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Focal frontal (de)oxyhemoglobin responses during simple arithmetic

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ABSTRACT

Near-infrared spectroscopy (NIRS) is a functional brain imaging method able to study hemodynamic changes during cortical activation. We studied the changes of oxy- and deoxyhemoglobin ([oxy-Hb], [deoxy-Hb]) with a 52-channel NIRS system during simple mental arithmetic in ten healthy volunteers over the prefrontal cortex. We found that eight of the ten subjects showed a relative focal bilateral increase of [oxy-Hb] in the dorsolateral prefrontal cortex (DLPFC) in parallel with a decrease in the medial area of the anterior prefrontal cortex (APFC). The [oxy-Hb] response in left DLPFC and APFC was significant, while the [deoxy-Hb] response was clearly smaller and not significant. These observations were discussed within the context of "focal activation/surround deactivation".

1. Introduction

Near-infrared spectroscopy (NIRS) is a recently developed technique that can reveal hemodynamic and metabolic changes during cortical activation. NIRS has been used to study hemodynamic responses (changes of oxy- and deoxyhemoglobin ([oxy-Hb], [deoxy-Hb])) to cognitive, visual, visuomotor and motor tasks (Franceschini et al., 2003; Herrmann et al., 2005; Herrmann et al., 2008; Hofmann et al., 2008; Shimada et al., 2004; Tanida et al., 2004; Wriessnegger et al., 2008). It is widely accepted that increases in [oxy-Hb] and slight decreases in [deoxy-Hb] are typical for activation (Buxton et al., 2004; Obrig et al., 1996; Strangman et al., 2002). Especially the PET study of Fox and Raichle (1986) could show that such a pattern of increasing [oxy-Hb] and decreasing [deoxy-Hb] is considered to reflect brain activation.

It is known that the frontal cortex plays a major role in solving a mental arithmetic (MA) task. Previous neuroimaging studies using functional magnetic resonance imaging (fMRI) exploring arithmetic tasks revealed left-sided and/or bilateral activation of the ventrolateral (VLPFC) and dorsolateral (DLPFC) prefrontal cortex (Kawashima et al., 2004; Menon et al., 2000; Rickard et al., 2000) during simple arithmetic operations like one-digit addition, subtraction and multiplication tasks.

Indeed, several NIRS studies have demonstrated the implication of the prefrontal cortex (PFC) during MA (Tanida et al., 2004; Bauernfeind et al., 2008; Hock et al., 1995; Hoshi et al., 1994; Hoshi and Tamura, 1993) but most of them used either only one or two NIRS channels. For example Tanida et al. (2004) investigated the relationship between asymmetry of the prefrontal cortex activity and the automatic nervous system (ANS) response during a mental arithmetic (MA) task. They found increases of [oxy-Hb] and total hemoglobin (=[oxy-Hb]+[deoxy-Hb]) associated with decreases of [deoxy-Hb] in the bilateral PFC. In contrast, Bauernfeind et al. (2008) performed a one-channel NIRS-study on MA tasks resulting in a prefrontal decrease of [oxy-Hb]. These different results might be due to the different type and duration of the MA tasks, the positioning of the optodes and the limited number of channels.

In recent years, NIRS technology was used alternatively to the electroencephalography (EEG) as a sensor technology for a non-invasive Brain-Computer Interface (BCI; Coyle et al., 2007; Sitaram et al., 2007; Luu and Chau, 2009; Bauernfeind et al., 2008; Pfurtscheller et al., in press). In the case of a NIRS-based (optical) BCI the user performs a mental task (e.g. motor imagery, mental calculation, and auditory imagery) and induces herewith hemodynamic changes recordable over the prefrontal or motor cortex areas. The optode placement especially over the prefrontal cortex is useful, because such a NIRS system is more practical and user-friendly and so suitable for application out of the lab. Furthermore online signal detection with an optical BCI could be relatively easier with antagonistic activation patterns, which means Hb responses displaying an opposite polarity (e.g. [oxy-Hb] increase and decrease) at different optode locations. Taken these into account the aim of the present study was to determine whether a simple arithmetic task can elicit focal changes of [oxy-Hb] and [deoxy-Hb] over prefrontal optode locations which can be used for future optical BCI systems.

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2. Material and methods

2.1. Subjects and experimental procedure

The investigations were carried out on a group of ten paid University students (five males and five females, all right-handed) aged 26.1 ± 2.7 years (mean ± SD). The subjects abstained from caffeine before recording, were seated in a comfortable armchair, and gave written informed consent before the experiment. The study was approved by the ethics committee of the Medical University of Graz.

