RESEARCH ARTICLE

Cortical activation patterns to spatially presented pure tone stimuli with different intensities measured by functional near-infrared spectroscopy

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Abstract

Functional near-infrared spectroscopy (fNIRS) is an emerging technique for the assessment of functional activity of the cerebral cortex. Recently fNIRS was also envisaged as a novel neuroimaging approach for measuring the auditory cortex activity in the field of in auditory diagnostics. This study aimed to investigate differences in brain activity related to spatially presented sounds with different intensities in 10 subjects by means of functional near-infrared spectroscopy (fNIRS). We found pronounced cortical activation patterns in the temporal and frontal regions of both hemispheres. In contrast to these activation patterns, we found deactivation patterns in central and parietal regions of both hemispheres. Furthermore our results showed an influence of spatial presentation and intensity of the presented sounds on brain activity in related regions of interest. These findings are in line with previous fMRI studies which also reported systematic changes of activation in temporal and frontal areas with increasing sound intensity. Although clear evidence for contralaterality effects and hemispheric asymmetries were absent in the group data, these effects were partially visible on the single subject level. Concluding, fNIRS is sensitive enough to capture differences in brain responses during the spatial presentation of sounds with different intensities in several cortical regions. Our results may serve as a valuable contribution for further basic research and the future use of fNIRS in the area of central auditory diagnostics.

KEYWORDS

auditory cortex, auditory diagnostics, functional near-infrared spectroscopy, laterality effects, neuroimaging, spatial sound presentation

1 | INTRODUCTION

In cases of severe hearing loss or deafness, hearing can be restored as far as possible using a cochlear implant (CI; for an overview, see Kral & O'Donoghue, 2010; Krueger et al., 2008). The implant replaces the function of the inner ear by stimulating the auditory nerve by means of electrical currents. Generally in the case of CI users, but especially in children, the objective assessment of whether this stimulation reaches the cerebral cortex and triggers the desired auditory sensations is difficult. This is primarily caused by the fact that the use of traditional neuroimaging modalities (for an overview, see Friston, 2009) such as electroencephalography (EEG), magnetoencephalography (MEG),

positron emission tomography (PET), or functional magnetic resonance imaging (fMRI) is restricted. In addition to questions of cost and accessibility (McLane et al., 2015) or the use of ionizing radiation (limited repeatability), these modalities also include contraindications due to electrical artefact's (Gilley et al., 2006; Viola, Thorne, Bleeck, Eyles, & Debener, 2011; Viola et al., 2012) or ferromagnetic components (Teissl, Kremser, Hochmair, & Hochmair-Desoyer, 1998; Teissl, Kremser, Hochmair, & Hochmair-Desoyer, 1999) of the implant. Thus, another reliable method for verification, which is frequently applicable, and bedside usable, is required.

Functional near-infrared spectroscopy (fNIRS; for a review, see Ferrari & Quaresima, 2012) seems to be a very promising approach

in this regard. The fNIRS method is an emerging noninvasive optical technique for the *in vivo* assessment of cerebral oxygenation (changes of oxygenated [oxy-Hb] and deoxygenated hemoglobin [deoxy-Hb] concentration). The measured signals strongly correlate with the fMRI blood-oxygen-level-dependent (BOLD) signal (Steinbrink et al., 2006; Strangman, Culver, Thompson, & Boas, 2002) but compared to fMRI, fNIRS has a limited penetration depth (about 25 mm, Okada et al., 1997). The physiological basis for using fNIRS to measure cortical activity is the interaction between the neuronal (electrical) activity and changes in the cerebral hemodynamic (neurovascular coupling; for details, see Hillman, 2014; Leithner & Royle, 2014; Vanzetta & Grinvald, 2008). These changes are further associated with brain activity (Malonek et al., 1997; Malonek & Grinvald, 1996; Villringer, Planck, Hock, Schleinkofer, & Dirnagl, 1993; Wolf et al., 2002). A decrease in [deoxy-Hb] accompanied by an increase in [oxy-Hb] of two- to threefold magnitude indicates local cortical activation (Malonek & Grinvald, 1996; Obrig & Villringer, 2003; Strangman et al., 2002). In contrast, increases in [deoxy-Hb] accompanied by decreases of [oxy-Hb] indicate a cortical deactivation (Obrig & Villringer, 2003; Raichle et al., 2001; Raichle & Snyder, 2007). Although [deoxy-Hb] responses appear to be more localized and topographically closer to activated areas (Kaiser et al., 2014; Kleinschmidt et al., 1996) than the changes in [oxy-Hb] (Bauernfeind, Wriessnegger, Daly, & Müller-Putz, 2014; Malonek & Grinvald, 1996; Obrig & Villringer, 2003), [deoxy-Hb] changes seem to exhibit lower signal-/contrast-to-noise ratio (Huppert, Hoge, Diamond, Franceschini, & Boas, 2006; Strangman et al., 2002; Ye, Tak, Jang, Jung, & Jang, 2009) and to have less cortical origin than [oxy-Hb] (Gagnon et al., 2012). Both signals are strongly correlated to the fMRI blood-oxygen-level-dependent (BOLD) signal (Steinbrink et al., 2006; Strangman et al., 2002), but with a slightly better correlation of [oxy-Hb] (Strangman et al., 2002); however, this remains controversial (Ye et al., 2009). Finally, the [oxy-Hb] responses seem to show a higher reproducibility (retest) in single-subject analysis and group investigations (Plichta et al., 2007). Beside the hemodynamic response due to local cortical activation, the recorded signals contain influences generated from physiological processes not originating in the central nervous system. Different sources of systemic signals, located in the tissue overlaying the brain (superficial scalp interference) and in the brain tissue itself, can influence the recording. These signals, including quasi-periodic physiological rhythms like heart pulsation, breathing cycles, or low-frequency oscillations of the blood pressure but also task-evoked changes (systemic global influences; for details, see Bauernfeind et al., 2014), can mask the cerebral activation patterns. Therefore, also an effective reduction of these influences is required (Bauernfeind, Böck, Wriessnegger, & Müller-Putz, 2013; Bauernfeind et al., 2014; Boas, Dale, & Franceschini, 2004; Heinzel et al., 2013; Kirilina et al., 2013). In recent years, fNIRS has been used primarily for cognitive, visual, or motor neurosciences (for an overview, see Bauernfeind, 2012; Ferrari & Quaresima, 2012). The application of fNIRS alone or with other measurement methods (multimodal measurement) has recently been proposed as a promising approach in the area of auditory research

