTICAL ACTIVITY IN PARKINSON'S DISEASE: A FNIRS STUDY

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Abstract. In this paper, a new combined approach, based on Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) technique and functional Near Infrared Spectroscopy (fNIRS), was applied for treatment and monitoring of patients affected by bilateral Parkinson's disease (PD). On one side, MRgFUS enables non-invasive thalamotomy by combining FUS for tissue ablation and MR for targeting and monitoring. On the other side, fNIRS allows to monitor, non-invasively and without strict motion restriction even in a daily life environment, cortical neural activity related dynamics of both oxygenated and deoxygenated haemoglobin (HbO and HbR, respectively). In particular, the changes of cortical activation pattern in PD patients, with respect to age matched healthy control subjects, were analysed, while performing left and right hand finger tapping (LFT and RFT, respectively), before MRgFUS treatment, and at two different time intervals after the treatment. By comparison with the pre-treatment session, significant activations were predominantly observed one week after the treatment, with patterns recalling those of control group, and partially lost one month later, likely because of the neurodegenerative nature of PD. In addition, activations were more marked for LFT task, being the treatment performed on the right hemisphere. These results appear promising in view of the application of fNIRS for neurorehabilitation, especially in those clinical settings where traditional neuroimaging techniques cannot be applied.

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders in elder age, affecting about 2% of the people 65 years of age and older (de Rijk *et al.* 2000), with some of the principal signs related to the motor system being tremor, movement slowness, gait instability and rigidity (Savitt *et al.* 2006). PD is principally treated with pharmacological therapies based on dopamine precursors such as the levodopa (Cotzias *et al.* 1969). However, surgical approaches have reemerged as an alternative to pharmacological therapies due to both theoretical and technological advances in neurosciences. In particular, deep brain stimulation (DBS) (Bergman *et al.* 1990; Hariz and Hariz 2013) has been largely used in the last decades due to its adaptability and reversebility, allowing also to perform bilateral interventions. However, other than having high costs, DBS introduces new challenges, such as intracranial hemorrhages, stroke, and infections (Bronstein *et al.* 2011). For this reasons, alternative techniques have been studied and tested, and one of the most promising in this sense is Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) (Weintraub and Elias 2017; Jung and Chang 2018). It is an innovative surgical procedure which allows perfoming non-invasive thalamotomies through a combination of focalised ultrasounds to ablate tissues and Magnetic Resonance to target the ablation spot and monitor the surgery progress. Such a technique has been already applied successfully in many cases, such as to treat essential tremors (Chang *et al.* 2015; Chang *et al.* 2018) and obsessive-compulsive disorders (Jung *et al.* 2015a), and it is currently being tested for other pathologies such as cancer (Furusawa *et al.* 2006; Catane *et al.* 2007; Lamsam *et al.* 2018). Remarkably, only few preliminary studies have so far focused on the MRgFUS treatment of PD: they showed that patients' quality of life was generally better with respect to the pre-treatment phase even six months (Fasano *et al.* 2017) and one year (Jung *et al.* 2019) after MRgFUS treatment. Nevertheless, in some cases side effects occurred and patients' conditions got worse after one month.

To date, mechanisms underlying MRgFUS treatment have been studied principally through the visualization of brain connectivity during resting state with functional Magnetic Resonance Imaging (fMRI) (Martínez-Fernández *et al.* 2018). However, when dealing with movement disorders, it would be important to monitor the effects on the motor neural network when performing movements or tasks. In this context, functional Near Infrared Spectroscopy (fNIRS) is a relatively new imaging technique based on the optical absorption of near-infrared light (having wavelength in the 700-900 nm range) by the blood, which is strictly related to the concentration of chromophores such as oxygenated and deoxygenated haemoglobin (HbO and HbR, respectively) (Arenth *et al.* 2007; Irani *et al.* 2007; Leff *et al.* 2011). With respect to other common imaging techniques, including fMRI, Positron Emission Tomography (PET) and Computed Tomography (CT), fNIRS presents several advantages such as lower costs and higher portability. In particular, it allows measurements even when an individual is performing motor tasks, such as walking and running (Suzuki *et al.* 2004), or manipulation of complex objects (Hatakenaka *et al.* 2007; Ikegami and Taga 2008). In certain situations, these aspects make fNIRS a better choice even though some limitations are still present, such as low spatial resolution, as well as limited ability to measure signals from deep brain structures. The aforementioned reasons can explain why fNIRS is becoming a useful tool in neurological rehabilitation, for example for monitoring the recovery from brain damage (Mihara and Miyai 2016).

