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Bedside Assessment of Residual Functional Activation in Minimally Conscious State Using NIRS and General Linear Models

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Abstract— **Near Infrared Spectroscopy (NIRS) was employed for the detection of possible residual functional activations in two patients in minimally conscious state. An "ad hoc" protocol for somatosensory and motor stimulations was created and administered to the patients, synchronously to NIRS recordings. One healthy subject was also assessed with the same task for comparison. Results from the healthy subject globally agree with the literature. Moreover, we could obtain significant results from the patients data. Indeed, in one patient, the NIRS channels showing activation completely correspond to regions of residual cortex underneath. In the second patient, though, together with possible residual intact cortex insulae, some channels match large cystic formations, with fluid gathering.**

I. Introduction

Near InfraRed Spectroscopy (NIRS) is an optical technology which allows the detection of changes in chromophores concentration, by using light at specific wavelengths. Moreover, by selectively employing light in the frequencies probing the oxygenated and deoxygenated hemoglobin species (HbO and HHb respectively), NIRS can provide measurements of their concentration changes over time, usually referred to as [HbO] and [HHb]. On their turn, these latter can provide valuable clinical indication, as they are closely involved in functional brain activation [1].

The portability, ease-of-use and relatively low cost that NIRS has reached, together with the absence of relevant adverse effects, make this technology especially appealing for those applications in which the severity of the disease/condition, the lack of patient's cooperation and the difficulty/contraindication of patients' mobilization play a major role [2].

To our knowledge, NIRS application to patients in Vegetative State (VS) and Minimally Conscious State (MCS) has never been reported, despite these two conditions could dramatically benefit from bedside assessment of residual neurofunctional activity [3].

In the present contribution we report a first attempt of functional assessment in two patients in MCS. We describe the NIRS recording procedure, the stimulation protocol applied and data processing steps, which include General Linear Models employment [4]. We compare the results with those obtained from one healthy volunteer. Last, we discuss the relevant findings and limitations encountered during the assessment.

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II. Materials and Methods

A. NIRS hardware and montage

In this study, a commercial NIRS device was used (CE marked). An elastic cap of proper head size was fitted on the subject's head. The cap had been previously tailored for a 2-set, 32 channels montage, centered over the motor and somatosensory brain areas (fig. 1). Channels were numbered as depicted in fig. 1. Moreover, one channel probing the prefrontal cortical activity and one measuring the contribution of the superficial (i.e. non-neuronal) layers of the head were added in Fp1 standard position, for signal quality check through multidistance recording approach (see [4] for details). NIRS recordings were performed at two different wavelengths (760nm and 830nm), in order to selectively probe oxygenated and deoxygenated haemoglobin species (HbO and HHb respectively) in the brain.

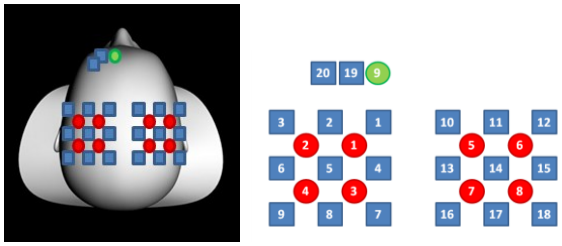

Figure 1. Left: illustration of NIRS cap design. In this representation, nasion is on top of figure, and inion is at the bottom. Injectors (I) are depicted in red, while receivers (R) are depicted in blue. Frontally, one injetctor for signal quality check (IC) is depicted in green. Right: corresponding montage numbering.

B. Stimulation protocol

After an initial 60 s rest period, the experimenter administered three different task blocks (corresponding to three experimental conditions) to each subject:

- *Somatosensory stimulation*: the experimenter laid the subject's hands over a battery-powered vibrating pillow. The patient remained in this condition for 60s. Due to this stimulation, activation in the somatosensory brain areas corresponding to the hands was expected.
- *Passive movement stimulation*: the experimenter took hold of the subject's hands and passively moved them for 60s. Activation in the motor brain areas corresponding to the hands was expected.
- *Active movement stimulation*: the experimenter repeatedly asked the subject to move his hands and

showed her own hands to the subject, while opening and closing. This procedure aimed to rise at least some motor imagery. A waiting period of 60s was designed, in order to test the possible capability of the subject to perform some kind of autonomous hand movement. Due to this stimulation, activation in the hand motor cortex was expected as well.

The three task blocks were repeated four times each, always in the same order. Passive *movement condition*, indeed, was intended to have a facilitating effect with respect to the *active movement condition.* All the task blocks were interleaved with a 30s rest period. The whole test was administered with no interruption, during the same testing session.