The subjects were asked to serially subtract a one-digit number from a two-digit number (e.g. 97 − 4) as quickly as possible for 12 s. The numbers were presented visually on the monitor at the beginning of each trial. There was a 28 s pause at the end of each trial, so each trial lasted 40 s. During the pause, the subjects were instructed not to move and to stay relaxed by just looking at the black screen. In sum 24 trials were collected. To avoid enhancement of 3rd order blood pressure waves (De Boer et al., 1986) or their sub-harmonics an experimental paradigm with 12 s activity phase and 28 s pause was chosen. It is very important to control this type of waves since they have large magnitudes and can mask task-related changes (Bauernfeind et al., 2008; Coyle et al., 2004; Elwell et al., 1999).

2.2. Data acquisition and processing

A continuous wave system (ETG-4000, Hitachi Medical Co., Japan) was used to record brain oxygenation. The multi-channel system measures the change of [oxy-Hb] and [deoxy-Hb] in the unit of mM mm and consists of 16 photo-detectors and 17 light emitters (3 × 11 grid), resulting in a total of 52 channels. The sampling rate was set to 10 Hz. The distance between source and detector was 3 cm. The lowest line of channels was arranged along the FP1–FP2 line of the international EEG 10–20 system, with channel 48 exactly at the FP1 position (Fig. 1). In order to allow a probabilistic reference to cortical areas underlying the measurement channels and to make the results comparable to results provided by similar fMRI studies (e.g. Kawashima et al., 2004; Menon et al., 2000; Rickard et al., 2000) we used a procedure which projects topographical data based on skull landmarks into a 3D reference frame (MNI-space, Montreal Neurological Institute) optimized for NIRS analysis (Singh et al., 2005). So for each NIRS channel position (Fig. 1), a set of MNI coordinates (*x*, *y*, and *z*) with an error estimated (SD) was calculated. For further details on the corresponding anatomical structures see Okamoto et al. (2004).

After a visual inspection of the raw NIRS data, channels with poor signal quality were marked (in three subjects; two, four and nine channels respectively). Afterwards, a common average reference (CAR) spatial filter was used to remove global influences (e.g. changes in heart rate or respiratory influences). Therefore, for every time point, the mean of all non-marked channels was calculated and subtracted from each channel. For artifact reduction, a 0.09 Hz low pass Butterworth filter of order 4 with 60 dB in the stop band was designed. Additionally, a 0.01 Hz high pass filter was used to remove baseline drifts. For further details, see Bauernfeind et al. (2008). The subject with nine marked channels displayed too many artifacts and was removed from further analysis and a second subject showed no reliable pattern and was also omitted.

2.3. Calculation of task-related changes and topographic distribution

The mean task-related concentration changes of [oxy-Hb] and [deoxy-Hb] referred to a 10 s baseline interval prior to the task (seconds − 10 to 0) were calculated for each non-marked channel. For the marked channels, the changes were calculated by interpolating the surrounding channels.