and central auditory diagnostics (for a first review, see Saliba, Bortfeld, Levitin, & Oghalai, 2016). Special attention therefore is given to the promising benefits for the possible application in CI users (Saliba et al., 2016).

To date, however, only a few research groups have investigated concepts in studies on the alternative or combined use of fNIRS. The existing literature is limited and focuses mainly on higher level auditory processing or speech and language studies (Saliba et al., 2016). Therefore, further fundamental research on lower level auditory perception (e.g., auditory modulation by sound intensity) is necessary to investigate the future use of fNIRS on CI user (Chen, Sandmann, Thorne, Herrmann, & Debener, 2015), the application of fNIRS in the field of auditory diagnostics (Bauernfeind, Haumann, & Lenarz, 2016), and to exploit the full potential of fNIRS in these areas. This study aims to minimize this lack of information by studying cortical responses to auditory stimuli presented spatially (binaural, monaural right, and left) with different sound intensities. Several studies using different recording techniques (EEG, MEG, PET, fMRI; for an overview, see Supporting Information, Table S1 in Neuner et al., 2014) have found auditory modulation of cortical responses to binaural presented stimuli with different sound intensities in the primary auditory cortex (PAC), but also in other areas apart from the PAC. Different fMRI-studies (for a review see Uppenkamp & Röhl, 2014) have also found a systematic change of activation (an almost linear increase in the BOLD signal) in these areas with increasing sound intensity while the activated region (volume) grows nonlinear (Uppenkamp & Röhl, 2014). However, up to now, no clear evidence thereon was found using fNIRS. There was only one fNIRS study, performed by Chen et al. (2015) which found evidence of a significant modulation of the hemodynamic responses by perceived loudness, but not by sound intensity. Regarding spatially presented monaural sounds different studies using EEG, MEG, PET, or fMRI found stronger contralateral responses (contralaterality effect, for an overview see Woldorff et al., 1999). Further, for binaural stimulation (partially stronger; binaural summation, Loveless, Vasama, Mäkelä, & Hari, 1994), neural responses were found in both hemispheres. To the best of our knowledge, there was as yet no fNIRS study also investigating these findings in detail. This article will address the following scientific questions:

- Is fNIRS sensitive enough to capture the brain responses in different cortical regions which are involved in these sound processing?
- Is it possible to find differences in the brain responses to stimuli with different sound intensity?
- Is it possible to find differences in the brain responses to spatially presented sound stimuli?

We hypothesized that the fNIRS signals, such as the fMRI BOLD responses, would reflect higher sound intensities by stronger hemodynamic responses in temporal regions responsible for auditory processing. Furthermore, we hypothesized that monaural presented stimuli will induce contralaterality effects (larger hemodynamic responses in temporal regions contralateral to the stimulated ear) and binaural stimulus presentation will result in bilateral cortical activation patterns.

2 | MATERIALS AND METHODS

2.1 | Subjects and experimental procedure

Ten adult hearing subjects (six males and 4 females) aged 29.5 ± 9.1 years (mean $\pm$ SD) took part in the experiment. All participants were right-handed, with normal or corrected-to-normal vision, and with normal hearing ability (hearing level ≤ 20 dB) measured at 500, 1000, and 2000 Hz in each ear. No significant difference in the hearing level at each frequency between left (0.5 kHz: 11.0 ± 5.8 dB; 1 kHz: 7.0 ± 4.0 dB; 2 kHz: 6 ± 6.2 dB) and right ear (0.5 kHz: 8.0 ± 5.6 dB; 1 kHz: 6.5 ± 5.0 dB; 2 kHz: 5.5 ± 7.2 dB) were found. Furthermore, the interaural difference at stimulus frequency (1 kHz, details see below) was ≤ 10 dB for each participant, with a group mean of 4.5 ± 3.5 dB. All participants gave informed written consent to the study. The study was approved by the local ethics committee (Hannover Medical School) and is in accordance with the ethical standards of the Declaration of Helsinki. The participants were not paid for their participation.

