Functional NIRS to detect covert consciousness in neurocritical patients

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HIGHLIGHTS

- Cerebral response to music could be detected by fNIRS with an easy experimental protocol.
- Variation of low frequency oscillations is a possible biomarker of cortical responsiveness.
- fNIRS responsiveness was associated with consciousness and might predict the clinical outcome.

ABSTRACT

Objective: This pilot study assesses the feasibility to detect covert consciousness in clinically unresponsive patients by means of functional near infrared spectroscopy (fNIRS) in a real intensive care unit setting. We aimed to verify if the hemodynamic response to familiar music measured with fNIRS varies according to the level consciousness of the patients.

Methods: 22 neurocritical patients and 6 healthy controls were included. The experiment consisted in 3 subsequent blocks including a first resting state recording, a period of music playback and a second resting state recording. fNIRS measurement were performed on each subject with two optodes on the forehead. Main oscillatory frequencies of oxyhemoglobin signal were analyzed. Spectral changes of low frequency oscillations (LFO) between subsequent experimental blocks were used as a marker of cortical response. Cortical response was compared to the level of consciousness of the patients and their functional outcome, through validated clinical scores.

Results: Cortical hemodynamic response to music on the left prefrontal brain was associated with the level of consciousness of the patients and with their clinical outcome after three months.

Conclusions: Variations in LFO spectral power measured with fNIRS may be a new marker of cortical responsiveness to detect covert consciousness in neurocritical patients. Left prefrontal cortex may play an important role in the perception of familiar music.

Significance: We showed the feasibility of a simple fNIRS approach to detect cortical response in the real setting of an intensive care unit.

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1. Introduction

Clinically unresponsive neurocritical patients may present a wide spectrum of disorders of consciousness. The term minimally conscious state (MCS) was coined in 2002 to describe patients with severely altered consciousness in which evidence of self or environmental awareness still could be detected (Giacino et al., 2002), distinguishing it from the vegetative state (VS), or unresponsive wakefulness syndrome (UWS), as some authors prefer to call it, especially when used in public debate (Kondziella et al., 2019, Laureys et al., 2010, von Wild et al., 2012). Detecting covert awareness is of paramount importance for physicians confronted...
with prognostication (Claassen et al., 2019, Schiff, 2017). However, discriminating between MCS and UWS presents a challenge for clinicians. The clinical assessment of MCS versus UWS has an estimated 30–40 % error rate (Giacino et al., 2018, Schnakers et al., 2009). Therefore, complementary instrumental methods to detect covert consciousness are needed (Hammond et al., 2021). Functional near-infrared spectroscopy (fNIRS) is a promising, strictly non-invasive bed-side tool which could assist the identification of covert consciousness by detecting biomarkers of cerebral activity in response to external stimuli (Kempny et al., 2016, Molteni et al., 2013, Zhang Y. et al., 2018). Some feasibility studies have already proposed experimental paradigms with auditory presented mental-arithmetic tasks (Kurz et al., 2018) or motor imagery tasks (Kempny et al., 2016, Li et al., 2021) for this purpose. All these studies examined the relative changes of hemoglobin oxygenation during the tasks. Studying the relative changes of oxygenated (O2Hb) and deoxygenated (HHb) hemoglobin in a time-course analysis is one of the most common approaches to fNIRS data analysis. Unfortunately, there is still no validated methodology to concretely interpret this cerebral hemodynamic information in a clinically useful way. To this end, the investigation of hemodynamic oscillations of cerebral cortex by means of fNIRS, rather than the standard time-course analysis of hemoglobin oxygenation, may have theoretical and practical advantages. This approach bases on the physiological hypothesis that neural processes may show specific signatures in electrical and hemodynamic frequency bands. For example, covarying oscillatory activity in different regions of the cortex may reflect local and global spread of information in the brain (Buzsáki and Watson, 2012, Sasai et al., 2011). Yuen et al. (2019). Neural coupled hemodynamic oscillations have already been described with functional magnetic resonance imaging (fMRI) and may also be observed by fNIRS (Fanti, 2014). The main functional information in fNIRS signal has been identified within the low-frequency region of the spectrum. In particular, low-frequency oscillations (LFO), centered around 0.1 Hz (Obrig et al., 2000), correspond to the most commonly studied frequency of blood-oxygen-level-dependent (BOLD) functional MRI (fMRI) signal. Indeed, LFO are thought to partially reflect neuronal coupled hemodynamic activity (Smitha et al, 2017, Zuo et al., 2010). LFO are in part produced by local autoregulatory vasomotion of terminal arterioles, under the control of the sympathetic nervous system (Sassaroli et al., 2012). However, LFO are also influenced by the systemic Mayer waves, which are rather enigmatic oscillations of blood pressure mediated by the sympathetic nervous system and also present in the cerebral circulation (Julien, 2020).

Fortunately, frequency domain analysis allows to easily exclude frequency bands of physiologic interfering signal (like heartbeat and respiration) and to maintain but the spectral regions that are likely to contain information on cerebral activity. To develop a fNIRS based tool that is useful in clinical practice, we aimed to identify shifts in main frequencies of hemodynamic oscillations revealing cortical response to an external sensory input. Auditory stimulation with preferred music can elicit cortical response in healthy subjects, we found an increase of spectral plasticity (Sihvonen et al., 2017, Verger et al., 2014). In a previous study with healthy subjects, we found an increase of spectral power of LFO within the HbO2signal measured by fNIRS, while exposed to preferred music, followed by a decrease in LFO spectral power after the end of music (Bicciato et al., 2021). Therefore, for the current study, the measured hemodynamic response to music was defined by this pattern of change in LFO spectral power during and after music exposure. The purpose of this pilot study was to verify if the hemodynamic response to music measured by fNIRS varies according to the level of patient consciousness assessed with clinical scales. Secondly, we aimed to test if the response to music correlated with the clinical outcome of the patients after 3 months. This is, as far as we know, the first feasibility study applying fNIRS frequency domain analysis to detect clinically covert consciousness.