In this paper, we report preliminary results of a wide investigation carried out in order to probe the reliability of fNIRS as a monitoring tool for patients affected by PD and treated with MRgFUS. Specifically, in the adopted protocol, three sessions of both LFT and RFT were carried out by 5 patients, respectively before, one week after and one month after they underwent treatment with MRgFUS. During these sessions, changes in HbO and HbR concentrations were measured and the acquired data were compared with those obtained from 3 healthy participants, to assess whether the MRgFUS treatment allowed a recovery at a neural activity level. MRgFUS was found to induce significant HbO and HbR concentration changes, with respect to pre-surgery phase, mainly one week after the treatment, with activation patterns more similar to the control group, and for LFT task. These findings were interpreted as due to the neurodegeneration of PD and to the unilaterality of the treatment.

Although the low number of analysed patients could limit the validity of this study, the obtained results are in agreement with those reported in other papers (Fasano *et al.* 2017; Jung *et al.* 2019), and support fNIRS as a low-cost monitoring procedure in the field of neurorehabilitation when motor areas of the cerebral cortex must be controlled, expecially in cases in which habitual neuroimaging protocols cannot be applied.

2. Materials and methods

2.1. Subjects. 5 patients from IRCCS Centro Neurolesi "Bonino-Pulejo" of Messina (Italy), affected by Parkinson's disease (age range 62-79, 2 female; subject identification code 1 to 5), participated in the experiment (demographic data are reported in Table 1). All patients were treated on the most affected hemisphere (the right one). Furthermore, 3

ID	Neurological disorder	Affected hemisphere	Age	Sex
1	Parkinson	Right	76	m
2	Parkinson	Right	75	m
3	Parkinson	Right	79	f
4	Parkinson	Right	62	m
5	Parkinson	Right	67	f
C1	None	None	66	m
C2	None	None	68	f
C3	None	None	71	m

Table 1. Demographic data for both Parkinson's disease patients and control subjects.

subjects with no neurological diseases participated in the experiment as control subjects (subject identification code C1, C2 and C3). The study procedures were approved by

Local Ethics Committee of IRCCS Centro Neurolesi "Bonino-Pulejo" and informed written consent was obtained from all participants.

2.2. Setup and protocol. The experiment consisted of three different sessions:
- before the MRgFUS treatment (S0);
- one week after the MRgFUS treatment (S1);
- one month after the MRgFUS treatment (S2).

Each of these sessions included two finger-tapping tasks, one performed with the left hand (LFT) and the other with the right (RFT). Each task begun with a 10 s rest phase to allow signal stabilization, then finger-tapping execution periods of 25 s were alternated with 15 s rest phases in order to have six couples of task-rest phases. The duration of the total finger-tapping session was 250 s (Fig. 1).

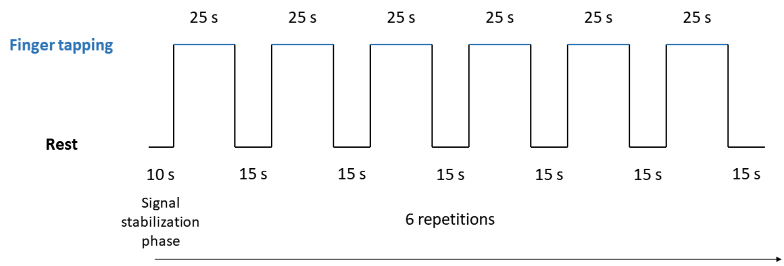

Figure 1. Experimental protocol for left/right finger tapping tasks. The total duration of a session was 250 s. The blue lines specify when finger tapping was executed with respect to rest phases.