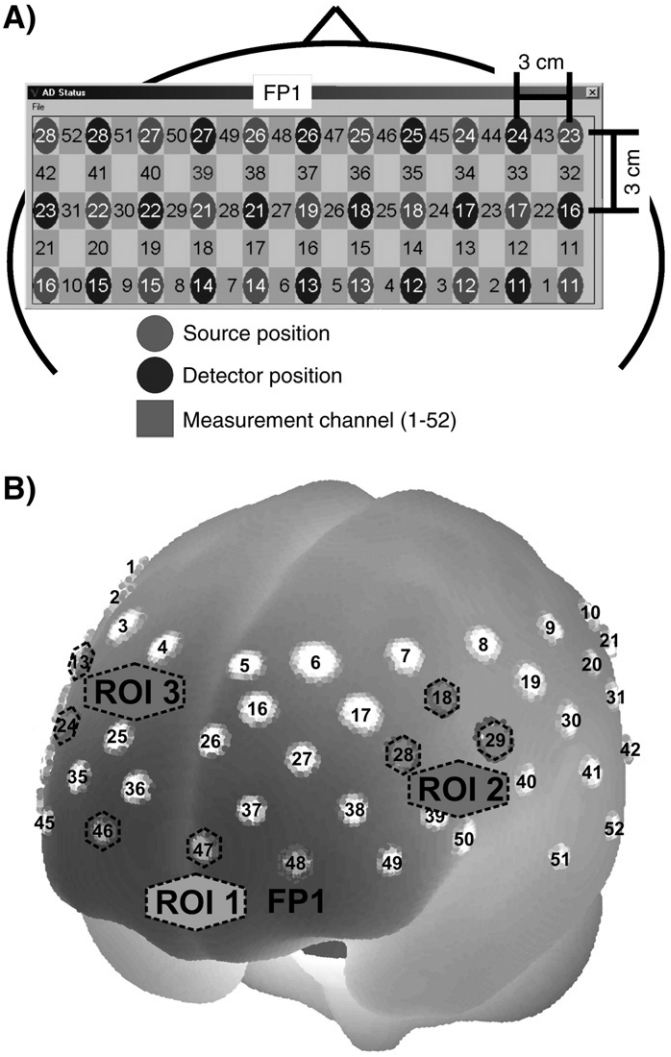

Fig. 1. A) Schematic illustration of the multi-channel array (52 channels, 3 × 11 grid). B) Projections of the NIRS channel positions on the cortical surface. Positions are overlaid on a MNI-152 compatible canonical brain which is optimized for NIRS analysis (Singh et al., 2005). The lowest line of channels was arranged along the FP1–FP2 line of the international EEG 10–20 system, with channel 48 exactly at the FP1 position. The centers of the circle regions represent the locations of the most likely MNI coordinates for the NIRS channel projected on the cortical surface. The edges represent the boundaries defined by the standard deviation.

The topographic distributions during the tasks are further visualized by plotting the [oxy-Hb] and [deoxy-Hb] values at their corresponding spatial position. A 2-D interpolation on a fine Cartesian grid was used to generate a scalp distribution. Two different points in time are illustrated. The first point between 0 and 2 s corresponds to the cue presentation and start of the task; the second point between 10 and 12 s corresponds to the end of the task. [oxy-Hb] and [deoxy-Hb] are visualized in different plots, but use the same scale. Increases are plotted in blue and decreases in red (no activation is plotted in white).

Examples of the hemodynamic responses at all 52 channels are displayed in Figs. 2 and 3.

2.4. Statistical analysis

Two 3 × 5 repeated measures of analyses (ANOVA) on the data were performed separately for [oxy-Hb] and [deoxy-Hb]. The two factors, “regions of interest” (ROI: frontal, left, right), and “time” (baseline, seconds 8–10, seconds 10–12, seconds 12–14, and seconds

14–16), were used as within-subject variables. The MNI coordinates and anatomical locations of the included channels are given in Table 1 and Fig. 1B. Additionally we calculated effect size measures (η^2) to obtain information on how strong the effects are (Cohen, 1988) and checked our data for outliers (Stevens, 2002). No outliers were found.

3. Results

Eight out of ten subjects displayed a relative focal bilateral increase of [oxy-Hb] accompanied by a [deoxy-Hb] decrease in the DLPFC (marked by gray broken line ellipses in the right upper panel of Fig. 2B). In parallel, they showed a decrease of [oxy-Hb], accompanied by a [deoxy-Hb] increase, in most channels overlaying the medial area of the anterior prefrontal cortex (APFC) (Fig. 2B, marked by a black broken line ellipsis).

Fig. 2 presents the grand average hemodynamic responses ([oxy-Hb], [deoxy-Hb]) during the task. The largest and thus most stable [oxy-Hb] decreases in the map are localized at channels 48 (FP1 position) and 37 (~3 cm posterior to FP1). The largest [oxy-Hb] increases can be found on the left hemisphere at channel 28 and on the right hemisphere at channel 24. The peak latency of the hemodynamic responses in the MA task at second 15, and the delay of the onset of the [oxy-Hb] decrease in the order of 2 s, is both clearly visible.