The subjects performed a passive listening task consisting of six different auditory stimuli (1 kHz sine wave, amplitude modulated by 4 and 10 Hz sine waves; sampled at 44.1 kHz; modified from Chen et al., 2015). Stimuli were presented spatially (binaural "Bin" & monaural left "MonL" and right "MonR") via earphones with two different intensities ("HIGH-" and "LOW-"; Supporting Information, Figure S1). As monaural stimuli will be perceived less loud (~ 8 dB, depending on the sound pressure level (SPL); Fastl, 2007) loudness adjustment was performed according to the work of Whilby, Florentine, Wagner, and Marozeau (2006). Based on an SPL of 40 dB for low intensity and 70 dB for high intensity for the binaural condition, we adjusted the intensities for the monaural conditions to 48 and 79 dB, respectively.

For each subject 2 (intensity: "HIGH-", "LOW-") $\times$ 3 (Spatial: "Bin", "MonL", "MonR") $\times$ 10 trials plus 10 additional trials without stimulation ("Silence") were recorded in a random order (total 70 trials). The trials were recorded in 5 runs (14 trials per run with each stimuli type appearing twice). Each trial consisted of an auditory stimulus presented for 10 s ("Silence": no stimulus within this time) followed by a fixed pause of 20 s taking into account the time needed for the hemodynamic response to return back to baseline (Malonek & Grinvald, 1996). In addition, an intertrial interval randomly varying in duration from 0 to 5 s was included to reduce temporal adjustment of the subjects to the paradigm. The whole recording lasted around 45 min including breaks of about 1 min between the runs. During the experiment, the subjects were placed comfortably in a semi-supine position (about 30° – 50° elevation of head). No attempt was made to control the subjects thought content. Subjects were instructed to carefully listening to the presented sounds and avoiding head movements during the measurement. They were told to restrict movements like swallowing to the pause and intertrial interval.

2.2 | Data acquisition and processing

For fNIRS recording, a multichannel system (ImagentTM, ISS Inc., Champaign, USA; Figure 1a) was used to measure and calculate the change

of [oxy-Hb] and [deoxy-Hb] in the unit of mMmm (Ferrari & Quaresima, 2012) with a sampling frequency of 8 Hz, using a modification of the Beer–Lambert law approach. The multichannel system comprises 12 photomultiplier tube based detectors and 16 sources (two wavelengths each source, 690 nm and 830 nm, combined in one emitter) coupled to optical fibers (Figure 1b,c). Sources and detectors were arranged over both hemispheres (8 sources and 6 detectors per hemisphere) resulting in a total of 38 channels (Figure 1d). The distance between sources and detectors was 3 cm. Sources and detectors were mounted in a custom made cap (Figure 1e) arranged above the temporal cortex regions of both hemispheres and adjusted to the electrode positions T7 (Ch. 9) and T8 (Ch. 28, see Figure 1d) according to the international EEG 10–20 system (Homan, Herman, & Purdy, 1987). Due to the characteristics of the recording method (requires the same fixed distance of each emitter and detector of a specific recording channel), the underlying cortical areas might differ between subjects. To allow a probabilistic reference to cortical areas underlying the channels and enable subject comparison a procedure (Singh, Okamoto, Dan, Jurcak, & Dan, 2005) which projects topographical data based on skull landmarks into a 3D reference frame (MNI-space, Montreal Neurological Institute) was used. For each fNIRS channel position (Figure 1d), a set of MNI coordinates (x, y, and z) was calculated together with an error estimate (SD). The centers of the circle regions represent the locations of the most likely MNI coordinates for the fNIRS channel projected on the cortical surface. The edges represent the boundaries defined by the standard deviation (Figure 1f).

For the subsequent processing steps and analysis, only the [oxy-Hb] data were used. [oxy-Hb] was chosen as this parameter has a slightly higher correlation with the fMRI-BOLD response than [deoxy-Hb] (Strangman et al., 2002). Furthermore, [oxy-Hb] is a more suitable and robust parameter to investigate cortical activity (Gagnon et al., 2012; Huppert et al., 2006; Issa, Bisconti, Kovelman, Kileny, & Basura, 2016; Plichta et al., 2007; Strangman et al., 2002; Ye et al., 2009; for details, see Introduction) especially after the reduction of physiological noise influences (Bauernfeind et al., 2013, 2014). In summary, the choice of [oxy-Hb] thus allows a robust investigation and comparability of our results with previous fMRI studies (due to the lack of relevant fNIRS literature). After a visual inspection of the raw fNIRS data by an expert, channels with poor signal quality (measurement noise) were removed. Additionally, trials containing motion artifacts were excluded for calculating task-related changes and topographic distributions. A common average reference (CAR) spatial filtering approach (Bauernfeind et al., 2013, 2014) was used to reduce global influences from the [oxy-Hb] signals. The idea behind the application of CAR is the fact that the global interfering signals influence all channels and hence can be reduced by calculating the mean of all channels and subtracting it from each single channel and for each time point. A further benefit of the CAR method is its suitability not only to reduce quasi-periodic influences but also task-evoked physiological noise (for details, see Bauernfeind et al., 2014). For further artifact reduction (cardiac pulsation and respiration, for a review, see Scholkmann et al., 2014), a 0.08 Hz low-pass Butterworth filter of order 3 was used. Additionally, a 0.015 Hz high-pass Butterworth filter of order 5 was used to remove