A single session of LFT and RFT was performed by control subjects. Data acquisition was performed through a Hitachi ETG-4100 NIRS system, equipped with near-infrared light emitters at two wavelengths (695 nm and 830 nm, respectively) and operating at a sampling rate of 10 Hz. The configuration matrix chosen for the experiment was composed by 3×5 optodes (8 sources and 7 detectors), 22 channels in total (on average 13 ± 1 channels for the right hemisphere and 9 ± 1 channels for the left hemisphere). This matrix was positioned slightly above the forehead to acquire signal from the prefrontal, motor and parietal cortices. Channel spatial registration from real coordinates to Monteral Neurological Institute (MNI) coordinates was performed through dedicated software, using the inion, the pre-auricular points anterior to the left and right ears, and the nasion as references.

Subjects' hair were cut before starting each session to reduce the noise due to their presence. Other sources of noise could be still present and were unavoidable, such as the scalp depth or the head conformation. Collected data were analysed by the NIRS-SPM

(Statistical Parametric Mapping) software (version 4, revision 1) (Jang *et al.* 2009; Ye *et al.* 2009; Tak *et al.* 2010, 2011; Li *et al.* 2012), developed for MATLAB© R2009a (MathWorks Inc., Natick, MA), and with MATLAB© R2009a itself.

2.3. Measurement model. The basis of a fNIRS measure is the Modified Beer-Lambert Law (MBLL), which describes light absorption in a non-uniform scattering medium as a biological tissue (Cope and Delpy 1988). Assuming HbO and HbR being the only chromophores involved, the optical density change $\Delta\rho(\lambda,r,t)$ can be written as:

$$\Delta\rho(\lambda,r,t) = -ln\left(\frac{I(\lambda,r,t)}{I_0(\lambda,r)}\right) = d(r)l(r)[a_{HbO}(\lambda)\Delta c_{HbO}(r,t) + a_{HbR}(\lambda)\Delta c_{HbR}(r,t)], \tag{1}$$

where λ is the incident radiation wavelength, r the cerebral cortex position in 3D (x,y,z) space, and t the time. $I_0(\lambda,r)$ represents the initial radiation intensity, $I(\lambda,r,t)$ the radiation intensity at time t, $a_{HbX}(\lambda)$ the extinction coefficient of the HbX chromophore (where X stands for O or R), $\Delta c_{HbX}(r,t)$ the change in concentration of the HbX chromophore, $d(r)$ the differential path-length factor (DPF), and $l(r)$ the distance between source and detector (this last assumed to be at position r).

In order to estimate the change in concentration for both HbO and HbR, measurements at two different wavelenghts, namely λ_1 and λ_2, must be performed. If we assume that $d(r)$ does not depend on λ, the matrix formulation of the equation 1 can be written as:

$$\begin{bmatrix}\Delta\rho(\lambda_1,r,t)\\ \Delta\rho(\lambda_2,r,t)\end{bmatrix} = d(r)l(r)\begin{bmatrix}a_{HbO}(\lambda_1) & a_{HbR}(\lambda_1)\\ a_{HbO}(\lambda_2) & a_{HbR}(\lambda_2)\end{bmatrix}\begin{bmatrix}\Delta c_{HbO}(r,t)\\ \Delta c_{HbR}(r,t)\end{bmatrix} + \begin{bmatrix}w(\lambda_1,r,t)\\ w(\lambda_2,r,t)\end{bmatrix}, \tag{2}$$

where $w(\lambda_i,r,t)$ is the additive noise for the i-th wavelength ($i = 1,2$).
In order to obtain the signal $S_{HbX}(r,t)$ for the haemoglobins, the inverse matrix of the extinction coefficients must be multiplied for equation 2:

$$\begin{bmatrix}S_{HbO}(r,t)\\ S_{HbR}(r,t)\end{bmatrix} = d(r)l(r)\begin{bmatrix}\Delta c_{HbO}(r,t)\\ \Delta c_{HbR}(r,t)\end{bmatrix} + \begin{bmatrix}\varepsilon_{HbO}(r,t)\\ \varepsilon_{HbR}(r,t)\end{bmatrix}, \tag{3}$$

where $\varepsilon_{HbX}(r,t)$ is the additive zero mean Gaussian noise for the HbX chromophore.