C. NIRS and MRI examinations

NIRS recordings were performed with written consensus of the healthy subject and patients' legal guardians. Examinations were performed during the administration of the protocol described in section *B*. Additionally, a morphologic brain MR scan was acquired from the patients with a commercial 3T MR machinery (Philips, Eindhoven, the Netherlands). In order to obtain an accurate cortical anatomic localization of possible NIRS activations, the coordinates of the NIRS channels were computed in the MNI space and superimposed over the MR images (see fig.5, in the discussion section, for one example). NIRS channels locations were calculated as a virtual point midway, between injector and detector positions (marked in MRI by means of vitamin E pills). NIRS data were visually inspected for artefact removal, and then low pass filtered at 0.0400 Hz, so as to preserve the task/rest frequency introduced by the stimulation protocol.

Continuous tracks were then segmented into epochs starting at the beginning of each task block, and ending 30 s after the end of the blocks. In doing so, 12 epochs, lasting 90 s each, were extracted. Epochs were first averaged according to the stimulation type, and then grouped, in order to obtain a grand average. Last, General Linear Model was run on the time-continuous data [5]. Three different regressors, modeling the three different stimulation types, were designed and tested (data not shown). Then, an overall boxcar regressor modeling the task, regardless to the stimulus type, was created and tested. Results are shown in fig. 2 for the healthy subject, and in fig 3 and 4 for the patients.

D. Subjects

One healthy male adult aged 28, with no history of brain injury, nor ischemia, nor neurologic diseases, is compared here with two patients in MCS (Patients A and B).

Patient A is a male. He had no previous neurological history, when he was involved in a bicycle accident, at the age of 15, and he had a severe traumatic brain injury (TBI). Four months later, he was enrolled in the present assessment. At the time of NIRS exam, Glasgow Outcome Score (GOS,[6]) was 2, and LOCFAS [7] was 3. He could gaze upon objects and people, also by orienting the head, he could answer "yes" / "no" by slightly moving the head and he could punch with the right hand on the right leg, when annoyed. MRI showed signs of diffuse axonal injury in the bilateral white matter, enlargement of the lateral ventricles (right>left) and a large contusion in the right putamen. Extensive laminar necrosis affected the right rolandic cortex (motor cortex), and part of the temporal pole and occipital lobe on the same side.

Patient B is a male aged 27. When he was 18 years and 4 months old, he had a severe TBI due to a motorbike accident. During the acute phase, clinical MRI demonstrated severe damage of the left hemisphere, with large cystic lesions involving fronto-parietal and temporo-insular regions, where brain parenchyma was severely disrupted. Residual areas of cerebral cortex could be recognized in the upper-posterior frontal lobe, parieto-occipital lobe and mesial temporal lobe. In these regions the white matter was markedly thinned and hardly detectable. The right hemisphere showed cortical-subcortical lesions in the fronto-mesial region and fronto-parieto-insular region. The ventricular system was extremely enlarged. He was admitted to Neurorehabilitation Unit after four months (124 days) from the event. At the time of NIRS examination, GOS was 3 and LOCFAS was 3. He could fix and partially follow people around him, and he spontaneously moved the superior extremity and the left hand.

The study was approved by E.Medea Ethical Comittee.

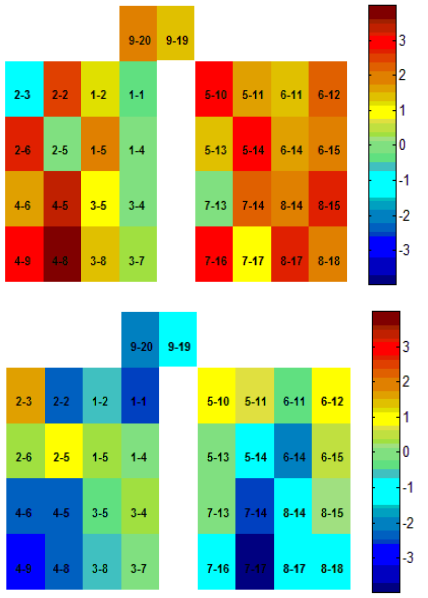

Figure 2. T-statistic maps over the brain of the healthy subject (all conditions): HbO map is on top; HbR is at the bottom. Values of the T-statistics range from -4 to +4: HbO map shows generalized positive values of the T-statistics. Specifically, significant activation ($p<0.05$) is observed centroparietally, over the left hemisphere (ch 4/9 and 4/8). A possible activation is also detected over the right hemisphere, in between ch 7/16 and 7/17. Channels 9/19 and 9/20 tested the superficial and deep activations over the frontal (non-motor) area respectively, for assessing proper probing of the cortex during NIRS measurement.