2. Methods

2.1. Participants

We included 22 patients at the Neurocritical Care Unit (NCCU) of the University Hospital Zurich with different levels of consciousness. Exclusion criteria were age ≤ 18 years, documented moderate or severe hearing loss, and hemodynamic or respiratory instability at the time of the experiment according to the judgement of the treating physicians. Intravenous analgo sedation with sufentanil, midazolam, propofol, dexmedetomidine or clonidine was not considered an exclusion criterion, as we assumed that sedation would affect both - clinical as well as measured cortical response to auditory stimulation. Given the exploratory nature of the study, patients were included by convenience sampling. We compared the cohort of patients to a group of 6 healthy controls. The data of the control group has been previously published (Bicciato et al., 2021). The study was approved by the local ethics committee. Written assent was given by legal representatives, as all patients were incapable of judgment.

2.1.1. Demographic characteristics of the patients

Mean age [SD] of the patients was 68.8 years (±10.9). 7 patients were men (32 %). 16 patients were mechanically ventilated, 6 were breathing spontaneously (3 of them through a tracheostomy). Two patients were deeply sedated to treat a status epilepticus. The main underlying pathological conditions of selected patients were mainly severe subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), ischemic stroke and status epilepticus (Table 1). As a control group we had 6 healthy, right-handed volunteers (2 females, 4 males). Mean age was 41.2 years (±12.6).

2.1.2. Clinical assessment of the patients

The clinical level of consciousness of the patients was independently assessed every hour by the treating nurses and physician at the NCCU using the Richmond Agitation Sedation Scale (RASS) and Glasgow Coma Scale (GCS). For the experimental analysis we considered the closest clinical assessment (which was never more than one hour from the experiment). The GCS score evaluates the best eye, verbal and motor response to external stimuli. In patients under sedation, the clinical assessment registered the current state of consciousness and did not consider the previous state of consciousness before sedation. Patients showed clinically different levels of vigilance according to the GCS (from GCS 3 to 14) and RASS (from −5 to +3). In mechanically ventilated patients the assessment of verbal response is not possible, and can be estimated only partially by the eye and motor components of GCS (e.g. evaluation of attempts to speak) (Cheng et al., 2017, Rutledge et al., 1996). The presence of apnea may further bias GCS assessment (Teasdale et al., 2014). Unfortunately, we could not categorize the patients with disorders of consciousness using a gold standard measure such as the Coma Recovery Scale Revised CRS-R (Giacino et al., 2004), or other clinical tools such as the Outline of UnResponsiveness (FOUR) (Alnojuelu et al., 2019, Foo et al., 2019) and the Simplified Evaluation of CONsciousness Disorders
Patients were divided into three different groups. Group A included patients able to open the eyes and follow commands, group B included patients unable to follow commands but able to open the eyes after external stimulation, group C included patients unable to open the eyes or follow commands. No patients included in this study were able to follow the commands without being able to open the eyes. Further, data on mortality after 3 months was assessed according to the medical reports. All the patients were grouped in a simplified way, merely according to the purpose of our study, besides using the standard clinical scores, these are not routinely assessed and documented more times per day in the setting of an NCCU, as it is the GCS and RASS. For the Table 2: Group A (responsive) consisted of patients able to open the eyes and follow commands, group B (partially responsive) included patients unable to follow commands but able to open the eyes after external stimulation, patients of group C (unresponsive) could not open the eyes or follow commands. No patient included in this study was able to open the eyes. Patients included in this study were unable to open the eyes or follow commands. No patients included in this study were able to follow the commands without being able to open the eyes. Further, data on mortality after 3 months was assessed according to the medical reports. The GOS after 3 months and Glasgow Outcome Scale (GOS) after 3 months were analyzed by the treating physicians. Possible lateralization of brain lesions in CT/MRI and magnetic resonance imaging (MRI) of all patients were collected through medical reports. Cerebral computer tomography (CT) and magnetic resonance imaging (MRI) of all patients were assessed according to the medical reports. All the patients were grouped in a simplified way, merely according to the purpose of our study, besides using the standard clinical scores, these are not routinely assessed and documented more times per day in the setting of an NCCU, as it is the GCS and RASS. For the purpose of our study, besides using the standard clinical scores, patients were grouped in a simplified way, merely according to the eye and motor response. We identified three groups of patients (Table 2): Group A (responsive) consisted of patients able to open the eyes and follow commands, group B (partially responsive) included patients unable to follow commands but able to open the eyes after external stimulation, patients of group C (unresponsive) could not open the eyes or follow commands. No patient included in this study was able to follow the commands without being able to open the eyes. Further, data on mortality after 3 months and Glasgow Outcome Scale (GOS) after 3 months were analyzed by the treating physicians. Possible lateralization of brain lesions in patients with ischemic stroke and intracranial bleeding was assessed according to cerebral imaging. The GOS after 3 months was assessed according to cerebral imaging. The GOS after 3 months was assessed according to cerebral imaging. The GOS after 3 months was assessed according to cerebral imaging. The GOS after 3 months was assessed according to cerebral imaging.