It is possible to obtain the DPF parameter $d(r)$, both in time domain and frequency domain systems, by evaluating the temporal point spread function (Zhao *et al.* 2002). Nonetheless, as said before, other conditions, such as the scalp depth and the head conformation, can alter fNIRS measurements, resulting in the introduction of subject-dependent scattering effects. As a consequence, the analysis in terms of the raw magnitude of chromophore concentration changes could be challenging, and a Generalized Linear Model (GLM) is generally used to help reducing the impact of such negative effects.

2.4. Generalized Linear Model (GLM) and wavelet Minimum Description Length (wavelet-MDL) detrending. Generalized Linear Model is a standard procedure widely employed for the analysis of both fMRI and fNIRS results (Ye *et al.* 2009). It allows describing a measured quantity in terms of a linear combination of N explanatory variables plus an error term. The GLM matrix formulation can be written as:

$$\mathbf{S} = \mathbf{X}\beta + \varepsilon, \tag{4}$$

where $\mathbf{S}$ is the M-dimensional vector (where M is the number of time samples) of the hemodynamic signal $S_{HbX}(r,t_i)$, taken as dependent variable, ε is the M-dimensional vector of noise $\varepsilon_{HbX}(r,t_i)$, β is a L-dimensional vector of unknown strength response variables (where L is the number of such indipendent variables), and $\mathbf{X}$ is the matrix of the model design, representing the predictor for the signal, to be specified first.

The signal can be thought as the convolution of a stimulus function (due to the alternation of rest and task phases) and a hemodynamic response function (HRF). In our study, for the model specification, the canonical HRF composed by two gamma functions (Jang *et al.* 2009; Ye *et al.* 2009; Tak *et al.* 2010, 2011; Li *et al.* 2012) was convoluted with a stimulus function that was equal to 0 during rest phase and equal to 1 during task phase. Such convolution represented the independent variable.

Because fNIRS signals are generally affected by a global drift, we also included in the analysis the wavelet Minimum Description Length (wavelet-MDL) algorithm described in (Jang *et al.* 2009). Following this rationale, equation 4 becomes:

$$\mathbf{S} = \mathbf{X}\beta + \theta + \varepsilon, \tag{5}$$

where θ is the vector for the global drift.

To test the null hypothesis of no significant activation for a channel with respect to a reference phase (the rest phase), a t-statistics coefficient can be calculated for the model of equation 5 (Jang *et al.* 2009). Here, this statistics was applied to both HbO and HbR signals (the $\mathbf{S}$ vector) for each patient separately, always using the NIRS-SPM software (Jang *et al.* 2009; Ye *et al.* 2009; Tak *et al.* 2010, 2011; Li *et al.* 2012). Group analysis was performed for the control subjects (C group) and for the PD patients. For this purpose, the method of global alignment of interpolated maps of the patients, present in the NIRS-SPM software, was used. The p-value was corrected using the expected Euler characteristics (Jang *et al.* 2009; Ye *et al.* 2009), with a threshold value of 0.05.

2.5. fNIRS data preprocessing. Before any further processing, fNIRS HbO and HbR data were low-pass filtered with the canonical HRF filter to remove high-frequency noise and temporal correlations, which means that the residual signal at the specific time is correlated with its temporal neighbors. This was done according to the precoloring method, which has been shown to be more effective, with respect to the prewhitening method, in calculating activation maps (Jang *et al.* 2009; Ye *et al.* 2009). Finally, baseline correction was performed again, subtracting the new value of concentration change at initial time.