FIGURE 1 (a) Picture of the fNIRS recording system Imagent™ (ISS Inc., Champaign, USA). (b) Plastic (detector) and (c) metal ferrule (source) based fibers with corresponding probe holder (ISS Inc., EASYCAP GmbH). (d) Schematic illustration of the bilateral 38-channel array. (e) Array mounted on a custom made cap (EASYCAP GmbH). (f) Projections of the sources (squares), detectors (circles), and fNIRS channel positions (white areas) on the cortical surface. Positions are overlaid on an MNI-152-compatible canonical brain (Singh et al., 2005)

baseline drifts (Bauernfeind, Leeb, Wriessnegger, & Pfurtscheller, 2008; Chen et al., 2015).

2.3 | Calculation of task-related changes and topographic distribution

Mean task-related changes of [oxy-Hb] referred to a 5 s baseline interval prior to the task (seconds -5 to 0) were averaged for each channel. Channels with poor signal quality were substituted by interpolation (mean of the surrounding channels; for details, see Bauernfeind et al., 2014; Kaiser et al., 2014). Such an interpolation of channels can be seen as a spatial smoothing of the hemodynamic pattern (Wriessnegger et al., 2012) and parts of the missing information will be preserved. Such a procedure is clearly preferable over the total loss of information which would occur by excluding bad channels. The topographic distributions during the tasks are further visualized by plotting the values at their corresponding spatial positions (for details, see Pfurtscheller, Bauernfeind, Wriessnegger, & Neuper, 2010).

Afterward, the averages of 5 regions of interest (ROI; Supporting Information, Figure S2), covering temporal, frontal, central, and parietal areas of both hemispheres were computed by using the MNI coordinates of the fNIRS channel projections. ROI1 was defined by channels overlaying detectable (the primary auditory cortex is unfortunately not detectable due to limited penetration depth; Okada et al., 1997) superolateral regions of the temporal lobe

(Moerel, Martino, & Formisano, 2014), comprising secondary and tertiary auditory areas (Brodmann areas (BA) 21, 22, and 42). ROI2 was defined as a sub region of ROI1 comprising channels overlaying only caudal (posterior) parts of BA 22 and lateral parts of BA 42 which are detectable by fNIRS. On the dominant cerebral hemisphere, this subregion includes Wernicke's area which is involved in the comprehension or understanding of written and spoken language (Démonet et al., 2002). On the nondominant hemisphere, this area is known to play a fundamental role in nonverbal sound processing. ROI3 comprises channels overlaying orbital, triangular, and opercula parts of the inferior frontal gyrus (IFG) comprising BA 44 (pars opercularis), BA 45 (pars triangularis), and BA 47 (pars orbitalis). On the left hemisphere, this region includes Broca's area (represented as areas BA 44 and 45), which plays an essential role in various speech and language functions (Fazio et al., 2009), like speech production. ROI4 includes channels overlaying lateral parts of the premotor (BA 6), primary motor (BA4), and primary somatosensory cortex (BA 1, 2, and 3). Finally, ROI5 consists of channels overlaying the inferior parietal lobule comprising angular gyrus (BA 39) and supramarginal gyrus (SMG, BA 40). This region seems to be involved in a variety of tasks like semantic processing, word reading and comprehension, number processing, default mode network, memory retrieval, and attention and spatial cognition (Seghier, 2013). The calculated MNI coordinates of the ROI-midpoints, based on all subjects, are presented in Table 1.

TABLE 1 MNI coordinates and related Brodmann and anatomical areas of the ROI midpoints (based on 10 subjects)

Hem.	ROI	MNI-space			Cortical areas	
		x	y	z	BA	
Left	1	-67	-21	-4	21	MTG
	2	-67	-32	9	42	STG
	3	-57	25	6	45	IFG
	4	-63	-12	37	4	PrG
	5	-66	-40	35	40	IPL
Right	1	68	-21	-1	22	STG
	2	70	-31	10	22	STG
	3	60	25	9	45	IFG
	4	65	-14	40	4	PrG
	5	66	-41	37	40	IPL

Abbreviations: BA = Brodmann's area; IFG = inferior frontal gyrus; MTG = middle temporal gyrus; PrG = precentral gyrus; STG = superior temporal gyrus; SMG = supramarginal gyrus. Subject-specific ROI information can be found in Supporting Information, Tables S1 and S2.