### Table 1

Demographic Data and Clinical Assessment of Patients. y: years. M: male. F: female. RASS: Richmond Agitation Sedation Scale. GCS: Glasgow Coma Scale. GOS: 3-months Glasgow outcome scale. Group A: responsive patients (open the eyes and follow commands); Group B: partially responsive patients (open the eyes, do not follow commands); Group C: unresponsive patients (no eye opening, do not follow commands). R/L/No: right/left or no lateralization of brain lesions in CT/MRI. aSAH: aneurysmatic subarachnoid hemorrhage. ICH: intracerebral hemorrhage. NCSE: non convulsive status epilepticus.

| Patient | Gender | Age (y) | RASS | GCS | Group | GOS | Mechanical Ventilation | Tracheostomy | Underlying Pathology | Brain Lesion Lateralization | Days from admission | Sedation |
|---------|--------|---------|------|-----|-------|-----|----------------------|-------------|----------------------|--------------------------|----------------------|---------|
| 1       | M      | 75      | -5   | 3   | C     | 1   | Yes                  | No          | ischemic stroke      | R                        | 3                    | No       |
| 2       | F      | 78      | -4   | 6   | B     | 2   | Yes                  | No          | aSAH                 | No                       | 8                    | No       |
| 3       | F      | 78      | -4   | 3   | A     | 1   | No                   | aSAH        | R                    | 3                        | No                   | No       |
| 4       | F      | 68      | -5   | 3   | C     | 1   | Yes                  | No          | aSAH                 | No                       | 11                   | No       |
| 5       | F      | 66      | -3   | 1   | A     | 1   | Yes                  | Yes         | Encephalitis         | No                       | 9                    | No       |
| 6       | F      | 56      | -2   | 7   | B     | 3   | No                   | Yes         | SDH                  | R                        | 17                   | No       |
| 7       | F      | 74      | -2   | 9   | B     | 1   | No                   | Yes         | aSAH                 | No                       | 12                   | Midazolam 15 mg/h; Propofol 150 mg/h; Sufentanil 15 mcg/h |
| 8       | M      | 72      | 1    | 9   | A     | 4   | No                   | No          | ICH                  | L                        | 18                   | No       |
| 9       | M      | 75      | -4   | 4   | B     | 1   | Yes                  | No          | SAH                  | No                       | 11                   | No       |
| 10      | F      | 53      | -3   | 8   | C     | 4   | Yes                  | No          | ICH                  | L                        | 20                   | No       |
| 11      | F      | 58      | -4   | 4   | C     | 3   | Yes                  | Yes         | aSAH                 | No                       | 14                   | No       |
| 12      | F      | 71      | -3   | 9   | B     | 3   | Yes                  | Yes         | NCSE                 | No                       | 9                    | No       |
| 13      | F      | 61      | -1   | -   | B     | -   | Yes                  | Yes         | NCSE                 | No                       | 1                    | No       |
| 14      | F      | 65      | -4   | 4   | B     | 4   | No                   | No          | ICH                  | L                        | 9                    | No       |
| 15      | F      | 69      | -4   | 7   | B     | 4   | Yes                  | Yes         | NCSE                 | No                       | 6                    | No       |
| 16      | M      | 68      | 0    | 11  | A     | 3   | Yes                  | Yes         | ischemic stroke      | R                        | 8                    | No       |
| 17      | F      | 60      | -3   | 8   | A     | 4   | Yes                  | Yes         | aSAH                 | No                       | 21                   | No       |
| 18      | M      | 31      | -2   | 10  | A     | 5   | Yes                  | No          | Neoplasia            | R                        | 13                   | Clonidine 150 mcg/Tag |
| 19      | F      | 58      | -1   | 9   | B     | 2   | No                   | Yes         | ICH                  | L                        | 21                   | No       |
| 20      | F      | 73      | -4   | 6   | B     | 5   | Yes                  | No          | aSAH                 | L                        | 6                    | Midazolam 20 mg/h; Sufenta 10 mcg/h |
| 21      | M      | 63      | 0    | 11  | A     | 4   | Yes                  | No          | Encephalitis         | No                       | 16                   | No       |
| 22      | F      | 53      | -4   | 3   | C     | 5   | Yes                  | No          | NCSE                 | No                       | 15                   | No       |

### Table 2

Patients were divided into three different groups. Group A included patients able to open the eyes and follow commands, group B included patients unable to follow commands but able to open the eyes after external stimulation, group C included patients unable to open the eyes or follow commands. No patients included in this study were able to follow the commands without being able to open the eyes.

2.2. Experiment design

The subjects or their relatives were preliminarily asked about their musical preferences. If the information was available, the patients were made listen to their favorite music. If no information about musical preference was available, we arbitrarily played the first Brandenburg concert of Johann Sebastian Bach (BWV 1046). The patients or the relatives could choose any kind of music, vocal or instrumental. We used disposable headphones for sound playback. Music was played on a Samsung S8 mobile phone, the volume was always set below the security lock provided by the device. Since the audible tone depends on the decibel of the transmission as well as the hearing of the test person, no standard value could be selected. Whenever the patients could not be asked directly, the examiners tested the volume setting themselves to ensure easily audible music while avoiding noise disturbance. The experiment consisted of 3 blocks including an initial and a final period of resting state recording, separated by periods of music playback: baseline 1 (b1), music (m), baseline 2 (b2). Each block (baseline 1, music, baseline 2) lasted from 4 to 7 minutes. A duration between 4 and 7 minutes was sufficient to detect LFO. The duration of the blocks was determined according to the time available in regard to other standard diagnostic procedures and required routine care (e.g. frequency of needed tracheal suction).
If the music pieces were shorter than the defined experimental blocks, they were repeated in loop mode. The first baseline block was preceded by a block of five minutes “dummy run” for calibration and verification of signal quality. See Fig. 1.