For statistical analysis, the averages of 3 channels of each ROI (ROI1: APFC, channels 46, 47 and 48; ROI2: left DLPFC, channels 18, 28 and 29; ROI3: right DLPFC, channels 13, 23 and 24) were calculated. The results of the 3×5 analysis of variance (ANOVA) revealed the following significant findings: For [oxy-Hb] the main effect of ROI revealed significance ($F(2,14)=27.93$; $p<0.01$; $\eta^2=0.80$). Furthermore the interaction ROI×time showed significance ($F(8,56)=24.37$; $p<0.01$; $\eta^2=0.78$). The Bonferroni posttest showed a significant change of [oxy-Hb] over left and frontal sites for all time periods compared to the baseline (Fig. 2A, lower panels). For [deoxy-Hb] no significant main effect of ROI: ($F(2,14)=2.61$; $p<0.11$; $\eta^2=0.27$) could be found. Although the interaction ROI×time showed significance ($F(8,56)=3.29$; $p<0.01$; $\eta^2=0.32$) the Bonferroni posttest showed no significant changes of [deoxy-Hb] compared to the baseline. Only in the later time

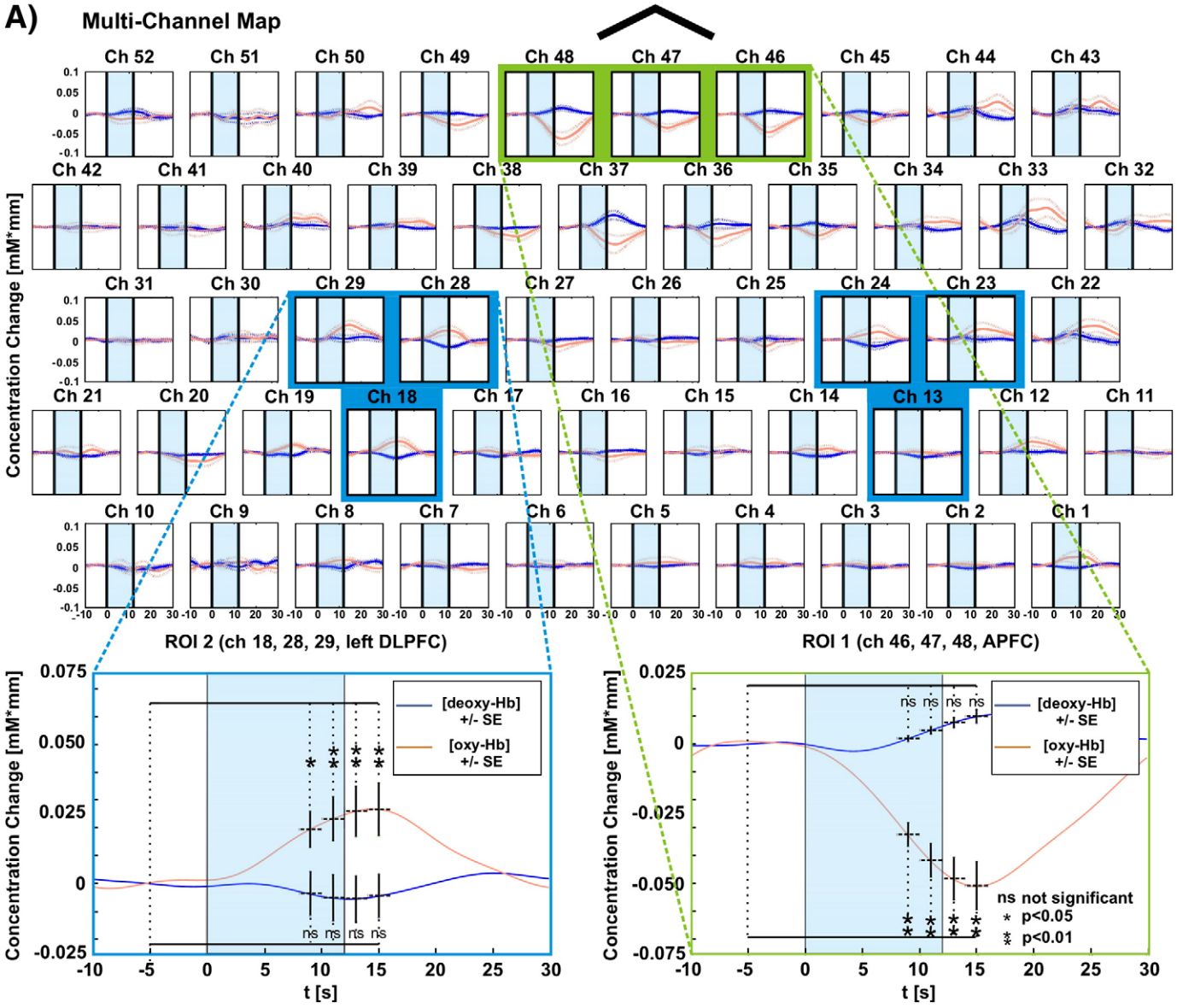

Fig. 2. A) Grand average (8 subjects) concentration changes (mean ± SE) of [oxy-Hb] and [deoxy-Hb] (upper panel) and averaged responses with significant changes for ROI2 and ROI1 (lower panels). B) Topographic distributions during the tasks at two different points in time (seconds 0–2; seconds 10–12). The focal bilateral increase of [oxy-Hb] in the DLPFC in parallel with the decrease of [oxy-Hb] in the medial area of the APFC are marked by gray and black broken line ellipses, respectively.