III. Results

The healthy subject could accomplish autonomously the *somatosensory*, *passive,* and *active movements* tasks with no visible motor fatigue. At the end of the protocol, he did not report any discomfort. During the s*omatosensory* stimulation, mild focal activation was detected over ch. 3/7 (left hemisphere, HbO increase, and concurrent HHb

decrease). GLM analysis provided significance for HHb only. Over the right hemisphere we could only observe a weak HHb decrease synchronous with the task, which was not significant. No relevant HbO changes were observed for this condition.

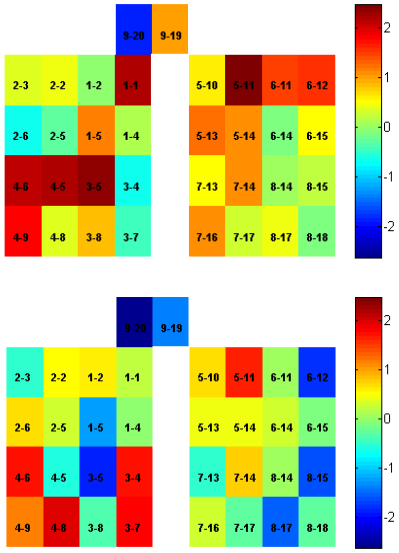

Figure 3. T-statistic maps over the brain of patient A (all conditions): HbO map is on top; HbR is at the bottom. Values of the T-statistics range from -2.5 to +2.5: HbO map shows multiple positive values of the T-statistics. Specifically, significant activation ($p<0.05$ for HbO and HHb) is observed centrally, over the left hemisphere (ch 3/5). No activation is found over the right central area. Though, test channel 9/20 did not provide confirmation about signal quality for the depth compartment.

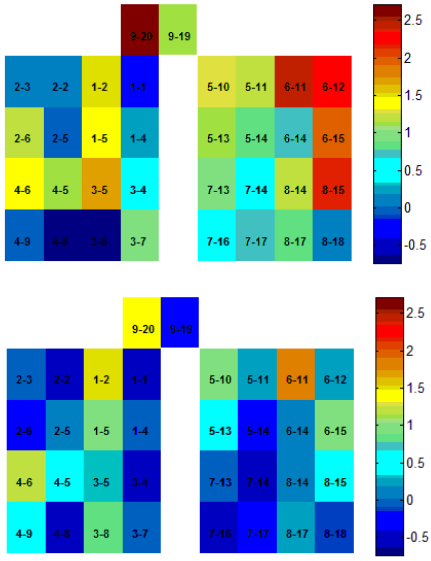

Figure 4. T-statistic maps of Patient B (all conditions): HbO map is on top; HHb is at the bottom. HbO map shows some antero-lateral voxels providing values of T-statistics approaching 2.5 over the right hemisphere (significant at p-val<0.05). A possible, though non-significant, activation is also detected over channel 3/5, on the left.

Passive movement condition, on the other hand, elicited bilateral focal activation in ch. 4/5 and 6/14. GLM assessed that both activations were at the very limit of significance, being HbO in ch. 4/5 and 6/14 and HHb in 6/14 slightly above the statistic threshold ($p<0.05$), and being HHb in 4/5 slightly below. The two areas were located centrally, as they were positioned more anteriorly with respect to the activation detected in the *somatosensory* condition. Last, during the *active movement* task the subject was left free to perform a self-paced handgrip task. Activation was observed in several channels, bilaterally. Specifically, ch. 4/5, 4/8 and 4/9 provided a significant pattern of activation on the left, confirmed by both HbO and HHb tracks; ch. 7/14 showed significant pattern of activation on the right. Overall GLM maps, including all conditions (fig.2) show a bilateral activation pattern, centered over the centroparietal brain area.

During the NIRS examination, the patients were still. They accomplished the *somatosensory* and *passive movement stimulation* tasks. During the *active movement* condition, they could not move the hands autonomously, and the experimenter could not observe any sign of engagement in the task. During the s*omatosensory* stimulation, weak activation was detected for Patient A over ch. 3/5 (HbO increase, and HHb decrease), and for Patient B over ch. 3/8 and 4/9, synchronously with the task blocks. P*assive movement stimulation* elicited HbO increase and concurrent HHb decrease over ch. 1/5, 4/5 and, much more relevantly, over ch 3/5 in Patient A; and over ch. 2/5 and 4/9 in patient B. *Active movement condition* rose weak activation of ch. 4/5 in Patient A and of ch. 4/6 in Patient B. GLM was then applied for the extraction of overall activations: processing provided the T-statistics maps shown in fig. 3 and 4. Significant T-values ($p<0.05$), for both HbO and HHb were found for Patient A over ch. 3/5 (3/4 was significant for HbO only). In Patient B, significance was observed for HbO over the right hemisphere, frontolaterally, and at left, over 3/5. A complex pattern of negative T-values was found for HHb, which is at the moment hard to disentangle. Nevertheless, channels 3/5 and 1/5 could candidate for bearing residual motor activation in this patient. The reader should note that colour scales in fig. 2, 3 and 4 are different.

