

DESCRIPTION

“A method to obtain a near-infrared spectroscopy cerebral signal”

5 Technical field of the invention

The invention relates to a method to obtain a near-infrared spectroscopy cerebral signal in a subject using a cyclic cerebral stimulation at a given task frequency, where the cerebral signal is clean, not presenting interfering components from other parts of the body, so the cerebral signal corresponds
10 mainly to brain activity.

Background of the invention

Based on the neurovascular coupling principle, functional near-infrared spectroscopy (fNIRS) aims at detecting the hemodynamic changes evoked by neuronal oxygen consumption. NIRS is a non-invasive optical imaging technology,
15 and it has been widely used to measure brain, mostly cortical, activity through relative concentration changes in oxygenated (HbO) and deoxygenated (HbR) hemoglobin (for reviews see: Obrig & Villringer, 2003; Pinti et al., 2018).

20 A major challenge in fNIRS research is to reliably disentangle the hemodynamic response due to neurovascular coupling from other confounding components (Tachtsidis & Scholkmann, 2016). fNIRS changes caused by brain activity are naturally low in amplitude and unfortunately also overlap with other fluctuations that do not originate in the cerebral cortex, mainly: (i) systemic
25 hemodynamic activity detectable in both cerebral and extracerebral regions (Bauernfeind, Wriessnegger, Daly, & Müller-Putz, 2014; Minati, Kress, Visani, Medford, & Critchley, 2011; Tachtsidis et al., 2009), (ii) local blood flow changes in superficial tissue layers across the head (Kirilina et al., 2012), and (iii) instrumental noise and other artifacts. The first two, far from being simply spontaneously
30 generated, can also be evoked by cognitive, emotional or physical tasks. If the modulation of these non-cortical task-related components of the signal mimics the dynamics of the brain activation of interest they could become an important source of interference and noise (Nambu et al., 2017; Näsi et al., 2013; Zimeo Morais et al., 2017). So much so that Takahashi et al. (2011) showed that the task-related

skin blood flow (SBF) changes could explain over 90% of the NIRS signal on a verbal fluency experiment, while Minati et al. (2011) further demonstrated the strong confounding effect of arterial blood pressure (ABP) fluctuations.

5 To better infer the presence of a functional response, experimental protocols attempt to increase statistical power by repeating the stimuli a sufficient number of times, interspersed with contrast conditions in which a different response (or none) is expected. To this end, fNIRS experiments often used blocked or event-related designs, depending on whether one wants to analyze sustained
10 or transient responses, respectively (Pinti et al., 2018). Event-designs use short-duration stimuli, normally randomized in order and separated by a constant or jittered inter-stimulus interval. Block-designs attempt to maintain mental engagement by presenting stimuli within a condition for a long enough time interval, followed by a different condition or a resting inter-stimulus interval (Amaro &
15 Barker, 2006). To investigate the interaction between 'sustained' and 'transient' responses, mixed designs can also be used (Petersen & Dubis, 2012).

 Depending on the stimulus presentation strategy, different analysis methods have been developed to make inference about the functional
20 hemodynamic response and isolate it from confounding interferences (for a review see Sungho Tak & Ye, 2014). Although classic averaging strategies provide robust results, the usual averaged-based statistical tests, such as t-test or ANOVA, do not allow estimating the shape or time-course of fNIRS signals, so they have been progressively replaced by more powerful methods. These include the general
25 linear model (GLM) framework (K. Friston, Ashburner, Kiebel, & Nichols, 2007; Schroeter, Bücheler, et al., 2004), data-driven approaches as principal component analysis (PCA) and independent component analysis (ICA) (Kohn et al., 2007; Yiheng Zhang, Brooks, Franceschini, & Boas, 2005) and dynamic state-space modeling (Diamond et al., 2006; Kolehmainen, Prince, Arridge, & Kaipio, 2003).
30 GLM is one of the most widely adopted statistical framework to quantify how well the measured fNIRS signals fit a hemodynamic model that reflects the expected neural response. It exploits the good temporal resolution of fNIRS and allows for including different covariates within the regression model (e.g. physiological signals). In its most basic form, the model is obtained by convolving a

hemodynamic response function (HRF) with a stimuli function that encodes the hypothesized time course of the neuronal response (Koh et al., 2007; Sungho Tak & Ye, 2014). Therefore, GLM is a hypothesis-driven approach that requires the combination of a specific HRF (often taken from fMRI studies) and other nuisance
5 regressors to construct the linear model, which might not be obvious depending on the task type, brain region and participant's idiosyncrasy. Moreover, GLM demands special caution when applied to fNIRS signals due to some statistical issues (Huppert, 2016; Huppert, Diamond, Franceschini, & Boas, 2009; Koh et al., 2007). In contrast, PCA and ICA methods only rely on general statistical assumptions as
10 orthogonality and independence, respectively. Although useful for separating the mixed components that make up the fNIRS signals, they require additional processing to elucidate which of them are task-related and which are not, particularly difficult when extracerebral and cerebral responses are correlated (Zhou, Sobczak, McKay, & Litovsky, 2020). State-space models, mainly based on
15 the Kalman filter, allow building complex hemodynamic models to describe the time varying characteristics of the fNIRS signals and estimate the HRF. Although dynamic analysis appears to provide better estimates of the HRF and better account for non-stationary signals, it still requires improvements in model specifications and state-space estimators.