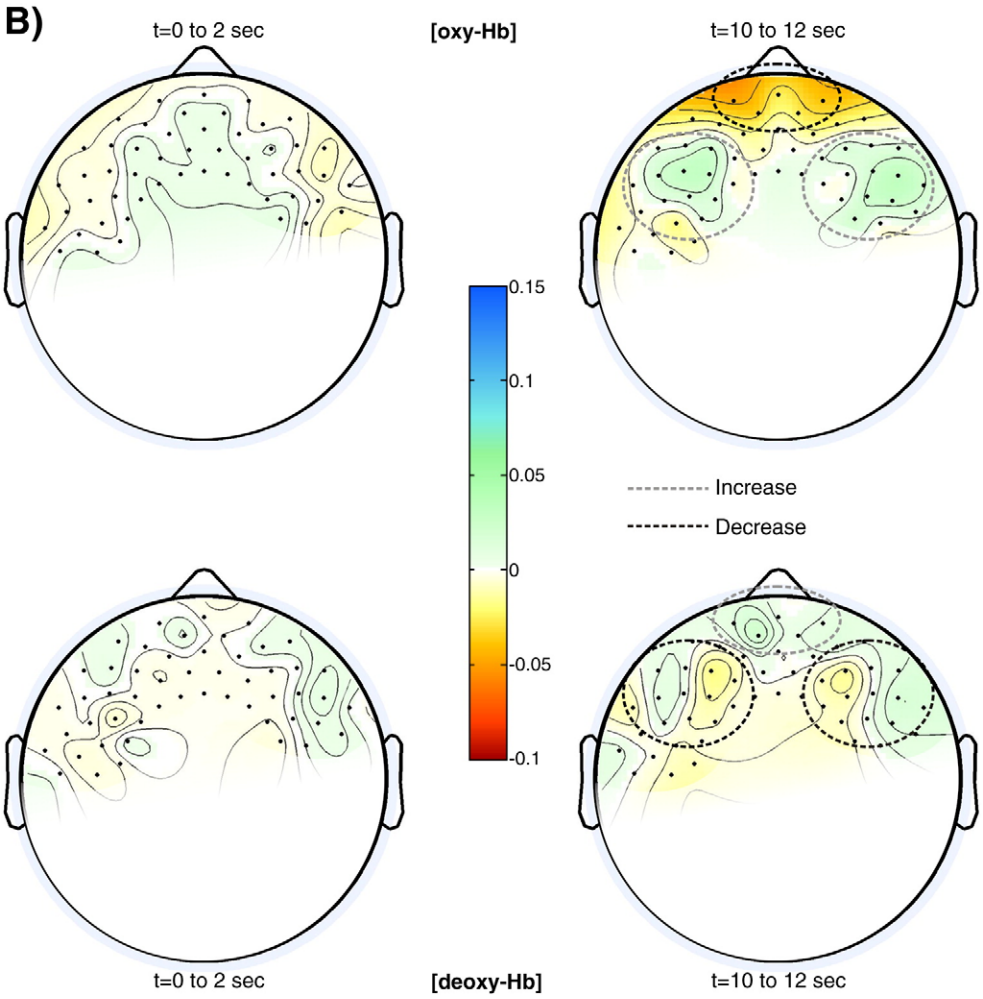

Fig. 2 (*continued*).

periods significant differences between the frontal and the left and right ROI could be found.

Fig. 3 shows the hemodynamic responses for a representative subject. This subject also shows a relative focal bilateral increase of [oxy-Hb] in the DLPFC in parallel with a decrease of [oxy-Hb] in the medial area of the APFC. The largest [oxy-Hb] decrease is localized at channel 37 (~3 cm posterior to FP1, Fig. 3, lower panel left), the largest [oxy-Hb] increases can be found on the right hemisphere at channel 24 (Fig. 3, lower panel right). Note that neighboring channels (channels 27 and 28; channels 24 and 25, marked by broken line ellipses) display significant [oxy-Hb] responses with opposite polarity, which underlines the focal increase/decrease of [oxy-Hb] and [deoxy-Hb] in frontal areas.