2.4 | Statistical analysis

For statistical analyses (IBM SPSS V.23), we calculated a $5 \times 2 \times 2 \times 3$ repeated measure analysis of variance (ANOVA). The within-subject factors involved the ROIs (ROI1–ROI5), the hemispheres (left, right), the intensity of the auditory cues ("HIGH-", "LOW-") and their spatial presentation (binaural "Bin" & monaural left "MonL" and right "MonR").

We further investigated the effects of the experimental conditions for each hemisphere separately by calculating two $5 \times 2 \times 3$ ANOVA for repeated measurements on the mean [oxy-Hb] changes. To further investigate possible laterality effects, we additionally calculated a 2 (hemisphere) $\times 2$ (intensity) $\times 3$ (spatial) ANOVA for repeated measurements on mean [oxy-Hb] changes for each of the 5 ROIs separately. All statistical analysis were performed on [oxy-Hb] values during a time window of seconds 10–12, which corresponds to the end of the task. For post hoc analysis, we performed paired sampled *t* tests.

Whenever the sphericity assumption was violated, Greenhouse–Geisser corrected values were used for further analysis. The alpha value for significance was set to 0.05 and the Bonferroni correction was applied to eliminate the problem of multiple comparisons.

3 | RESULTS

The results of the repeated four-way measure ANOVA with the factors ROI (1–5), hemisphere (left, right), intensity ("HIGH-", "LOW-"), and spatial presentation (binaural "Bin" & monaural left "MonL" and right "MonR") revealed a significant main effect of ROI ($F_{(4;36)} = 3.219$; $p = .023$) for the [oxy-Hb] concentration changes. Furthermore, a significant ROI $\times$ intensity interaction ($F_{(4;36)} = 3.81$; $p = .011$) was found.

The results of the two repeated three-way measure ANOVAs (ROI $\times$ intensity $\times$ spatial), for each hemisphere separately, on the mean [oxy-Hb] changes are presented in the next sections.

3.1 | Left hemisphere

The $5 \times 2 \times 3$ ANOVA on [oxy-Hb] values revealed a significant main effect on the factor ROI ($F_{(4;36)} = 2.66$; $p = .048$) and a significant ROI $\times$ intensity interaction effect ($F_{(4;36)} = 2.99$; $p = .034$). Follow-up paired-samples *t* tests indicated significant differences only in ROI1 ($t_{(9)} = 2.643$; $p = .027$) and ROI5 ($t_{(9)} = -3.48$; $p = .007$) for the pair "HIGH-MonR" – "LOW-MonR." This indicates that sounds with higher intensity reveal a significant stronger activation (a higher [oxy-Hb] level) in ROI1 and a significant stronger deactivation (a lower [oxy-Hb] level) in ROI5 compared to sounds with lower intensity.

3.2 | Right hemisphere

Also in the right hemisphere, a significant main effect for ROI ($F_{(4;36)} = 3.23$; $p = .023$) and a significant interaction ROI $\times$ intensity ($F_{(4;36)} = 4.31$; $p = .06$) was found for [oxy-Hb] concentration changes. We performed several paired-samples *t* tests to compare [oxy-Hb] concentration changes between the different intensities and spatial representation conditions. The results showed significant differences only for ROI3 and ROI4 for the monaural spatial presentation. We found significant differences in ROI 4 between "HIGH-MonL" and "LOW-MonL" ($t_{(9)} = -2.27$; $p = .049$) indicating a stronger deactivation for the "HIGH-" condition. For "HIGH-MonR" compared to "LOW-MonR," significant differences were found in ROI 3 ($t_{(9)} = 3.701$; $p = .005$) and ROI4 ($t_{(9)} = -3.482$; $p = .007$). This indicates that right side presented sounds with higher intensity reveal a significant stronger activation (a higher [oxy-Hb] level) in ROI3 and a significant stronger deactivation (a lower [oxy-Hb] level) in ROI4 compared to sounds with lower intensity.

3.3 | ROIs

The $2 \times 2 \times 3$ ANOVAs on [oxy-Hb] values, for each ROI separately, revealed a significant main effect on the factor intensity: $F_{(1;9)} = 6.55$; $p = .031$ and a significant hemisphere $\times$ spatial interaction effect ($F_{(2;18)} = 4.42$; $p = .027$) only for ROI4. Follow-up paired-samples *t* tests indicated significant differences between the hemispheres only for condition "LOW-MonR" ($t_{(9)} = -3.161$; $p = .012$) in ROI4. This indicates a significant stronger deactivation (a lower [oxy-Hb] level) in the left hemisphere.

Comparing the [oxy-Hb] responses between monaural left "MonL" and right "MonR" stimulus presentation for both intensities revealed only significant differences for the "LOW-" condition. In more detail, we found significant differences between monaural right low and monaural left low in ROI1 ($t_{(9)} = 2.408$; $p = .039$; left hemisphere) and ROI4 ($t_{(9)} = -3.884$; $p = .004$; right hemisphere). This indicates a higher [oxy-Hb] level (stronger activation) in ROI1 for condition "LOW-MonL" compared to "LOW-MonR" in the left hemisphere and a lower oxygenation level (stronger deactivation) in ROI4 for "LOW-MonL" compared to "LOW-MonR" in the right hemisphere.