2.6. Evaluation of HbT task-related increments. To better understand the effects of MRgFUS on each hemisphere across the different sessions, we calculated the average difference in concentration changes for the total haemoglobin (HbT = HbO + HbR) between right and left hemispheres (laterality) of the task-related increments. Such an analysis was performed according to the following steps:

- the channel configuration of each subject was separated into left hemisphere (LH) and right hemisphere (RH) sub-groups;
- for each channel, the difference in mean HbT concentration changes between task and rest phases, normalized to the maximum absolute value during task phase, was calculated;
- for both LH and RH sub-groups, the mean values among the corresponding channels were estimated;
- for both LH and RH sub-groups, the mean values among subjects were calculated;
- for LFT, mean LH sub-group values were subtracted to mean RH sub-group values.

3. Results and discussion

Using the GLM analysis described before, data collected from each participant were analysed separately. Due to the different initial neurophysiological conditions and to the different efficacy of MRgFUS treatment on each patient, a moderate inter-individual variability among the activation maps of different patients was found for both HbO and HbR during LFT and RFT tasks, as it can be seen from their concentration changes over time reported in Fig. 2, for ID 2 and ID 3 patients, obtained from channel N = 21 (in the right hemisphere) for LFT and N = 15 (in the left hemisphere) for RFT, as example.

Moreover, other variables such as physiological baseline properties, task performance, attention and/or motivation could have contributed to this variability (Holper *et al.* 2009). For what concerns the temporal evolution of the density change curves, phase differences among all sessions were generally observed for both HbO and HbR, during both LFT and RFT tasks. Worth of note, a similar trend was observed for sessions S2 and S0, consisting in a more oscillating signal with respect to that revealed for session S1, as can be seen in the examples shown in Fig. 3. Interindividual differences were present in all three sessions, and were accounted through the analysis at group level.

HbO group-averaged activation maps are shown in Fig. 4. In the case of session S0, group analysis presented significant enhancements in the left hemisphere during LFT task. As far as session S1 is concerned, a significant increase for HbO concentration was found in the left hemisphere during RFT task. Finally, for session S2, significant changes in HbO concentration were found in the right hemisphere for LFT, and in both hemispheres for RFT.

Figure 5 reports the group-averaged activation maps of HbR. In the case of session S0, no significant changes are detected in HbR concentrations, for both LFT and RFT.

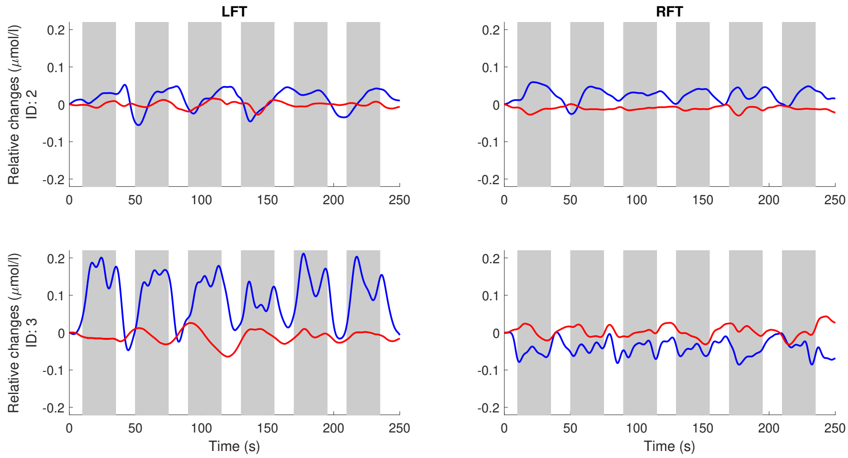

Figure 2. Examples of HbO (blue line) and HbR (red line) concentration changes during session S0, taken from subjects ID 2 and ID 3, during the execution of LFT (on the left) and RFT (on the right), as obtained from channel N = 21 for LFT and N = 15 for RFT.