2.3. fNIRS measurement

Data acquisition and analysis were performed with OXYMON Mk III and Oxysoft (version 3.0, 103.3, Artinis Medical Systems B. V., Elst, The Netherlands). Measurements were carried out by applying two optodes on the forehead bilaterally 2 cm above the mediopupillary line (Fig. 2), just above the Fp1 and Fp2 locations of 10–20 EEG System. Each optode contained one main light source and one light detector. The distance between the main light source and the light detector was 35 mm. In 12 of the 22 patients an auxiliary short channel was placed at 10 mm from the detector. The optical signal of the short channel was subtracted from the main signal to reduce the effect of the superficial signal originating from the scalp by using the “subtract” function of Oxysoft software.

Using a short channel (at least <15 mm) in fNIRS research is encouraged by many authors, as an effective way to remove superficial scalp cardiac pulsation. The low bandpass filter of 0.4 Hz was chosen between 0.007 and 0.4 Hz (filter order = 8, type = Butterworth). Raw fNIRS data were set to zero-line and band-pass filtered as well as separately for the two subgroups with and without short channel, to verify if the superficial skin signal or the acquisition method itself had an influence on the results. The sampling frequency was set at 25 Hz. The differential pathlength factor (DPF) was set at 6. Concentration of O2Hb was automatically computed according to the modified Lambert–Beer law by Oxysoft software.

2.4. Processing of fNIRS-data and statistical analysis

Analyses were performed in MATLAB R2019b (Mathworks, Natick MA, USA). Although O2Hb and HHb signals were obtained, we only chose O2Hb to perform statistical analyses due to its superior signal-to-noise ratio (Bicciato et al., 2021, Wolf et al., 2011). Raw fNIRS data were set to zero-line and band-pass filtered between 0.007 and 0.4 Hz (filter order = 8, type = Butterworth). The filtering removed physiological noise such as respiration and cardiac pulsation. The low bandpass filter of 0.4 Hz was chosen to minimize the loss of information and was consistent with the value used in the previous study with healthy subjects (Bicciato et al., 2021). However, a low pass filter of 0.4 Hz may have included some respiratory activity “noise” (normal respiratory rate in healthy adults 16–20 breaths per minute). To exclude that our results were driven by different respiratory rates among the group of patients, we also recalculated them with a low pass filter of 0.2 Hz. The results are shown in the Appendix (Table A1). The signal was segmented by the different blocks b1, m, and b2 according to the time points registered during the experiment. Artifacts were manually excluded from the segments. The length of each block varied from 4 to 7 minutes according to the total length of the measurements in each subject. Within the measurements performed in each subject the length of the blocks was kept rather constant (the maximal difference in block duration for a subject was ±30 seconds). We defined a region of interest in the spectral band of LFO. For the purpose of the further analysis LFO were defined between 0.04 and 0.4 Hz, or 0.2 Hz (Andersen et al., 2018, Obrig et al., 2000, Pierro et al., 2012, Pinti et al., 2018b).

Changes of spectral power in the LFO region between subsequent experimental blocks were calculated through the ratio between mean power in the LFO frequency region in the subsequent blocks: i.e. LFO.Ratio from baseline 1 to music (LFO.Ratio b1→m), from music to baseline 2 (LFO.Ratio m→b2). A supplementary analysis showing the values of LFO.Ratio from baseline 1 to baseline 2 (LFO.Ratio b1→b2). For a better graphical representation, the ratios were transformed with the natural logarithm (Ln).

\[
\text{LFO.Ratio baseline 1 to music } = \text{Ln}\left(\frac{\text{mean}[\text{LFO Power music}]}{\text{mean}[\text{LFO Power baseline 1}]}\right)
\]

\[
\text{LFO.Ratio music to baseline 2 } = \text{Ln}\left(\frac{\text{mean}[\text{LFO Power baseline 2}]}{\text{mean}[\text{LFO Power music}]}\right)
\]

Average LFO.Ratio was calculated and compared in the three patient groups A, B and C and healthy controls. Simple linear regression with GCS, RASS was performed. The association of LFO.Ratio to clinical parameters was calculated as a whole group as well as separately for the two subgroups with and without short channel, to verify if the superficial skin signal or the acquisition method itself had an influence on the results. The outcome measure GOS was divided in GOS 1–2, including patients dead or in UWS after 3 months, and GOS 3–5, including patients from minimally conscious state to normal consciousness after 3 months. Further subgroup-analyses were performed considering the lateralization of the cerebral lesions in CT or MRI and the presence or absence of a short channel in the fNIRS-measurement.

2.5. Collection of systemic vital parameters and statistical analysis

During the experiment mean arterial pressure (MAP), heart rate (HR), oxygen saturation (SpO2) and respiratory rate (RR) were continuously monitored and recorded in a subset of the patients (n = 15).

In the healthy subjects only SpO2, HR and RR but not MAP were monitored. All signals were acquired by means of Philips Intellivue system (Philips Medical systems, Boeblingen, Germany) that communicated data to a CNS Data Collector (Moberg ICU Solutions, Ambler, Philadelphia, USA). We collected and exported the data from the CNS monitor using our proprietary data collection system ICU Cockpit. Signals were sampled at 1.024 Hz.

We computed a summary statistic describing the parameter in two periods, a pre-experiment period of 30 min duration ending ten minutes prior to the start of the experiment, and a second per-
iod lasting the length of the experiment, i.e. from start of baseline 1 to end of baseline 2. We used a d-prime (d') sensitivity measure to quantify the change in the variable from pre-experiment to experiment. d'-measures change in the variable in units of standard deviations. It is defined as:

$$d'(x) = \frac{(x_{\text{exp}} - x_{\text{pre}})}{\sqrt{0.5(\sigma_{\text{exp}}^2 + \sigma_{\text{pre}}^2)}}$$

Here $x_{\text{exp}}$ is the average value of the parameter $x$ in the experiment period, and $x_{\text{pre}}$ is the average value of the parameter in the pre-experiment period. $\sigma_{\text{exp}}$ and $\sigma_{\text{pre}}$ are the standard deviations of the parameter in the respective periods. This measure normalizes for the variance in the data that may be caused by disturbances to the patient and brings all parameters to the same scale. For each group, A, B and C, and each physiological signal (MAP, SYSP, HR or SPO2) we computed the d'-values (as above) as well as the difference in the median value of each signal in the experiment period – pre-experiment period (30 min period, 40 min prior to experiment onset), i.e.

$$m(x) = \text{median}(x_{\text{exp}}) - \text{median}(x_{\text{pre}})$$

Results of the comparison of cardiovascular parameters between subject groups are shown in the Appendix (Fig. A1–4).