FIGURE 2 Group-specific ($N = 10$) multichannel ROI map illustrating the mean [oxy-Hb] patterns of “MonR” (Red), “Bin” (Black), and “MonL” (Magenta) for “HIGH-” (solid) and “LOW-” (dashed) stimulus intensity during stimulus presentation (seconds 0–10) and half of the pause interval (seconds 10–20). Further significant differences in the average concentration changes are indicated by arrows

For better visualization, see Figure 2, which depicts all these findings for both hemispheres. The figure shows the ROI-related hemodynamic [oxy-Hb] responses over all 10 subjects for the presented binaural “Bin” (black) and monaural left “MonL” (magenta) and right “MonR” (red) sounds with “HIGH-” (solid line) and “LOW-” (dashed line) intensities. Furthermore, Table 2 shows the calculated [oxy-Hb] values in the window of seconds 10–12 for all ROIs and conditions. Cortical activations (increase in [oxy-Hb]) were found in the “HIGH-” conditions in ROI1, ROI2, and ROI3 of both hemispheres in nearly all conditions (with two exceptions, both in ROI2). On the left hemisphere, we found a decrease in [oxy-Hb] during the “MonR” stimulus presentation and on the right hemisphere during the “Bin” presentation. Clear deactivation patterns (decrease in [oxy-Hb]) were found in ROIs 4 and 5 of both hemispheres during all conditions. In contrast to the “HIGH-” conditions for the “LOW-” conditions, the picture of cortical activation/deactivation is less clear and more divergent (for details, see Table 2).

As the group analysis revealed fewer significant differences between the different tasks as expected, further investigations at the level of individual subjects (Supporting Information, Table S3) were performed. In the first step, investigations of differences on the single

channel level for “HIGH-” versus “LOW-” binaural (“Bin”), monaural left (“MonL”), and right (“MonR”) stimulus presentation were conducted. Comparing both intensities, significant differences ($p < .05$, t test) in the channel-related [oxy-Hb] responses were found in all subjects in at least two presentation types. In more details for “HIGH-Bin” versus “LOW-Bin,” 7 out of 10 subjects (70%) exhibited significant differences. Also 70% of the subjects showed significant differences for “HIGH-MonL” versus “LOW-MonL” stimulus presentation. Corresponding to the group-related results, the most subjects (90%) exhibited significant differences for “HIGH-MonR” versus “LOW-MonR” on the single channel level. As an example, Figure 3 depicts the cortical responses of a subject (S2) with pronounced patterns for “Bin,” “MonL,” and “MonR” in the “HIGH-” conditions. Comparing both intensities (“HIGH-” minus “LOW-” contrast), this subject displays in all conditions bilateral, but slightly more left lateralized [oxy-Hb] contrast increases in channels mainly overlaying ROI1, ROI2, and ROI3. In parallel, decreases in the [oxy-Hb] contrast are mainly localized to channels overlaying ROI4 and ROI5.

In a further step, ROI-related investigations were performed on the single subject level. Also at the ROI level, 7 out of the 10 subjects

TABLE 2 Calculated (in mMmm) [oxy-Hb] group values (mean $\pm$ SD) between seconds 10 and 12, which corresponds to the end of the task, for all ROIs and conditions

Hem.	ROI	[oxy-Hb] mean $\pm$ SD											
		HIGH						LOW					
		MonR		Bin		MonL		MonR		Bin		MonL	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
LH	1	0.0082	0.0130	0.0052	0.0118	0.0079	0.0108	<i>-0.0025</i>	0.0056	0.0007	0.0118	0.0059	0.0075
	2	<i>-0.0031</i>	0.0129	0.0006	0.0101	0.0034	0.0090	0.0038	0.0083	0.0037	0.0133	<i>-0.0011</i>	0.0119
	3	0.0037	0.0177	0.0024	0.0205	0.0132	0.0210	<i>-0.0025</i>	0.0139	0.0022	0.0139	0.0034	0.0134
	4	<i>-0.0072</i>	0.0122	<i>-0.0035</i>	0.0145	<i>-0.0098</i>	0.0115	<i>-0.0015</i>	0.0064	<i>-0.0022</i>	0.0056	<i>-0.0062</i>	0.0060
	5	<i>-0.0167</i>	0.0203	<i>-0.0084</i>	0.0182	<i>-0.0088</i>	0.0219	0.0011	0.0110	0.0023	0.0171	<i>-0.0047</i>	0.0144
RH	1	0.0059	0.0152	0.0020	0.0064	0.0053	0.0141	0.0022	0.0069	0.0000	0.0066	0.0017	0.0062
	2	0.0000	0.0150	<i>-0.0010</i>	0.0090	0.0033	0.0135	0.0048	0.0091	<i>-0.0020</i>	0.0070	<i>-0.0002</i>	0.0084
	3	0.0112	0.0125	0.0099	0.0172	0.0108	0.0167	<i>-0.0010</i>	0.0130	0.0000	0.0153	0.0066	0.0113
	4	<i>-0.0078</i>	0.0143	<i>-0.0083</i>	0.0102	<i>-0.0163</i>	0.0150	0.0049	0.0079	<i>-0.0082</i>	0.0184	<i>-0.0066</i>	0.0084
	5	<i>-0.0081</i>	0.0176	<i>-0.0050</i>	0.0156	<i>-0.0077</i>	0.0173	0.0037	0.0146	<i>-0.0043</i>	0.0249	<i>-0.0038</i>	0.0129

Deactivations (decrease in [oxy-Hb]) are indicated in *italic*; the strongest patterns (increases and decreases) are further indicated in bold.