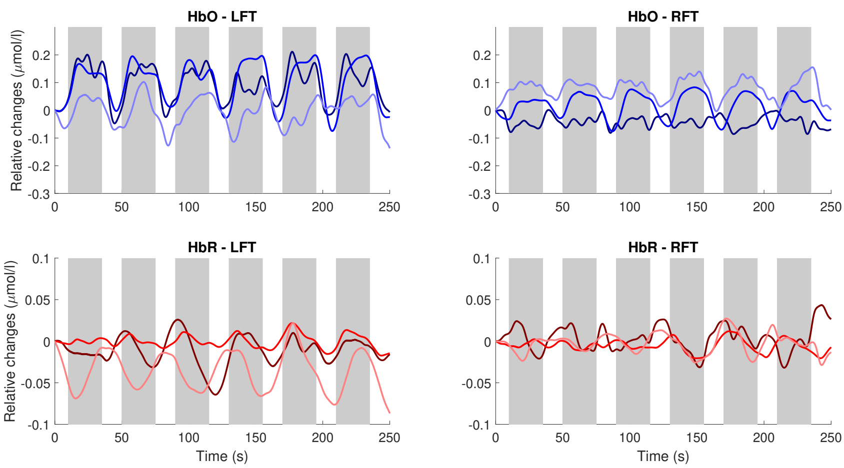

Figure 3. Examples of HbO (blue line) and HbR (red line) changes during session S0, S1 and S2, taken from subjects ID 3, during the execution of LFT (on the left) and RFT (on the right), as obtained from channel N = 21 for LFT and N = 15 for RFT. S0, S1 and S2 are indicated by progressively lighter colors.

For what concerns session S1, a significant decrease for HbR concentration is revealed in

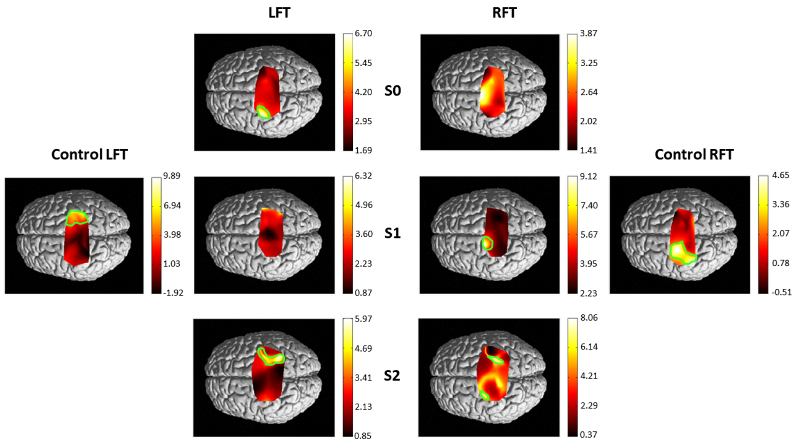

Figure 4. Group-average activation maps of HbO, during the three sessions (S0, S1, S2) of both LFT and RFT tasks. For comparison, the control group-average activation maps of HbO during LFT and RFT are shown on the respective sides. The regions with significant activations are enclosed in a green line. See text for details.

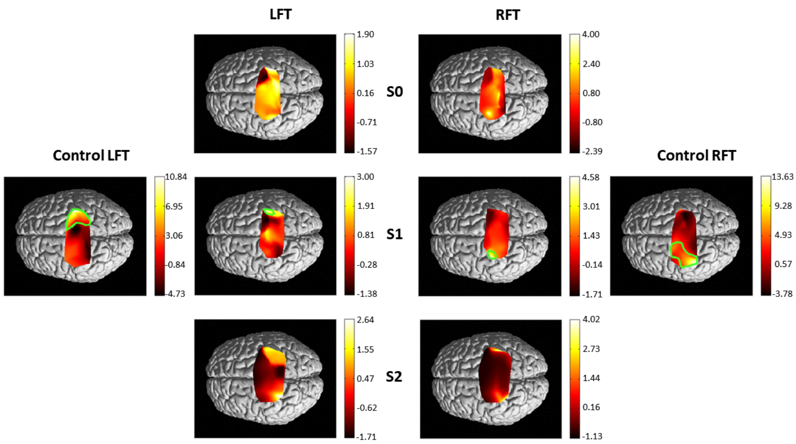

Figure 5. Group-average activation maps of HbR, during the three sessions (S0, S1, S2) of both LFT and RFT tasks. For comparison, the control group-average activation maps of HbR during LFT and RFT are shown on the respective sides. The regions with significant activations are enclosed in a green line. See text for details.

the right hemisphere during LFT, and in the left hemisphere during RFT. Finally, during session S2, no significant changes in HbR concentration were observed.