3. Results

3.1. fNIRS measurement

Mean spectral power in the LFO region for each hemisphere was calculated in each experiment block (b1, m, b2). LFO.Ratio was then obtained for the transition b1-m and m-b2. Values for every patient are shown in Table 3. As LFO.Ratio is expressed in a natural logarithmic form positive value indicate an increase in LFO spectral power, while negative values indicate a decrease. The values of LFO.Ratio of the healthy subjects had previously been published (Bicciato et al., 2021). LFO.Ratio_{b1->m} values are shown in the Appendix Table A2.

3.1.1. Correlation of LFO.Ratio to clinical assessment

3.1.1.1. Group analysis. Fig. 3 shows boxplots with the LFO.Ratio_{b1->m} and LFO.Ratio_{m->b2} for both hemispheres in the three different patient groups of clinical responsiveness and in the healthy subjects (HS). After the Kruskal Wallis test for LFO.Ratio_{b1->m}, in the left hemisphere, we could reject the null hypothesis that the four groups come from the same distribution at $p < 0.01$ (Fig. 3A). Analyzed pairwise, group C ($n = 6$) showed significantly lower LFO.Ratio_{b1->m}, compared to group A ($n = 7$, Wilcoxon rank-sum 54, $p < 0.05$) and to healthy subjects ($n = 6$, Wilcoxon rank-sum 22, $p < 0.01$). Group B ($n = 9$) did not show significant difference with the other groups (Wilcoxon rank-sum test). In the right hemisphere no significant differences in LFO.Ratio_{b1->m} could be found among the 3 patient groups and the HS (Fig. 3B) (Kruskal Wallis test, and pairwise Wilcoxon rank-test), even after lowering the low band pass filter from 0.4 to 0.2 Hz. LFO.Ratio_{m->b2} in the left hemisphere (Fig. 3C) showed a lower median value in healthy subjects than in the patients. This difference was significant in direct comparison with the group A (ranksum 26, $p < 0.05$). No significant differences could be found in LFO.Ratio_{m->b2} in the right hemisphere (Fig. 3D). LFO.Ratio_{b1->m} on the right hemisphere showed very modest or no correlation to GCS and RASS. LFO.Ratio_{b1->m} in the left hemisphere was also present considering the patient subgroups separately: with short channel, Spearman’s rho = 0.5, $p < 0.05$, $N = 16$; and without short channel Spearman’s rho = 0.6, $p < 0.05$, $N = 6$. 

Fig. 2. A. Optode placed on the forehead of a patient about 2 cm above the mediopupillary line. B. During the functional near infrared spectroscopy (fNIRS) measurement in the intensive care unit data of the vital parameters were acquired by a monitor.
3.1.2. Correlation of LFO Ratio to outcome assessment

Fig. 5 shows a boxplot with the LFO.Ratio \(_{b1->m}\) and LFO.Ratio \(_{m->b2}\) for both hemispheres in patients divided into two outcome groups GOS 1–2 and GOS 3–5 and in HS. After the Kruskal Wallis test for LFO.Ratio \(_{b1->m}\) in the left hemisphere, we could reject the null hypothesis that the three groups come from the same distribution at \(p < 0.05\) (Fig. 5A). After direct comparison, LFO.Ratio \(_{b1->m}\) was significantly lower (rank-sum 65, \(p < 0.001\)) in patients with GOS of 1 or 2 (\(n = 8\), i.e. death or clinically in UWS, compared to HS (\(n = 6\)). In patients with GOS 3–5 (\(n = 13\)) no significant differ-

Table 3

| Patient | Left Hemisphere | Right Hemisphere |
|---------|-----------------|------------------|
|         | LFO.Ratio \(_{b1->m}\) | LFO.Ratio \(_{m->b2}\) | LFO.Ratio \(_{b1->m}\) | LFO.Ratio \(_{m->b2}\) |
| 1       | 0.0730          | 0.1963           | -0.0463          | -0.1926          |
| 2       | -0.1789         | -0.2221          | 0.0654           | 0.2352           |
| 3       | 0.4432          | 0.4771           | -1.6778          | 0.2512           |
| 4       | -0.1325         | 0.2664           | -0.0196          | -0.3066          |
| 5       | 0.1389          | 0.1711           | 0.2564           | -0.1917          |
| 6       | 0.5107          | -0.1422          | 0.2604           | 0.3432           |
| 7       | 0.2743          | 0.0802           | 0.1576           | 2.0567           |
| 8       | 0.5192          | 2.1028           | -1.4223          | 0.4441           |
| 9       | -0.4007         | 0.2555           | -1.4658          | 0.3932           |
| 10      | -0.2867         | 0.2437           | -1.3897          | 0.9363           |
| 11      | -0.6536         | 0.6382           | 0.1086           | 0.0033           |
| 12      | 0.8323          | -3.1862          | 0.6203           | -1.8557          |
| 13      | -2.1164         | 6.2336           | -2.7749          | 4.6939           |
| 14      | 0.0671          | -0.3583          | 0.1279           | -0.3515          |
| 15      | 0.4153          | -0.0651          | 0.2867           | -0.4892          |
| 16      | -0.1224         | 0.2640           | -0.1702          | -0.0229          |
| 17      | 0.6625          | 0.1998           | -0.7268          | -0.3326          |
| 18      | 0.7756          | 0.0320           | 0.1000           | -0.4807          |
| 19      | -1.0551         | 0.4970           | -0.6727          | 0.4029           |
| 20      | -0.5267         | -0.7661          | 0.0262           | 0.0875           |
| 21      | 0.5550          | 0.2995           | 0.4701           | -0.1401          |
| 22      | -0.4131         | -0.2770          | -0.4131          | -0.2770          |