20
Regardless of the strengths and weaknesses of each experimental method, all benefit from the inclusion of short-distance recordings to obtain a reference of the superficial layers contribution to fNIRS signals (for reviews see: Fantini, Frederick, & Sassaroli, 2018; Tachtsidis & Scholkmann, 2016; Sungho Tak & Ye,
25 2014). Multi-distance measurements are considered particularly effective in isolating the actual cerebral response. Nevertheless, some open questions remain regarding, for example, the ideal range for source-detector distances, the optimal number of short-channels and their arrangement relative to long-channels. Ideally, and since there is growing evidence of the heterogeneous nature of surface
30 hemodynamics (Wyser et al., 2020), each long-channel should be paired with at least one nearby short-channel. Unfortunately, such a precise spatial configuration of the paired measurements is not currently possible with the most commonly used NIRS devices today.

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It is therefore an objective of the present invention providing a method to obtain a near-infrared spectroscopy cerebral signal in a subject having only access to long and short channels.

5 Description of the invention

10 The present invention describes a method to obtain a near-infrared spectroscopy cerebral signal in a subject. In essence, the method comprises the steps of placing a near-infrared emitter and respective proximal and distal near-infrared detectors on the skin of the head of the subject; during a baseline recording stage with the subject in resting-state, recording by a computer near-infrared signals received from the near-infrared emitter in the proximal and distal near-infrared detectors, the recorded signals comprising a baseline deep-signal received by the distal near-infrared detector, and a baseline shallow-signal received by the proximal near-infrared detector; calculating by the computer a scaling factor between the amplitude of the baseline deep-signal and the baseline shallow-signal at a given task-frequency; with the subject undergoing a cyclic cerebral stimulation at the task-frequency during a stimulation recording stage, recording by the computer near-infrared signals received from the near-infrared emitter in the proximal and distal detectors, the recorded signals comprising a deep-signal received by the distal near-infrared detector, and a shallow-signal received by the proximal near-infrared detector. Then obtaining by the computer the cerebral signal at the task-frequency during stimulation by applying the scaling factor to the shallow-signal; and calculating the cerebral signal at the task-frequency as the difference between the deep-signal and the scaled shallow-signal, at the task-frequency. The steps of the method can be performed by a computer or a data processing apparatus programmed accordingly. The computer can be a single computer comprising software conveniently programmed to perform the steps of the method. Also, embedded devices or distributed computer systems, or other known computer arrangements could be used for carrying out the method, as known by the skilled person.

Advantageously, performing a cyclic cerebral stimulation at a given task frequency such as a cyclic cognitive task would induce periodic hemodynamic fluctuations measurable in fNIRS recordings, therefore an oscillatory state suitable

for effective analysis in the frequency-domain can be generated. To this end, mental arithmetic task within a cyclic block-design can be employed at a specific frequency, while performing multi-distance recordings on the forehead.

5 Previously, surface fluctuations were only considered annoying confounders that need to be remove, but in the present invention the fluctuations are viewed instead as carriers of valuable information, information that might prove essential not only to gain a better understanding of fNIRS data but also, and perhaps as important, to more precisely assess the full dynamics of the neuro-
10 visceral link, so the cerebral signal can be calculated from the deep-signal and the shallow-signal during cyclic cerebral stimulation at the given task frequency.

Task-related arousal mechanism requires a close interaction between cognitive function and autonomic control (Forte, De Pascalis, et al., 2019; Forte, Favieri, et al., 2019; Nicolini et al., 2014; Thayer & Lane, 2009; Wang et al., 2016).
15 Thus, the autonomic control appears to be associated with activity levels in executive brain regions, which allows an adaptive response to environmental demands. Conversely, autonomic dysfunctions may be related to the deterioration of certain cognitive functions, specifically of executive functions (Forte, De Pascalis, et al., 2019; Forte, Favieri, et al., 2019). This close coordination of extracerebral and cerebral responses with the task-frequency may have great functional value. The correct coupling between physiological resources may be the sign of proper cognitive and/or cardiovascular function and, its disruption, a potential early marker of cognitive decline and/or cardiovascular disease.
20 Therefore, the cerebral signal at the task-frequency, and its relation with extracerebral responses, can be useful for the diagnosis and assessment of dementias like Alzheimer's disease; neurodevelopment disorders like autism or ADHD, and autonomic dysfunctions, among other clinical entities involving brain functional changes.

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According to an embodiment of the invention, the cerebral stimulation is a mental or cognitive activity, such as a mental arithmetic task, so the near-infrared spectroscopy cerebral signal corresponds to the cerebral response caused by the mental or cognitive activity.

According to another embodiment of the invention, the cerebral stimulation can be a visual, or auditive, or olfactory, or gustative, or somatosensorial, or motor activity, so the near-infrared spectroscopy cerebral signal corresponds to the cerebral responses caused by the corresponding cerebral stimulation.

According to an embodiment of the invention, the step of obtaining the cerebral signal at the task-frequency during stimulation comprises obtaining by the computer the phase, it is, the phase angle, and amplitude of the cerebral signal.

As the cerebral signal is expected to have a frequency equal to the task-frequency, the components required for obtaining the cerebral signal are its amplitude and phase, as the frequency is already known. Therefore, the difference between the deep-signal and the scaled shallow-signal, filtered at the task-frequency, would provide the phase, it is, the phase angle, and amplitude of the cerebral signal.