4. Discussion

The purpose of the study was to investigate the spatio-temporal patterns of hemodynamic responses during a simple MA task in prefrontal brain regions. We found a relative focal bilateral increase (with a left hemispheric dominance) of [oxy-Hb] accompanied by a [deoxy-Hb] decrease in the DLPFC. In parallel, we found a decrease of [oxy-Hb] accompanied by a [deoxy-Hb] increase in most channels overlaying the medial area of the APFC. While the [oxy-Hb] changes revealed significance in both areas, the [deoxy-Hb] changes were not significant. The reason for the latter could be the small amplitude of the [deoxy-Hb] response. Theories of the hemodynamic response (e.g. Buxton et al., 2004) predict the [oxy-Hb] response to be larger than [deoxy-Hb], usually by a factor of 2 or more. Missing significant [deoxy-Hb] effects might be simply explained by the smaller amplitude of [deoxy-Hb]-responses, even when [deoxy-Hb] is better for localizing functions, and may correspond more closely to the BOLD response (Steinbrink et al., 2006). Therefore, it is not surprising that no significant [deoxy-Hb] responses were observed. For example, Hofmann et al. (2008) recently reported large [oxy-Hb] and small [deoxy-Hb] responses in a visual word recognition task and (Herrmann et al., 2008) large [oxy-Hb] and small [deoxy-Hb] responses during enhanced alertness.

First, the interesting finding of a significant simultaneous [oxy-Hb] increase and [oxy-Hb] decrease in different prefrontal areas during simple MA could be explained in the context of "focal activation/surround deactivation". Antagonistic activation patterns have been already described by brain activation studies using fMRI and EEG. For example Ehrsson et al. (2003) reported, in a foot movement execution and imagination task, a positive BOLD signal in the foot area and a negative BOLD in the hand area with slightly greater magnitude during real movements. This can be interpreted as "focal activation (positive BOLD)/surround deactivation (negative BOLD)". Furthermore Pfurtscheller and Neuper (1994) observed in their EEG study that the event-related desynchronisation (ERD) of alpha band activity does not occur in isolation, but is often accompanied by an increase in synchronization (ERS) in neighboring areas that correspond to the same or other modalities of information processing (Pfurtscheller and