Fig. 3. LFO.Ratio and groups of responsivity (LFO: low frequency oscillations). On the x-axis, healthy subjects (HS) and 3 different groups of patients (group A: patients able to open the eyes and to follow commands, group B: patients able to open the eyes but not to follow commands, group C: patients unable to open the eyes or follow commands) and healthy subjects (HS) are shown. A. LFO.Ratio from the first baseline block (b1) to music exposure (m) in the left hemisphere. B. LFO.Ratio from the first baseline block (b1) to music exposure (m) in the right hemisphere. C. LFO.Ratio from the music block (m) to the second baseline block (b2) in the left hemisphere. D. LFO.Ratio from the music block (m) to the second baseline block (b2) in the right hemisphere. Red crosses represent outliers.

### 3.1.2. Correlation of LFO.Ratio to outcome assessment

Fig. 5 shows a boxplot with the LFO.Ratio \(_{b1->m}\) and LFO.Ratio \(_{m->b2}\) for both hemispheres in patients divided into two outcome groups GOS 1–2 and GOS 3–5 and in HS. After the Kruskal Wallis test for LFO.Ratio \(_{b1->m}\) in the left hemisphere, we could reject the null hypothesis that the three groups come from the same distribution at \(p < 0.05\) (Fig. 5A). After direct comparison, LFO.Ratio \(_{b1->m}\) was significantly lower (rank-sum 65, \(p < 0.001\)) in patients with GOS of 1 or 2 (\(n = 8\), i.e. death or clinically in UWS, compared to HS (\(n = 6\)). In patients with GOS 3–5 (\(n = 13\)) no significant differ-

#### Table 3

| Patient | LFO.Ratio \(_{b1->m}\) | LFO.Ratio \(_{m->b2}\) |
|---------|------------------------|------------------------|
| 1       | 0.0730                 | 0.1963                 |
| 2       | -0.1789                | -0.2221                |
| 3       | 0.4432                 | 0.4771                 |
| 4       | -0.1325                | 0.2664                 |
| 5       | 0.1389                 | 0.1711                 |
| 6       | 0.5107                 | -0.1422                |
| 7       | 0.2743                 | 0.0802                 |
| 8       | 0.5192                 | 2.1028                 |
| 9       | -0.4007                | 0.2555                 |
| 10      | -0.2867                | 0.2437                 |
| 11      | -0.6536                | 0.6382                 |
| 12      | 0.8323                 | -3.1862                |
| 13      | -2.1164                | 6.2336                 |
| 14      | 0.0671                 | -0.3583                |
| 15      | 0.4153                 | -0.0651                |
| 16      | -0.1224                | 0.2640                 |
| 17      | 0.6625                 | 0.1998                 |
| 18      | 0.7756                 | 0.0320                 |
| 19      | -1.0551                | 0.4970                 |
| 20      | -0.5267                | -0.7661                |
| 21      | 0.5550                 | 0.2995                 |
| 22      | -0.4131                | -0.2770                |
ence could be found in comparison to GOS 1–2 or HS. In the right hemisphere, the Kruskal-Wallis test results among the groups GOS1-2, GOS3-5 and HS was not significant (Fig. 5B). However, in direct comparison, LFO.Ratio\textsubscript{b1->m} for the right hemisphere was significantly lower (rank-sum 61, p < 0.05) in patients with GOS1-2 (n = 8) compared to HS (n = 6). The Kruskal-Wallis test for LFO.Ratio\textsubscript{m->b2} on both hemispheres did not result in a rejection of the null hypothesis of no difference among groups (Fig. 5C and Fig. 5D). However, after direct comparison, HS showed lower LFO.Ratio\textsubscript{m->b2} than patients with GOS1-2 in the left hemisphere (rank-sum 59, p < 0.05).

3.1.3. Lateralization of the brain lesions
Fig. 6 shows a boxplot with the LFO.Ratio\textsubscript{b1->m} and LFO.Ratio\textsubscript{m->b2} for both hemispheres in patients divided according to the lateralization of their brain lesions – if present – and HS. After the Kruskal-Wallis test for LFO.Ratio\textsubscript{b1->m} in the left hemisphere we could not find a significant difference among the groups (Fig. 6A). However, in direct comparison, LFO.Ratio\textsubscript{b1->m} was significantly lower (rank-sum 61, p < 0.05) in patients with left lateralized lesions (n = 5) compared to HS (n = 6). In the right hemisphere, the Kruskal-Wallis test of LFO.Ratio\textsubscript{b1->m} Values among the patients and HS was not significant (Fig. 6B). Again, in direct comparison, LFO.Ratio\textsubscript{b1->m} in the right hemisphere was significantly lower (rank-sum 48, p < 0.05) in patients with left lateralized lesions (n = 5) compared to HS (n = 6). LFO.Ratio\textsubscript{m->b2} in both hemispheres did not show a significant difference across the groups (Kruskal-Wallis test) or in direct comparison between patients and HS (Fig. 6C and Fig. 6D).