According to an embodiment of the invention, the step of obtaining by the computer the phase and amplitude of the cerebral signal during stimulation comprises: determining by the computer a deep-signal phasor corresponding to the deep-signal during stimulation at the task-frequency, having: phase: the phase difference between the deep-signal and the shallow-signal at the task-frequency, and amplitude: the amplitude of the shallow-signal at the task-frequency; determining by the computer a shallow-signal phasor corresponding to the shallow-signal during stimulation at the task-frequency, having a reference phase (for example 0°), and an amplitude of the shallow-signal at the task-frequency, multiplied by the scaling factor; determining by the computer a cerebral-signal phasor by subtracting the shallow-signal phasor from the deep-signal phasor, it is, calculating their difference; and calculating by the computer the phase and amplitude of the estimated cerebral signal at the task-frequency. Advantageously, since the significant components of the frequency of the shallow-signal and the deep-signal are found to be at a frequency equal to the task-frequency, the cerebral signal can be obtained by appropriately combining phasors at the task-frequency derived from the shallow-signal and the deep-signal.

According to an embodiment of the invention, the phase difference between

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the deep-signal and the shallow-signal at the task-frequency is obtained by calculating by the computer an empirical transfer function in the frequency domain between the deep-signal and the shallow-signal and calculating by the computer the argument of the transfer function at the task-frequency, therefore an empirical
5 transfer function can be used to estimate by the computer the phase of the cerebral signal, corresponding to the functional brain activity, by obtaining the timed-coordination between extracerebral and cerebral responses.

According to an embodiment of the invention, the step of calculating by the
10 computer a scaling factor between the amplitude of the basal deep-signal and the basal shallow-signal at the task-frequency comprises calculating by the computer an approximation of a complex frequency dependent basal transfer function between the basal deep-signal and the basal shallow-signal and determine by the computer the scaling factor as the gain of the basal transfer function at the task-
15 frequency, therefore an empirical transfer function can also be used by the computer to estimate the gain of the functional brain activity, which can be applied for obtaining the cerebral signal. Therefore, both gain or amplitude and phase of the cerebral signal can be obtained by the computer using a transfer function applied to the deep-signal and shallow-signal.

20 According to an embodiment of the invention, the task-frequency is a frequency between 0,015 Hz and 0,07 Hz, so natural oscillations of the body, such as the oscillations caused by heart beating, breathing or Mayer arterial pressure waves does not affect the cerebral signal. Preferably, the task-frequency is a
25 frequency between 0,025 Hz and 0,05 Hz, such that the task-frequency is far enough from the known natural oscillations of the body. More preferably, the task-frequency is a frequency of 0,033 Hz, such that the corresponding period is 15 seconds, which can be easily measured for computing the duration of each period during the cyclic cerebral stimulation.

30 According to an embodiment of the invention, having a plurality of groups of near-infrared emitter and respective proximal and distal near-infrared detectors, grouped by regions of interest, the method further comprises averaging determine by the computer the shallow-signal and the deep-signal obtained for each group,

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so the signals are averaged, reducing the signal-noise ratio for each region of interest.

According to an embodiment of the invention, the step of the recording
5 during a stimulation comprises alternating semi-periods of stimulating in the
subject a cyclic mental task; and semi-periods of baseline resting, such that the
task-frequency is maintained during the recording phase, allowing to promote the
components of the deep-signal and shallow-signal at the task-frequency.
Therefore, it is also expected that the semi-periods of stimulating and the semi-
10 periods of baseline resting have the same duration.

A system to obtain a near-infrared spectroscopy cerebral signal in a subject
is also disclosed, the system comprising a device comprising a near-infrared
emitter and respective proximal and distal near-infrared detectors, adapted for
15 placing the near-infrared emitter and respective proximal and distal near-infrared
detectors on the skin of the head of the subject; and a computer comprising means
for carrying out the steps of: during a baseline recording stage with the subject in
resting-state, record near-infrared signals received from the near-infrared emitter
in the proximal and distal near-infrared detectors, the recorded signals comprising
20 a baseline deep-signal received by the distal detector, and a baseline shallow-
signal received by the proximal detector; calculate a scaling factor between the
amplitude of the baseline deep-signal and the baseline shallow-signal at a given
task-frequency; with the subject undergoing a cyclic cerebral stimulation at the
task-frequency during a stimulation recording stage, record near-infrared signals
25 received from the near-infrared emitter in the proximal and distal detectors, the
recorded signals comprising: a shallow-signal received by the proximal detector,
and a deep-signal received by the distal detector; obtaining the cerebral signal at
the task-frequency during stimulation by applying the scaling factor to the shallow-
signal; and calculating the cerebral signal at the task-frequency as the difference
30 between the deep-signal and the scaled shallow-signal, at the task-frequency. The
difference between the deep-signal and the scaled shallow-signal, at the task-
frequency, can be calculated by the computer as the difference of phasors of the
deep-signal and the scaled shallow-signal at the task-frequency, so the phase and
amplitude of the cerebral signal can be calculated by the computer in a non-

invasive way.