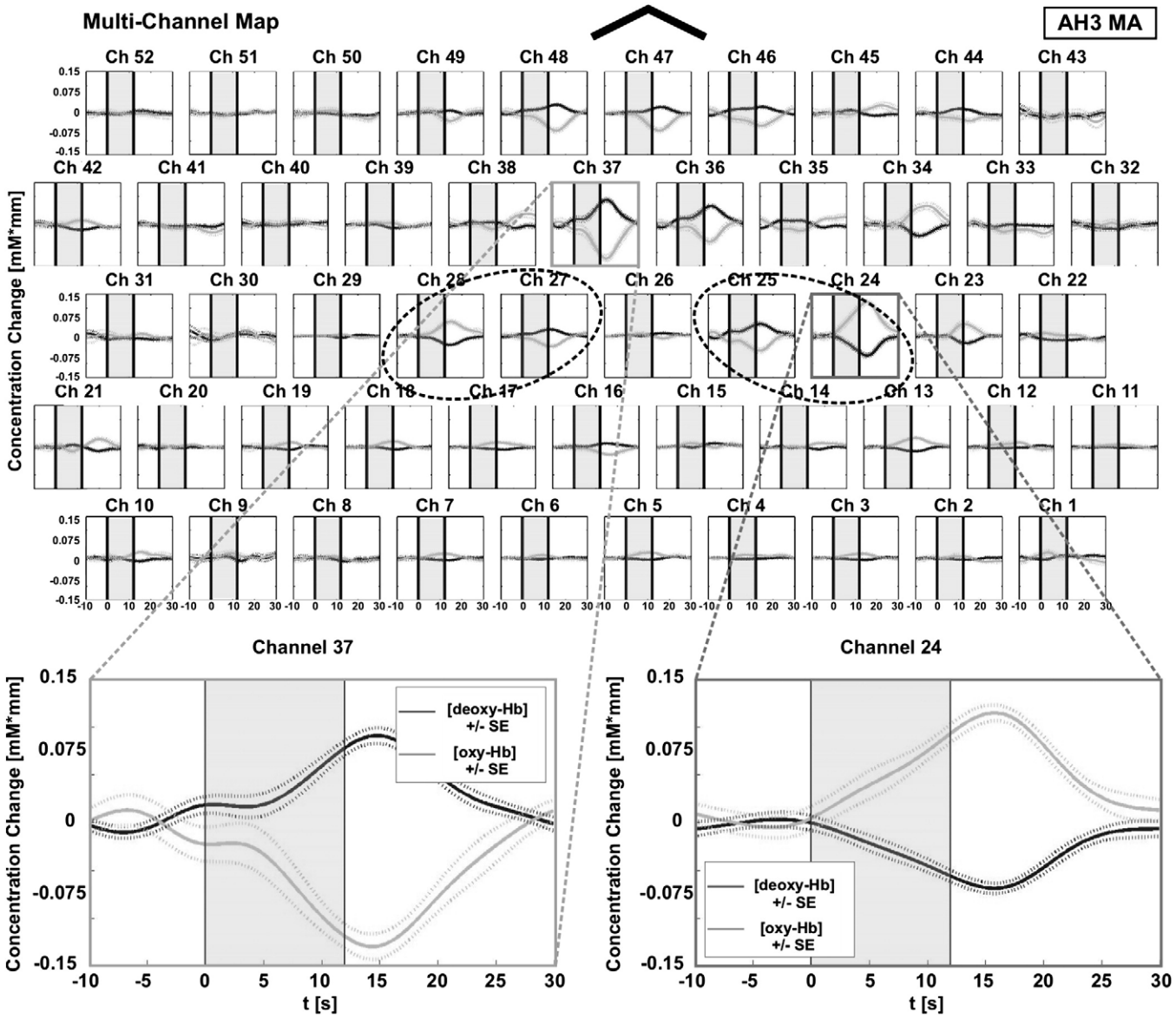

Fig. 3. Mean concentration changes (mean ± SE) during MA of a representative subject (AH3).

da Silva, 1999). This phenomenon was called "focal ERD/surround ERS" (Suffczynski et al., 1999). So, for example, foot movement or foot motor imagery results in a focal ERD at electrodes overlaying the foot representation area and/or the supplementary motor area, and in an ERS at electrodes overlaying the hand representation area.

How can such focal EEG and BOLD changes be interpreted? A study on inhibitory control of learned motor programs by Hummel and colleagues may give an answer (Hummel et al., 2002; Hummel et al., 2004). They found increased motor evoked potentials (MEPs) amplitudes, an amplitude decrease (ERD) of sensorimotor oscillations and a positive BOLD in the hand area during active retrieval of an acquired motor task. For the inhibition condition (the learned movement sequence was not executed) a significant reduction of MEPs together with an amplitude increase (ERS) of central 11–13 Hz oscillations and a negative BOLD was characteristic. Therefore we can conclude that a focal ERD and a positive BOLD characterize an activated neural structure, while an ERS of alpha band rhythms and a negative BOLD may characterize a deactivated or inhibited neural structure. Since recent fMRI–NIRS simultaneous measurements have documented that changes in the hemoglobin concentration are strongly correlated with the fMRI–BOLD signal (Strangman et al., 2002; Steinbrink et al., 2006) the reported antagonistic [oxy-Hb] response could be interpreted as another manifestation of a "focal activation/surround deactivation". While it is widely accepted that increases in [oxy-Hb] are typical for activation (Tanida et al., 2004; Obrig et al., 1996; Strangman et al., 2002) the interpretation of an [oxy-Hb] decrease is not so clear. Shimada et al. (2004) reported a significant decrease in prefrontal [oxy-Hb] during visual feedback of the moving hand in a reaching task and interpreted this decrease in terms of prefrontal "deactivation". Further Hofmann et al. (2008) reported on hemodynamic responses during lexical decisions on words and pseudowords using also a 52-channel Hitachi system. In the lexicality condition they found focal [oxy-Hb] increases in the superior frontal gyrus and left inferior parietal gyrus. Inspection of their corresponding topographic maps (Hofmann et al., 2008; Fig. 1A) gives evidence that optodes placed between these two activated areas show a deactivation ([oxy-Hb] decrease). Similarly results can be found for the second condition (word frequency, Fig. 1B) investigated there. Additionally antagonistic hemodynamic responses were also reported by Franceschini et al. (2003). They investigated the contra- and ipsilateral hemodynamic response of the sensorimotor cortex to unilateral voluntary movements, tactile, and electrical stimulation. For electrical stimulation, but not for voluntary movements and tactile

Table 1
Channel numbers, MNI coordinates, composite standard deviations for the estimation on the cortical surface (SD) and related Brodmann and anatomical areas of each ROI.