3.1.4. ROC analysis
The previous analyses suggested that LFO.Ratio\textsubscript{b1->m} in the left hemisphere could be the parameter to distinguish the patients according to their clinical assessment and their outcome measures. We performed a receiver operator characteristic analysis to quantify the predictive accuracy of left hemisphere LFO.Ratio\textsubscript{b1->m} in distinguishing the different patient/subject groups. First, LFO.Ratio\textsubscript{b1->m} could discriminate between the groups A and C with an excellent accuracy (AUC = 0.98). To test the receiver operating characteristic (ROC) for clinical outcome, we defined two possible outcomes after three months: bad (GOS 1–2) and good (GOS 3–5), analogous to Section 3.3.2. Considering the patient data only

![Fig. 4. Results from a simple regression analysis including patients and healthy subjects. X-axis: the Glasgow Coma Scale (GCS) of each subject, Y-axis: the change of low frequency oscillation (LFO) from the first baseline to music exposure (LFO. Ratio\textsubscript{b1-m}) in the left hemisphere. Spearman’s rho = 0.6, p < 0.01.](image)

![Fig. 5. LFO.Ratio for low and high GOS scores (LFO: low frequency oscillations; GOS: Glasgow Outcome Scale). Healthy subjects (HS) are compared to patients with high GOS scores (3–6) and low GOS scores (1–2). A. LFO.Ratio from the first baseline block (b1) to music exposure (m) in the left hemisphere. B. LFO.Ratio from the first baseline block (b1) to music exposure (m) in the right hemisphere. C. LFO.Ratio from the music block (m) to the second baseline block (b2) in the left hemisphere. D LFO.Ratio from the music block (m) to the second baseline block (b2) in the right hemisphere. Red crosses represent outliers.](image)
groups A-C), we obtained an AUC of 0.63, while including the HS group in the model (HS belonged to the group with good outcome) increased AUC to 0.74 (Fig. 7). For the sake of comparison, we also performed a ROC analysis using the GCS and RASS data to predict the outcome. In this case, considering the patient data only, we obtained an AUC of 0.49 (with GCS) and 0.62 (with RASS), i.e. both below the score for LFO.Ratio$_{b1->m}$ (0.63). Including the HS in the model, the AUC increased to 0.67 (GCS) and 0.7 (RASS), once again faring worse than for LFO.Ratio$_{b1->m}$ (0.74). Using ROC curve, we could identify a cut-off value of LFO.Ratio$_{b1->m} \geq 0.3964$ with maximal sensitivity (>84 %) but very low specificity (<12.5 %) to identify patients with a good outcome, and a second cut-off value of LFO.Ratio$_{b1->m} \geq 0.7488$ with maximal specificity (>84 %) but very low sensitivity (<12.5 %). Considering the subgroup B of partially responsive patients, using the cut-off value of LFO.Ratio$_{b1->m} \geq 0.3964$ we would have identified 3 of the 5 patients with good outcome after three months.

### 3.2. Cardiovascular parameters

We performed statistical tests of the null hypothesis that $d'$ values for each parameter are $= 0$ against the alternative hypothesis that they are $\neq 0$. We performed both a parametric (one sample t-test) and non-parametric (Wilcoxon signed rank test). No significant difference could be found comparing the pre-experiment phase and the music exposure phase. The results are summarized in Table 4.

| Parameter      | Average $d'$ | One Sample T-test | Wilcoxon Signed Rank Test |
|----------------|--------------|------------------|--------------------------|
| MAP            | $-0.12$ (n = 17) | $-0.28$ ($p = 0.78$) | $75$ ($p = 0.96$) |
| SYSP           | $0.67$ (n = 17) | $1.4$ ($p = 0.18$) | $49$ ($p = 0.2$) |
| HR             | $0.16$ (n = 17) | $0.36$ ($p = 0.72$) | $67$ ($p = 0.67$) |
| SPO2           | $0.32$ (n = 14) | $0.47$ ($p = 0.65$) | $39$ ($p = 0.43$) |

$n$ = number of patients; $p$ = p-value.
in Table 4, and shown in further detail in the Appendix (Figs. A2, A3, A4, A5).

3.2.1. Comparison of cardiovascular parameters between subject groups

We performed group level the Kruskal-Wallis test (Fig. 6A-D) to check if any of the medians was significantly different from the other groups. Even considering the three different groups of patients separately, no significant difference could be found comparing the pre-experiment phase and the music exposure phase.