To verify the efficacy of the MRgFUS treatment, we also report the time course of the HbT task-related increment laterality (Fig. 6), obtained as described in Materials and Methods section. Only the LFT case is reported, being patients treated on the right hemisphere.

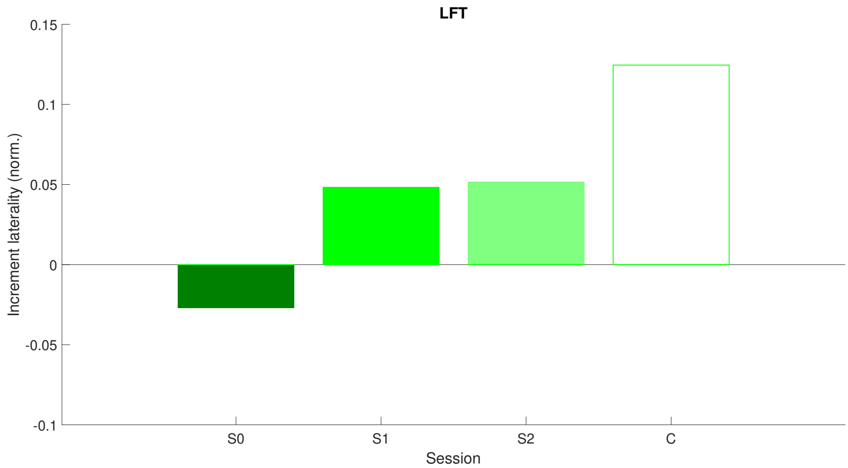

Figure 6. Average HbT task-related increment laterality, obtained as described in paragraph 2.6. The "C" column represents control group average.

Task-related increment laterality during LFT is observed to increase passing from S0 session, in which a higher change in HbT is present in the left hemisphere, to S1 session, where a higher change in HbT can be seen in the right hemisphere. Therefore, an evolution trend towards the control situation is observed.

These results give evidence of the effectiveness of MRgFUS treatment with respect to pre-treatment phase, at least in the observed follow-up time. The overall scenario appears in agreement with what reported in literature regarding the effects of unilateral thalamotomy with MRgFUS in patients with tremor other than essential tremor (Fasano *et al.* 2017; Jung *et al.* 2019), where an improvement in the patients' conditions immediately after the treatment, followed by a slight worsening one month later, is shown. Such results, then, highlight the validity of fNIRS for monitoring of neural activations in patients affected by PD. This could be important when traditional techniques, such as fMRI, cannot be employed, and when it is necessary to observe cortical activations during complex motor tasks.

4. Conclusions

In conclusion, we found that, after MRgFUS treatment, significant changes in HbO and HbR concentrations, resembling those in control group activation patterns, were predominantly observed in the S1 session, whereas in the case of S2 session, probably due to the neurodegenerative factor of the PD, conditions more similar to the pre-MRgFUS situation (S0 session) appeared. Nonetheless, they seemed to be improved, with respect to the pre-treatment phase, even one month later. Furthermore, the observed changes turned out to be principally related to LFT task, being the treatment performed on the right hemisphere.

These results, although preliminary and based on a low number of patients, which could not guarantee a generalization of the proposed approach, gave nevertheless evidence of the potentiality of fNIRS as a neuroimaging technique for monitoring the remodeling of neural connectivities, promoted by MRgFUS, in association with symptomatic improvements. In principle, this combined procedure could be employed within the clinical assessment of the human motor function, especially in patient populations and clinical settings where traditional neuroimaging methods are not suitable.

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