Brief description of the drawings

As a complement to the description provided herein and for the purpose of
5 helping to make the characteristics of the invention more readily understandable,
this specification is accompanied by a set of drawings, which by the way of
illustration and not limitation, represent the following:

Fig. 1 presents an example of a cerebral stimulation for a given task
10 frequency;

Fig. 2 presents an example of the placement of an emitter and respective
proximal and distal detectors on the skin of the head of a subject;

Fig. 3 presents a schema of the shallow and deep channels between the
emitter and detectors of Fig. 2;

15 Fig. 4 presents a recording of filtered signals of the shallow and deep
channels at the given task-frequency during the baseline and stimulation recording
phase of the cerebral stimulation of Fig. 1

Fig. 5a presents the gain of a transfer function between the filtered signals
of the shallow and deep channels during the baseline recording stage of Fig. 4;

20 Fig 5b presents the phase of a transfer function between the filtered signals
of the shallow and deep channels during the stimulation recording stage of Fig. 4;

Fig. 6a presents the averaged periods of the shallow signal and deep signal
of Fig. 4 during the stimulation recording stage;

Fig. 6b presents the scaled shallow signal and the deep signal of Fig. 6a;

25 Fig. 6c presents the obtained cerebral signal as the difference between the
scaled shallow signal and the deep signal of Fig. 6b;

Fig. 7 presents obtaining the cerebral signal as the difference between the
scaled shallow signal and the deep signal using phasors;

30 Fig. 8 presents another example of the placement of emitters and
respective proximal and distal detectors on the skin of the head of a subject;

Fig. 9 presents a schema of the shallow and deep channels between the emitters
and detectors of Fig. 8.

Detailed description of an embodiment of the invention

Fig. 1 presents an example of a cyclic cerebral stimulation at a given task-frequency f_t that can be used for obtaining the near-infrared spectroscopy fNIRS cerebral signal S_{CS} in a subject 1 using the method of the present invention through
5 a system 100 comprising a device 10 and a computer 20 adapted to perform the steps of the method.

The cerebral stimulation is a mental or cognitive activity, so the corresponding obtained cerebral signal S_{CS} will be related to this mental or
10 cognitive activity. Fig. 1 presents a cyclic cerebral stimulation at a given task frequency f_t is based on a block protocol designed as a cyclical pattern of mental effort, alternating semi-periods $Tt/2$ of mental math, with semi-periods $Tt/2$ of pause, of the same duration, i.e. regular repetitions of activation-rest, The idea behind this is to induce periodic hemodynamic changes in the form of cycles of
15 some kind of response to the subject 1 followed by a return to basal levels. In this way, such an oscillatory pattern may be analyzed by conventional spectral methods. This cyclical cerebral estimation can also be programmed in a computer.

20 As illustrated in Fig. 1, the cyclic cerebral stimulation is organized into three consecutive uninterrupted recordings: (i) 300 seconds of baseline in resting condition, as baseline recording stage t_1 (ii) 300 seconds of mental arithmetic task, as stimulation recording stage t_2 and (iii) 300 seconds of recovery in a relaxed state. In this case, the stimulation recording stage t_2 consist of 10 consecutive 30-
25 second trials, with a 30 second period Tt . Each trial began with a semi-period $Tt/2$ of 15 seconds of mental calculation, followed by a semi-period $Tt/2$ of 15-second pause of relaxation. To perform the mental math participants were asked to iteratively subtract a small number (between 5 and 9) from a three-digit number (between 100 and 199), as fast as possible. Both numbers, chosen randomly in
30 each trial, were presented on a 21.5" display monitor, 80 cm. away from the participants' eyes. Afterwards, the pause started by presenting the question "Result?" for 5 seconds, which prompted the participants to inform verbally of the final result of their mental calculations (to allow scoring the performance and ensuring that the participants were paying attention), followed by a soft image

during which the participants were instructed to relax. Two seconds before presenting the subtraction operands, a fixation cross was displayed in the middle of the computer screen to announce the beginning of the mental calculation. Further, during the stimulation recording stage t_2 the importance of making a mental effort was constantly emphasized, and not the amount or accuracy of the operations performed.

In this case, the 30-second period of the mental arithmetic trials corresponds to a task-frequency f_t of 0,033 Hz. This frequency was chosen so that it did not overlap with well know spontaneous fluctuations such as ABP (0,08 - 0,12 Hz), or very slow endothelial activity (0,01 – 0,02 Hz). Furthermore, the 15-second duration of mental effort accommodates that of a typical hemodynamic response, while the next 15-second pause allows a return to baseline levels, being an optimal inter-event interval to minimize overlaps between consecutive hemodynamic responses. However, other task-frequency f_t are also envisaged, for example frequencies between 0,015 Hz and 0,07 Hz, and preferably frequencies between 0,025 Hz and 0,05 Hz could also be used.

In this case the cyclic cerebral stimulation is a mental arithmetic task, it is, a mental or cognitive activity, so the cerebral signal S_{CS} to be obtained will be a response of the subject 1 to such mental or cognitive activity. However, in other embodiments, it is envisaged that the cerebral stimulation could be a visual, or auditive, or olfactory, or gustative or somatosensorial or motor activity, or even other activities depending on the cerebral signal S_{CS} to be obtained as a response of the subject 1.