4. Discussion

The purpose of this pilot study was to investigate fNIRS as a tool to detect hemodynamic response to auditory stimulation in prefrontal areas. According to previous observations on healthy subjects (Bajaj et al., 2014, Bicciato et al., 2021, Pierron et al., 2012), we defined the response to music as an increase of spectral power of HbO2 in the LFO region after the music begins and a decrease after it ends. Our results show an association between clinical assessment of consciousness (GCS, RASS) and left prefrontal response to music measured with fNIRS. In comparison to HS, patients with unfavorable clinical outcome (death or UWS after 3 months, i.e. GOS 1 or 2) did not show a reliable HbO2 response (i.e. low increase or no increase in LFO spectral power during music exposure and no sign of decrease in LFO spectral power after music). Although the better HbO2 response in HS may have been partially driven by other factors such as a younger median age, it is still noteworthy that patients with a favorable outcome did not show significant difference in HbO2 response, as compared to HS. The association with the level of consciousness and with the clinical outcome was stronger and more consistent across different statistical analyses for the initial increase in LFO spectral power in the left hemisphere. After grouping the patients according to their brain lesions, we found that patients with a left lateralized lesion showed a lower response to music in both hemispheres compared to healthy subjects on a pairwise level, even if we could not demonstrate a significant difference on group level (as the Kruskal-Wallis test was negative). No significant changes during music exposure could be found in mean values of MAP, SYSP, HR, SPO2. It was beyond the purpose of this study to deeply understand the mechanisms of neural perception of music. Future studies may combine fNIRS observations with fMRI and acoustic evoked potentials with more articulated experimental methods to investigate the neural correlates of music perception. Our simple experimental paradigm was designed to detect any kind of prefrontal response to auditory stimulation as a marker of consciousness of the patients. Since we did not include tests with different types of auditory stimuli such as white noise or “unpleasant” sounds, it remains unsolved if the cortical response we observed is specific to familiar music or is rather an unspecific frontal activation after auditory stimulation. Yet, our observations suggesting that left prefrontal area plays a role in music perception are consistent with previous studies (Bicciato et al., 2021, Carrière et al., 2020, Freitas et al., 2018). The role of left prefrontal areas may involve emotional processing of both music and language (Altenmüller et al., 2014, Proverbio and De Benedetto, 2018, Rogenmoser et al., 2016, Zhang D. et al., 2018). Left hemispheric dysfunction may explain the observed association between low degree of consciousness and low degree of left prefrontal response to music. In fact, language understanding is more often affected in patients with left lateralized brain lesions, and the ability to understand and follow commands is a crucial feature in most consciousness evaluation scales. This work has some obvious limitations. First, we analyzed a relatively small sample of subjects, even if comparable with other fNIRS studies. According to previous assessment in healthy subjects, LFO.Ratio_{m→b2} has a smaller effect size compared to LFO.Ratio_{m→b1} (Bicciato et al., 2021). Thus, an insufficient power of the study may explain why LFO.Ratio_{m→b2} showed only a very mild association with the level of consciousness and the clinical outcome. The experiment with patients was intentionally carried out in a real NCCU, therefore other sources of noise in the NCCU may have influenced the auditory stimulation. Additional optodes on other areas of the skull may have allowed to monitor the activity of other brain areas (e.g. temporal lobe). However, it would also have made the experiment more complicated, implying more cables and a longer preparation, thus excessively reducing time for routine patient care. Optodes on the forehead do not require cutting the hair of the patients to achieve a good signal quality, which is a possible cause of psychological discomfort for both patients and relatives. Clinical estimations of consciousness in intubated patients, even with standardized assessments such as the GCS, depends on an estimation of verbal abilities (attempts to speak) that are not very reliable (Teasdale et al., 2014). Using simplified clinical scales implies an important limitation, as we are aware of. The gold standard for consciousness evaluation would be the CRS-R (Giacino et al., 2004), however this scale would have been more time demanding and would have required a specific training. The FOUR (Almojuela et al., 2019, Fos et al., 2019) and SECONDS scores (Aubinet et al., 2021), would have given a greater accuracy to the clinical evaluation and should be considered for future studies. Unfortunately, the employment of clinical scales that do not belong to the normal routine would have required an additional training of the medical personal, that was not possible in preparation of our study. The fact that the clinical assessment was performed independently from the study investigators with standard clinical procedures, has, however, the advantage of low probability of an involuntary bias due to lack of blinding. Beside the GCS, we used a probative oversimplified patient categorization according to their ability to open the eyes and respond to commands. Group B included patients able to open the eyes but not follow commands, thus probably including both patients in UWS and patients with higher levels of consciousness such as in the MCS, as suggested by the Boxplots of Fig. 3A, showing for group B a median LFO.Ratio_{m→b1} between the median values of the group A and B with a wider spread of the data. Thus, the patients of group B with a good fNIRS response to music might be the ones with a higher level of consciousness, despite a poor performance in the clinical assessment (i.e. covert consciousness), while the patients with no fNIRS response might be the ones with a rather low level of consciousness. When asking a relative, they might have trouble knowing or remembering the patient’s taste in music; thus, recall bias should also be considered. We hypothesized that sedation may influence both clinical and cortical hemodynamic response to auditory stimulation: compared to the others, patients under sedation did not have significantly different values of LFO.Ratio_{m→b1} or LFO.Ratio_{m→b2}. However, sedatives as well as other drugs may have an unpredictable influence on cortical hemodynamics. In the comparison between patients and HS a main limitation is the lack of age-matching between the two groups (the average age of HS was 27.6 years less). Even if this limitation does not affect the patient comparison results, we cannot exclude that a younger age may be associated with higher rate of cerebral hemodynamic response. Indeed, a decrease of LFO in association to age related neurodegeneration has already been described, even though it is not clear if the magnitude its variation may also be age-dependent (Schroeter et al., 2003, Vermeij et al., 2014, Zeller et al., 2019). Clinical outcome after three months can be influenced by many other factors than cortical responsiveness alone at a given time, e.g. the pathophysiology of the underlying disease, eventual complications, or comorbidities. Therefore, finding a candidate fNIRS based predictor...
biomarker of consciousness and future clinical outcome despite many other influencing factors is a remarkable result. In the ROC analysis, fNIRS did not perform worse than clinical assessment as outcome predictor. As recently proposed (Kazazian et al., 2021, Othman et al., 2021, Pinti et al., 2020), new fNIRS markers of critical responsiveness may find application in the development of fNIRS-EEG and fNIRS-AEP integrated devices as well as in multimodal fNIRS and fMRI imaging.

5. Conclusions

We propose variation in LFO spectral power as a primary candidate biomarker of cortical responsiveness to detect covert consciousness in neurocritically ill. To further investigate LFO spectral power as a marker of cortical responsiveness, future research will require larger patients cohorts with disorders of consciousness and more accurate neurobehavioral assessment, to increase the certainty of consciousness diagnosis. Our work emphasizes the feasibility of a short experimental design that could be carried out in a real NCCU setting to apply fNIRS in patients with disorders of consciousness.

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Appendix A. Supplementary material

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