FIGURE 3 Topographic distributions (including ROI-related color-coded channel positions) of [oxy-Hb] patterns for a subject (S2) with pronounced patterns for "Bin," "MonL," and "MonR" in the "HIGH-" condition. [oxy-Hb] patterns during the task at one point in time (between 10 and 12 s, corresponds to the end of the task) are visualized in different plots, but use the same scale. Increases are plotted in red and decreases in blue (no changes are plotted in white). Further calculated [oxy-Hb] contrasts for "HIGH-" versus "LOW-" are shown. Channels with significant differences in the contrast are indicated by a dotted black line. For better comparability to fMRI studies, also the corresponding t maps are shown

show significant ($p < .05$) differences in at least one of the ROIs for one or more of the three “HIGH-” versus “LOW-” conditions. The remaining subjects exhibited in at least a trend ($p < .1$) in one of the ROIs. As an example, Figure 4 shows the ROI-related hemodynamic responses for the above presented subject (S2).

Further investigations in monaural stimulus presentation (contralaterality effect and hemispheric asymmetries) were performed for the “HIGH-” conditions. Comparison of “HIGH-MonL” versus “HIGH-MonR” stimulus presentation revealed significant differences in eight subjects on the single channel level. However, on the ROI level, these differences were found in only three subjects, two additional subjects exhibited a trend (for details see Supporting Information, Table S4). For a better visualization, Figure 5 shows the hemodynamic responses for a subject (S1) with significant differences between “HIGH-MonL” and “HIGH-MonR” and a subject (S2) with pronounced but similar [oxy-Hb] patterns for those tasks. Investigations concerning contralaterality effects were only performed on the ROI level (right versus left hemisphere) as no direct comparison on the single channel level between left and right hemisphere is possible. Significant laterality effects (Supporting Information, Table S4) were found in 6 out of the 10 subjects in at least one of the ROIs (stronger activations in ROIs 1–3; stronger deactivations in ROIs 4 and 5). Unfortunately, the results did not show a uniform picture for the significant, as well as nonsignificant effects. So for example in ROI1, only two subjects showed contralaterality effects for both presentation sides, whereas the remaining subjects showed contralaterality either for “HIGH-MonL” (three subjects) or “HIGH-MonR” (five subjects). Thus in total, in 12 out of 20 cases, contralaterality effects were found. A similar picture (for details, see Supporting Information, Table S4) can be found also in ROI2 (11 cases), ROI4 (11 cases), and ROI5 (13 cases). Only in ROI3 in the majority of cases (12), stronger ipsilateral activation patterns were found.

4 | DISCUSSION

The aim of this study was to investigate differences in brain activity related to spatially presented sounds with different intensities in 10 subjects by means of fNIRS. We expected stronger hemodynamic responses for higher sound intensities in regions responsible for auditory processing. We further expected that monaural presented stimuli will induce contralaterality effects (larger hemodynamic responses in auditory regions contralateral to the stimulated ear) and binaural stimulus presentation will result in comparable strong bilateral cortical activation patterns. We found significantly different activation patterns related to the different conditions and ROIs (Figure 2 and Table 2), but not as clear as initially expected, which might be due to differences in the attentional process (Sigalovsky & Melcher, 2006). It is known that prompting attention to a specific sound increases the activation induced by that sound (Grady et al., 1997; Jäncke, Mirzazade, & Shah, 1999). In our study, the subjects were only instructed to “passively attend” the presented stimuli. For example, some subjects may have paid more attention to the stimuli with the highest intensity which increases the differences in cortical activity between low and high

conditions. On the other hand, some subjects might have paid stronger attention to the stimulus with low intensity. In that case, the difference in activity between low and high condition is decreased. Furthermore, the same could also be possible for binaural or monaural stimulation. Thus, an influence of selective attention between the different conditions in our study cannot be excluded.