As shown in Fig. 2, for obtaining a near-infrared spectroscopy (fNIRS) cerebral signal S_{CS} in a subject 1 a near-infrared emitter 2 and two detectors 3, respectively a proximal detector 3a and a distal detector 3b, mounted on a device 10 of the system 100, are placed on the skin of the head of the subject 1, typically in the fronto-polar region. It will allow obtaining the near-infrared spectroscopy (fNIRS) cerebral signal S_{CS} in the subject 1 during cyclic cerebral stimulation at the given task frequency f_t ,

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The proximal detector 3a is placed closer to the emitter 2 than the distal detector 3b, for example, the proximal detector 3a is placed 14 mm from the emitter 2 and the distal detector 3b is placed 32 mm from the emitter 2. Naturally, other arrangements of various emitters 2 and detectors 3 in the device 10 are also possible and they can be used for obtaining the near-infrared spectroscopy cerebral signal S_{CS} in the subject 1 in a similar way as explained hereinafter.

The wavelength of the emitter 2 and detectors 3 will be adapted to detect the differences caused by the cerebral stimulation. For example, a near-infrared wavelength of 740 and 850 nm would be suitable for detecting relative changes in oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) concentration, consequently the cerebral signal obtained would be proportional to the adsorption of the emitted and received wavelengths.

Fig. 3, shows a representation of the shallow channel SS established between the emitter 2 and the proximal detector 3a and the deep channel DS established between the emitter 2 and the distal detector 3b. The emitter 2 can be a light emitting diode emitting the wavelength of interest, in this case, a wavelength of 850 nm, and the detectors 3 can be photodiodes or phototransistors, also known as optodes, adapted to receive the wavelength of interest and generating a corresponding electrical signal, that will be transmitted, for example wirelessly, and processed by a computer 20 of the system 100.

Figs. 4 to 7 are related to a method for obtaining a cerebral signal S_{CS} by a computer 20 based on detected changes in oxyhemoglobin (HbO), but other cerebral signals based on detected changes in other components at other wavelengths, such as deoxyhemoglobin (HbR) or even total hemoglobin (HbT) or isobestic point at 804-805 nm where the adsorption caused by HbO and HbR is the same could be used. Therefore, other wavelengths can be emitted or received as needed, depending on the variation of the component to be detected for obtaining the corresponding cerebral signal.

Fig. 4 shows an example of a recording of signals from the shallow channel SS and deep channel DS during the baseline recording stage t_1 with the subject in

resting-state and the stimulation recording stage t_2 , which are recorded by the computer 20. As previously explained, the stimulation recording stage t_2 comprises alternating semi-periods $T_t/2$ of stimulating in the subject 1 the mental task, and semi-periods $T_r/2$ of baseline resting, where the subject 1 recovers of the mental task, the semi-periods $T_t/2$ of stimulating and the semi-periods $T_r/2$ of baseline resting have the same duration. Advantageously, combining semi-periods $T_t/2$ of stimulating and the semi-periods $T_r/2$ of baseline resting induces a cyclic cerebral stimulation at the given task frequency f_t .

10 The signals presented in Fig. 4 have been adapted and filtered by the computer 20 around the task-frequency f_t so components of the signals at the same task-frequency f_t are obtained. In this case, the raw optical data of each detector 3 was converted to optical density, and then into oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) relative concentration changes via the modified Beer-Lambert law, in this case only oxyhemoglobin (HbO) relative concentration is presented for illustrative purposes. The data was digitally band-filtered by the computer 20 around the task-frequency f_t , in this case using a zero-phase filter with a filter width of 0,015Hz, other filtering and filter widths could be used for obtaining the signals around the task-frequency f_t without introducing a delay, or compensating such delay.

As it can be seen in Fig. 4, during the baseline recording stage t_1 with the subject in resting-state, near-infrared signals received from the near-infrared emitter 2 in the proximal and distal near-infrared detectors 3 at the task-frequency f_t were recorded by the computer 20, the recorded signals comprising a baseline deep-signal B_{DS} received by the distal near-infrared detector, and a baseline shallow-signal B_{SS} received by the proximal near-infrared detector.

During the stimulation recording stage t_2 , with the subject undergoing a cyclic cerebral stimulation at the task-frequency f_t according to the pattern of Fig. 1, near-infrared signals received from the near-infrared emitter 2 in the proximal and distal near-infrared detectors 3 at the task-frequency f_t were recorded by the computer 20, the recorded signals comprising a shallow-signal S_{SS} received by the proximal detector 3a, and a deep-signal S_{DS} received by the distal detector 3b.

Since fNIRS signals are dominated by confounding hemodynamics not originated in the cerebral cortex by functional activity, but with origin in blood flow changes in superficial tissues and by changes in systemic physiology that are present both in the superficial layers and in the brain tissue itself, even at different time scales. To address this issue, an effective strategy is the use of multi-distance measurements. Shallow components are removed from the deep-signals by assuming that short-separation recordings are sensitive only to extra-cerebral changes while long-separation recordings are sensitive to both extra-cerebral and cerebral activity.

Therefore, at the task-frequency f_t removing shallow components present in the shallow-signal S_{SS} from the deep-signal S_{DS} for obtaining the cerebral signal S_{CS} could be expressed by the following linear combination:

$$S_{CS} = S_{DS} - (KS_{SS})$$

Since these signals at the task-frequency f_t are considered to be sinusoids, only their amplitude and phase would differ.

The scaling factor K can be calculated by the computer 20 as the ratio of amplitudes between the baseline deep-signal B_{DS} and the baseline shallow-signal B_{SS} at the task-frequency f_t . Multiple other methods are known for calculating by a computer this scaling factor K as the ratio of amplitudes of the baseline deep-signal B_{DS} and the baseline shallow-signal B_{SS} , such as detecting the average peak to peak ratio between the baseline deep-signal B_{DS} and the baseline shallow-signal B_{SS} , or the ratio between the root mean square measurements of the baseline deep-signal B_{DS} and the baseline shallow-signal B_{SS} .