IV. Discussion

Results obtained from the healthy subject globally agree with the topography of upper limb motor and somatosensory activations, largely described in literature. Despite this, we could not obtain significant activation during the *somatosensory* condition. If, on one hand, the probing of somatosensory cortex by NIRS is possible, as demonstrated by other studies [8-9], the lack of significance we obtained is probably due to the protocol design, and more eliciting somatosensory stimuli should be administered. The impossibility for MCS patients to communicate pain, though, prevented us to increase the somatosensory stimulation load. *Passive movement,* and *active movement* confirmed the production of a functional motor pattern in the brain.

Patient A showed an overall unilateral activation, lower in modulus with respect to the healthy one, located in central position, over the left hemisphere, and consistent across task conditions. This met the expectations, and fully agreed with MRI findings, which depicted the dramatically compromised condition of the right hemisphere.

Patient B could provide a complex, quite rich pattern of activation, with HbO increase and HHb decrease over several channels. Globally, T-values were lower, if compared to the healthy subject, but statistical significance could be reached over more than one spot. Moreover, the registration of NIRS signal over a standard cortex and over the patient's MRI scans revealed possible activation of the left motor cortex, all the while rising doubts about the complete reliability of results in other locations. MRI depicted broad and patchy cortical disruption. The direct comparison of NIRS maps with MRI scans revealed that channel 3/5 was located over the patient's primary motor area, in correspondence with a region of residual cortex, where anatomically preserved tissue could still be observed, and where neuronal activity could still be postulated. On the other hand, high modulus of the T-statistics was also obtained for some channels corresponding to large cystic formations (see fig. 5 for an example). This anatomical evidence rose doubts about the complete functional origin of the statistics, and, in our opinion, brings to the fore the need of supplementary tools, in addition to the statistic threshold (p-value) for the acceptance/rejection of activations and to corrections for multiple t-test comparisons in GLM.

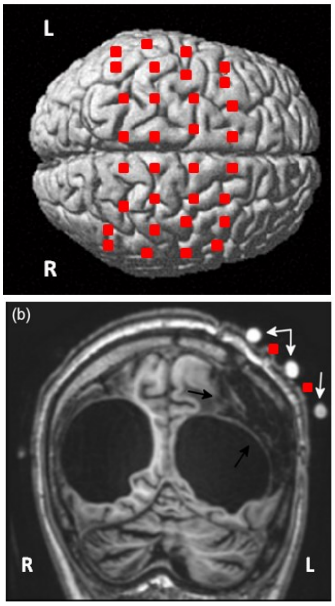

Figure 5. Top: Registration of NIRS montage over a standard cortex (frontal channels for signal quality check are omitted). Bottom: Coronal T1-weighted section of patient B demonstrates severe cortical and subcortical lesion in the left fronto-parietal hemisphere (black arrows). Vitamin E pills pinpoint the NIRS sites of injection and detection over the surface of the skull. Their position allowed the registration of each NIRS channel on MRI scans (white arrows in b)

Moreover, the expectation of negative HHb T-statistics in correspondence of positive HbO T-values was controverted for some channels: this fact could be explained by possible disruption of the integrity of the functional activation in MCS patients, and questions the similarity of the residual activation to the physiological coupling between increase in HbO and HHb decrease [10].

Last, we already mentioned that T-values of GLM maps were lower in patients than in the healthy subject. This finding could certainly be explained by the dramatic lack of involvement in the task provided by the patients. It should not be disregarded, though, that the atrophy of the brain structures and the presence of enlarged gaps with respect to the skull allow relevant fluid accumulation in most cases of MCS. In such situation, cerebrospinal fluid plays a major role in increasing the attenuation of the NIRS signal, due to the similarity of its optical properties to those of water. This could even lead to the need of some correction in the reconstruction of HbO and HHb tracks from photons counts.

To the authors' knowledge, this is the first preliminary work assessing functional activation in MCS patients with NIRS. As such, it introduces the issue of establishing some criterion for the identification of "residual activation" in MCS patients examined by NIRS. In the authors' perspective, this is the first step towards the assessment of NIRS applicability in functional studies of minimally conscious and vegetative states.

V. Conclusion

We showed the administration of an "ad hoc" protocol for the detection of possible residual functional activations in the MCS using NIRS. Significant evidences of residual functional capabilities were observed in two patients. Despite the encouraging results, a direct comparison of NIRS results with the MRI scans controverted some of the findings, while it confirmed others. This fact stresses at the same time the huge potentialities of NIRS devices to help in the assessment of minimally conscious and vegetative states, and the extreme caution needed in the interpretation of results.

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