ROI	Channel	MNI-space correspondence				Cortical areas	
		x	*y*	*z*	SD	BA	
1 APFC	46	23	72	8	4	10	SFG
	47	−8	73	6	5	10	MeFG
	48	−31	66	3	5	10	MFG
2 Left DLPFC	18	−51	23	41	5	9	MFG
	28	−47	39	28	6	46	MFG
	29	−61	11	28	6	9	IFG
3 Right DLPFC	13	48	31	42	5	9	MFG
	23	57	26	29	5	46	MFG
	24	45	62	29	5	46	MFG

BA, Brodmann area; SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; MeFG, medial frontal gyrus.

stimulation they observed an ipsilateral deactivation pattern in parallel with a contralateral activation pattern. They interpreted the absent deactivation in the ipsilateral side during voluntary movement and tactile stimulation by the insufficient subtraction of systemic changes due to the increase of heart rate. So the deactivation pattern caused by inhibition or decrease in activity of certain brain areas that do not pertain to the attended process may sometimes be canceled out by systemic changes. For that reason it is appropriate to remove these systemic influences by different signal processing approaches (for example using a CAR spatial filter as done in our study) to uncover the deactivation pattern. In addition, assuming that not every cognitive process must necessarily lead to an increase in heart rate and therewith resulting in higher [oxy-Hb] concentration in the brain, an alternative explanation might be the fact that [oxy-Hb] must be drained from one part of the brain (deactivation) to be delivered to another region (activation).

Second, the results reported are in line with fMRI studies that found bilateral activation of the VLPFC and DLPFC and the inferior and superior parietal cortex, primarily in the left hemisphere, during the performance of different arithmetic tasks (Kawashima et al., 2004; Menon et al., 2000; Rickard et al., 2000).

Furthermore spontaneous activity, as measured with fMRI in the resting awake brain, is organized in multiple highly specific functional anatomical networks, named "resting state networks" (RSNs) (Mantini et al., 2007). "Deactivation" in such RSNs may be interpreted as a reallocation of resources from default functions to goal directed functional states (Damoiseaux et al., 2006; Raichle and Snyder, 2007). This RSNs concept could explain the activations of bilateral DLPFC areas and simultaneous deactivation of medial areas of the APFC that we observed, supporting the "focal activation/surround deactivation" concept. This means that similar focal activation patterns can be observed with fMRI and NIRS. Although the study revealed interesting results concerning hemodynamic changes in the prefrontal cortex during MA, some limitations should also be mentioned. First of all, the small sample of subjects. Although we found statistically significant [oxy-Hb] changes in 8 out of 10 subjects, a bigger sample is needed to clarify some individual changes of [oxy-Hb] increase/decrease during MA. It has to be taken into consideration that all optodes were placed over the PFC which is the most elaborated neocortical structure of the human brain and receives and sends commands to many cortical as well as sub cortical structures (for review see e.g. Miller and Cohen, 2001). It has been demonstrated that the PFC is strongly involved in conscious intention (Haggard, 2005) and attentional processes, response selection and response inhibition (Hummel et al., 2004; Koechlin et al., 2003; Rubia et al., 2003). This complex structure of the PFC could be one reason that, in the multi-channel NIRS recordings, the individual channels displayed some variable responses in a few subjects (see Fig. 3).The variability in the hemodynamic patterns may be related to slow (<0.1 Hz) fluctuations of ongoing neuronal activity, as reported recently with fMRI (Logothetis et al., 2009).

In summary, the study demonstrates that significant [oxy-Hb] increases and [oxy-Hb] decreases can be found at optodes placed over the prefrontal cortex even during simple MA. This finding demonstrates for the first time that the phenomenon of "focal activation/surround deactivation" is not only found in EEG and fMRI data but also with multi-channel NIRS. Furthermore, there is evidence that the antagonistic hemodynamic response pattern during MA may be suitable in an optical BCI with good performance, and that only 2 prefrontal NIRS channels may be necessary to realize such BCI system.

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