Also, a transfer function strategy could be used by the computer 20 for calculating the scaling factor K , as transfer function models have become a popular approach to investigate the dynamic of cerebrovascular autoregulation (Claassen et al., 2015; Van Beek, Claassen, Rikkert, & Jansen, 2008), and they have also been used to remove systemic physiological noise from fNIRS signals

(Bauernfeind, Böck, Wriessnegger, & Müller-Putz, 2013; Florian & Pfurtscheller, 1997). Assuming that the shallow-signal S_{SS} has energy in the frequency range of interest, around the task-frequency f_t , and contain quasi-periodic oscillations, the transfer function $H(f)$ can be approximated from the experimental fNIRS data as
 5 (Zhang et al., 1998):

$$H(f) = \frac{CPSD_{ssds}(f)}{PSD_{ss}(f)}$$

For the time-series pair, shallow-signal S_{SS} and deep-signal S_{DS} are,
 10 respectively, the input and output signals used to obtain an approximation of the transfer function at the task-frequency f_t . From the complex-valued result, we obtained the magnitude (gain), corresponding to the scaling factor K which represents the relative change in μM between input and output, and the phase that carries their temporal coupling (phase difference or time-lag). For reporting the
 15 gain, data were converted by the computer 20 into percentage values, which will be the scaling factor K . Then, the scaling factor K can be considered the gain value of the basal transfer function bTF at f_t during “baseline”, it is, during the baseline recording stage t_1 , which represents the fraction of the magnitude of the shallow-signal S_{SS} present in the deep-signal S_{DS} when no significant cerebral
 20 signal S_{CS} component contributes.

Therefore, during the step of calculating the scaling factor K between the amplitude of the basal deep-signal B_{DS} and the basal shallow-signal B_{SS} at the task-frequency f_t an approximation of a complex frequency dependent basal transfer
 25 function bTF between the basal deep-signal B_{DS} and the basal shallow-signal B_{SS} can be computed by the computer 20 to determine the scaling factor K as the gain of the basal transfer function bTF at the task-frequency f_t , as shown in Fig. 5a.

The phase difference between the deep-signal S_{DS} and the shallow-signal
 30 S_{SS} at the task-frequency f_t can be obtained by determining by the computer 20 the delay between the deep-signal S_{DS} and the shallow-signal S_{SS} filtered at task-frequency f_t as known by the skilled person. However, this phase difference can also be obtained by calculating an empirical transfer function TF in the frequency domain between the deep-signal S_{DS} and the shallow-signal S_{SS} during the

stimulation recording stage t_2 and calculating by the computer 20 the argument of the transfer function TF at the task-frequency f_t , which is illustrated in Fig. 5b. Therefore, the scaling factor K and the phase difference that will be used to calculate the cerebral signal S_{CS} are obtained.

5

Fig. 6a shows an averaged period of the periods of the deep-signal S_{DS} and the shallow-signal S_{SS} , while Fig. 6b shows the signals of Fig. 6a where the scaling factor K has been applied by the computer 20 to the shallow-signal S_{SS} , thus reducing its amplitude.

10

Then, given the linear combination between the deep-signal S_{DS} and the shallow-signal S_{SS} for obtaining the cerebral signal S_{CS} previously explained, the cerebral signal S_{CS} at the task-frequency f_t can be calculated by the computer 20 as the difference, in phase and amplitude, between the deep-signal S_{DS} and the scaled shallow-signal KS_{SS} , at the task-frequency f_t , thus obtaining the cerebral signal S_{CS} depicted in Fig. 6c.

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Advantageously, since the deep-signal S_{DS} and the shallow-signal S_{SS} are sinusoidal signals with frequency the task-frequency f_t , the deep-signal S_{DS} and the shallow-signal S_{SS} can be expressed as a respective phasor vectors corresponding to a deep-signal phasor X_{DS} and shallow-signal phasor X_{SS} , having the amplitudes and phases of their corresponding sinusoidal signals, so the linear combination previously indicated can also be expressed as a linear combination of phasors as indicated below:

25

$$S_{CS} = S_{DS} - (KS_{SS})$$

$$A_{CS} \cos(2\pi f_t t + \phi_{CS}) = A_{DS} \cos(2\pi f_t t + \phi_{DS}) - KA_{SS} \cos(2\pi f_t t + \phi_{SS})$$

30

$$A_{CS} e^{j\phi_{CS}} = A_{DS} e^{j\phi_{DS}} - KA_{SS} e^{j\phi_{SS}}$$

$$X_{CS} = X_{DS} - KX_{SS}$$

It is expected for one of the phases between the phase of the shallow-signal

ϕ_{SS} and the phase of the deep-signal ϕ_{DS} to be a reference phase, typically a 0 degrees reference phase. In this case, the reference phase of 0 degrees is assigned to the phase of the shallow-signal ϕ_{SS} .

5 This way, the difference, in phase and amplitude, between the deep-signal S_{DS} and the scaled shallow-signal KS_{SS} can directly be calculated by the computer 20 as a phasor subtraction of the deep-signal phasor X_{DS} minus the shallow-signal phasor X_{SS} as graphically represented in Fig. 7, for obtaining a cerebral signal phasor X_{CS} with an amplitude and phase corresponding to the amplitude and phase
10 of the cerebral signal S_{CS} at the task-frequency f_t .

 Therefore, the step of obtaining the phase and amplitude of the cerebral signal S_{CS} during stimulation comprises determining by the computer 20 a deep-signal phasor X_{DS} corresponding to the deep-signal S_{DS} during stimulation at the
15 task-frequency f_t , having as phase the phase difference between the deep-signal S_{DS} and the shallow-signal S_{SS} at the task-frequency f_t , and amplitude the amplitude of the deep-signal S_{DS} at the task-frequency f_t ; and determining a shallow-signal phasor X_{SS} corresponding to the shallow-signal S_{SS} during stimulation at the task-frequency f_t , having a reference phase of 0 degrees, and as
20 amplitude the amplitude of the shallow-signal S_{SS} at the task-frequency f_t , multiplied by the scaling factor K . Naturally, alternatively the reference phase of 0 degrees could be the phase of the deep-signal phasor X_{DS} , or the reference phase could be any known phase, as only the phase difference is relevant.

25 Then, the phase and amplitude of the estimated cerebral signal S_{CS} at the task-frequency f_t can be calculated by the computer 20 by determining a cerebral-signal phasor X_{CS} by directly subtracting the shallow-signal phasor X_{DS} from the deep-signal phasor X_{DS} , as graphically represented in Fig. 7.

30 Although previously only one emitter 2 and a proximal detector 3a and distal detector 3b group was used, also other multichannel, wireless, continuous-wave NIRS device 10 could be used, such as the Brainspy28, from Newmanbrain, S.L., which employs four emitters 2 and ten detectors 3 forming a rectangular grid of 80x20 mm. In this case, each emitter 2 housed two light-emitting-diodes (LED) at

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wavelengths 740 nm and 850 nm. Through a precise switching cycle, the device
10 combines pairs of optodes at different separation distances, providing 16 short-
channels or shallow channels SS and 12 long-channels or deep channels DS that
corresponds to a source-detector distance of 14 and 32 mm respectively, as shown
5 in Figs. 8 and in more detail in Fig. 9. Moreover, it is also expected that the device
10 could measure and correct the ambient light contribution, and it can also it
incorporate a 3-axis accelerometer to account for head motion. Data can be
wirelessly transmitted (for example via Bluetooth) at a sample rate of 10 Hz to the
computer 20, that would execute the steps of processing the data to obtain the
10 near-infrared spectroscopy fNIRS cerebral signal S_{CS} .

As shown in Fig. 8, the NIRS probe can be applied onto the forehead,
centered on AFpz according to the international 10-5 system, mainly covering the
frontopolar area of the prefrontal cortex (PFC). It is expected that the optodes
15 contact the skin through an intermediate convex lens pressing the skin when the
probe is held firmly, in order to reduce cutaneous blood flow and, therefore, its
hemodynamic interference.

Advantageously, by having a plurality of groups of near-infrared emitter and
20 respective proximal and distal near-infrared detectors grouped by regions of
interest, the shallow-signal and the deep-signal obtained for each region can be
averaged, so the signal-noise ratio for each region of interest is improved, and a
better cerebral signal S_{CS} can be obtained per each region of interest.

25

CLAIMS

1. A method to obtain a near-infrared spectroscopy (fNIRS) cerebral signal (S_{CS}) in a subject (1), the method comprising the steps of:

5

- placing a near-infrared emitter (2) and respective proximal and distal near-infrared detectors (3) on the skin of the head of the subject (1);

10

- during a baseline recording stage (t_1) with the subject in resting-state, recording by a computer (20) the near-infrared signals received from the near-infrared emitter (2) in the proximal and distal near-infrared detectors (3), the recorded signals comprising:

15

- o a baseline deep-signal (B_{DS}) received by the distal detector (3b), and
- o a baseline shallow-signal (B_{SS}) received by the proximal detector (3a);

20

- calculating by the computer (20) a scaling factor (K) between the amplitude of the baseline deep-signal (B_{DS}) and the baseline shallow-signal (B_{SS}) at a given task-frequency (f_i);

25

- with the subject undergoing a cyclic cerebral stimulation at the task-frequency (f_i) during a stimulation recording stage (t_2), recording by the computer (20) near-infrared signals received from the near-infrared emitter (2) in the proximal and distal detectors (3), the recorded signals comprising:

30

- o a shallow-signal (S_{SS}) received by the proximal detector (3a), and
- o a deep-signal (S_{DS}) received by the distal detector (3b);
- obtaining by the computer (20) the cerebral signal (S_{CS}) at the task-frequency (f_i) during stimulation by:
 - o applying the scaling factor (K) to the shallow-signal (S_{SS}); and

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- calculating the cerebral signal (S_{CS}) at the task-frequency (f_t) as the difference between the deep-signal (S_{DS}) and the scaled shallow-signal (KS_{SS}), at the task-frequency (f_t).

5 2. Method according to claim 1 characterized in that the cerebral stimulation is a mental or cognitive activity.

 3. Method according to claim 1 characterized in that the cerebral stimulation is a visual, auditive, olfactory, gustative, somatosensorial or motor
10 activity.

 4. Method according to any of the preceding claims, characterized in that the step of obtaining by the computer (20) the cerebral signal (S_{CS}) at the task-frequency (f_t) during stimulation recording stage (t_2) comprises obtaining by the
15 computer (20) the phase and amplitude of the cerebral signal (S_{CS}).

 5. Method according to the preceding claim, characterized in that the step of obtaining by the computer (20) the phase and amplitude of the cerebral signal (S_{CS}) during stimulation comprises:
20

- determining by the computer (20) a deep-signal phasor (X_{DS}) corresponding to the deep-signal (S_{DS}) during stimulation at the task-frequency (f_t), having:

25 ○ phase (ϕ_{DS}): the phase difference between the deep-signal (S_{DS}) and the shallow-signal (S_{SS}) at the task-frequency (f_t), and

- amplitude (A_{DS}): the amplitude of the deep-signal (S_{DS}) at the task-frequency (f_t);

30 - determining by the computer (20) a shallow-signal phasor (X_{SS}) corresponding to the shallow-signal (S_{SS}) during stimulation at the task-frequency (f_t), having:

35 ○ phase (ϕ_{SS}): a reference, and

- amplitude (A_{SS}): amplitude of the shallow-signal (S_{SS}) at the task-frequency (f_i), multiplied by the scaling factor (K);
 - 5 - determining by the computer (20) a cerebral-signal phasor (X_{CS}) by subtracting the shallow-signal phasor (X_{DS}) from the deep-signal phasor (X_{DS}); and
 - calculating by the computer (20) the phase and amplitude of the
 - 10 estimated cerebral signal (S_{CS}) at the task-frequency (f_i)
6. Method according to any of the preceding claims, characterized in that the phase difference between the deep-signal (S_{DS}) and the shallow-signal (S_{SS}) at the task-frequency (f_i) is obtained by calculating by the computer (20) an
- 15 empirical transfer function (TF) in the frequency domain between the deep-signal (S_{DS}) and the shallow-signal (S_{SS}) and calculating by the computer (20) the argument of the transfer function (TF) at the task-frequency (f_i).
7. Method according to any of the preceding claims, characterized in
- 20 that the step of calculating by the computer (20) a scaling factor (K) between the amplitude of the basal deep-signal (B_{DS}) and the basal shallow-signal (B_{SS}) at the task-frequency (f_i) comprises calculating by the computer (20) an approximation of a complex frequency dependent basal transfer function (bTF) between the basal deep-signal (B_{DS}) and the basal shallow-signal (B_{SS}) and determine by the
- 25 computer (20) the scaling factor (K) as the gain of the basal transfer function (bTF) at the task-frequency (f_i).
8. Method according to any of the preceding claims, characterized in that the task-frequency (f_i) is a frequency between 0,015 Hz and 0,07 Hz.
- 30 9. Method according to the preceding claim, characterized in that the task-frequency (f_i) is a frequency between 0,025 Hz and 0,05 Hz.
10. Method according to the preceding claim, characterized in that the

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task-frequency (f_t) is a frequency of 0,033 Hz.

11. Method according to any of the preceding claims, characterized in that, having a plurality of groups of near-infrared emitter and respective proximal and distal near-infrared detectors, the method further comprises averaging by the computer (20) the shallow-signal (S_{ss}) and the deep-signal (S_{ds}) obtained for each group.

12. Method according to any of the preceding claims, characterized in that the step of recording by the computer (20) during the stimulation recording stage (t_2) comprises alternating:

- semi-periods ($T_i/2$) of stimulating in the subject; and
- semi-periods ($T_i/2$) of baseline resting.

13. Method according to the preceding claim, characterized in that the semi-periods of stimulating and the semi-periods of baseline resting have the same duration.

14. System (100) to obtain a near-infrared spectroscopy (fNIRS) cerebral signal (S_{cs}) in a subject (1), the system comprising:

a device (10) comprising a near-infrared emitter (2) and respective proximal and distal near-infrared detectors (3), adapted for placing the near-infrared emitter (2) and respective proximal and distal near-infrared detectors (3) on the skin of the head of the subject (1);

and a computer (20) comprising means for carrying out the steps of:

- during a baseline recording stage (t_1) with the subject in resting-state, record near-infrared signals received from the near-infrared emitter (2) in the proximal and distal near-infrared detectors (3), the recorded signals comprising:

o a baseline deep-signal (B_{ds}) received by the distal detector (3b), and

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- a baseline shallow-signal (B_{SS}) received by the proximal detector (3a);
- 5 - calculate a scaling factor (K) between the amplitude of the baseline deep-signal (B_{DS}) and the baseline shallow-signal (B_{SS}) at a given task-frequency (f_i);
- with the subject undergoing a cyclic cerebral stimulation at the task-frequency (f_i) during a stimulation recording stage (t_2), record near-infrared signals received from the near-infrared emitter (2) in the proximal and distal detectors (3), the recorded signals comprising:
 - 10 ○ a shallow-signal (S_{SS}) received by the proximal detector (3a), and
 - 15 ○ a deep-signal (S_{DS}) received by the distal detector (3b);
- 15 - obtaining the cerebral signal (S_{CS}) at the task-frequency (f_i) during stimulation by:
 - 20 ○ applying the scaling factor (K) to the shallow-signal (S_{SS}); and
 - 20 ○ calculating the cerebral signal (S_{CS}) at the task-frequency (f_i) as the difference between the deep-signal (S_{DS}) and the scaled shallow-signal (KS_{SS}), at the task-frequency (f_i).