As expected, we found increases in [oxy-Hb] on the group level for all “HIGH-” conditions in the temporal region (ROI1) of both hemispheres (primary, secondary, and tertiary auditory areas) which are well known to be sensitive to sound in general (Uppenkamp & Röhl, 2014). In addition, we also found activation patterns in frontal areas. In more detail, this activation was related to ROI3 overlaying orbital, triangular, and opercula parts of the IFG (BA 44, 45, and 47) of both hemispheres. Similar bilateral frontal activation patterns with high stimulus intensity were also found in several fMRI studies (Bilecen, Seifritz, Scheffler, Henning, & Schulte, 2002; Jäncke, Shah, Posse, Grosse-Ryken, & Müller-Gärtner, 1998; Neuner et al., 2014). It was speculated that a network, formed by the superior temporal gyrus (STG) and the IFG, which is also specifically associated with the retrieval and rehearsal of auditory information (Jäncke et al., 1998), plays thereon an important role. Contrarily, we found strong decreases in [oxy-Hb] in central (ROI4, overlaying parts of BA 6, 4, 3, 2, and 1) and parietal (ROI5, comprising BA 39 and 40) regions of both hemispheres. Such decreases might reflect a noninvolvement or deactivation (Raichle et al., 2001; Raichle & Snyder, 2007) of a particular cortical region. Especially, deactivation in the inferior parietal cortex is consistent across different tasks (Shehzad et al., 2009; Seghier, 2013) in general. This can be explained by the so called “default network” (Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001; Raichle & Snyder, 2007), a set of brain regions which deactivates during the performance of a given task compared to rest or baseline activity (Seghier, 2013). This “default network” is one of the most consistent resting-state networks (Smith et al., 2009).

From numerous fMRI studies (for a review, see Uppenkamp & Röhl, 2014), it is known that large portions of the auditory cortex (covering primary but also secondary and tertiary auditory regions) show systematic (e.g., linear relationship between BOLD signal and stimulus intensity) changes of activation with sound intensity. By comparing “HIGH-” and “LOW-” conditions in our study, we also found such differences. In more detail, we found significant differences for monaural (“MonL” & “MonR”) stimulus presentation in both hemispheres and different ROIs. For the left hemisphere, these differences occurred only for “MonR” stimulus presentation represented by a stronger activation in ROI1 and a stronger deactivation in ROI5 in the higher intensity condition. In the right hemisphere, these differences occurred beside “MonR” (stronger activation in ROI3 and stronger deactivation in ROI4) also for “MonL” stimulus presentation (stronger deactivation in ROI4). These results were also confirmed by the single-subject analysis were 90% of the subjects depicted significant differences on the single channel level for “MonR” but only 70% for “Bin” and “MonL.”

Concerning contralaterality effects, there exists evidence from different studies using varying neuroimaging modalities that monaurally presented stimuli will induce higher cortical activation patterns in

FIGURE 4 ROI-related hemodynamic responses for subject S2. ROI maps illustrate [oxy-Hb] patterns of “MonR” (red), “Bin” (black), and “MonL” (magenta) for “HIGH-” (solid) and “LOW-” (dashed) stimulus intensity during stimulus presentation (seconds 0–10) and half of the pause interval (seconds 10–20). Calculated [oxy-Hb] contrasts are shown in Green. Further significant differences and trends in the concentration changes are indicated by arrows and with asterisk (*) or via a superscript t (†), respectively

auditory areas contralateral to the stimulus presentation side (for an overview, see Woldorff et al., 1999). This effect might be explained by the anatomical organization of the auditory pathways. In our study, we

expected that monaural presented stimuli will also induce contralateral-ity effects (stronger hemodynamic responses in auditory regions contralateral to the stimulated ear) and that the loudness matched binaural

FIGURE 5 Topographic distributions and corresponding t maps (between 10 and 12 s) including ROI-related color-coded channel positions. Also ROI-related [oxy-Hb] patterns (during stimulus presentation and half of the pause interval) for “HIGH-MonL” (magenta) and “HIGH-MonR” (red) for two subjects (S1 and S2). Furthermore, calculated [oxy-Hb] contrasts (green) for “HIGH-MonL” versus “HIGH-MonR” are shown. Significant differences in the ROI-related concentration changes are indicated by arrows and with asterisk (*). Significant laterality differences between ROIs are indicated via color-coded arrows

stimulus presentation will result in comparable strong bilateral cortical activation patterns. Whereas the latter one, binaural presentation produces bilateral hemodynamic responses, could be confirmed by our

results, the contralaterality effect for monaural presented stimuli was absent. For “HIGH-” monaural stimulus presentation, neither in the “MonL” nor in “MonR” condition significantly stronger hemodynamic

responses in ROI1 contralateral to the stimulated ear was found. Only ROI4 showed a contralaterality effect for stimuli "LOW-MonR." Summarizing, we found relatively strong but comparable hemodynamic responses independent from contra- or ipsilateral stimulation. To investigate these discrepancies in more detail, we performed additionally a single-subject analysis. Also on the single-subject level, no clear picture could be found. Although we found significant laterality effects in six subjects in different ROIs, these subjects depicted contralateral and ipsilateral patterns. However, a similar outcome was also found in different fMRI studies. Although in these studies contralaterality effects during monaural stimulation occurred, they found also strong activations in the auditory cortex ipsilateral to the stimulated ear (Jäncke, Wüstenberg, Schulze, & Heinze, 2002; Lehmann et al., 2007; Woods et al., 2010; Woods, Herron, Cate, Kang, & Yund, 2011). Jäncke et al. (2002) assumed that "... a reasonably large amount of auditory information seems to be transferred via the ipsilateral pathways" but they speculated also that it might be the case "... that the ipsilateral auditory cortex receives strong input from the contralateral auditory cortex via the corpus callosum" (CC). A further explanation might be possible masking effects of cortical patterns in subregions of ROI1. For example, the ROI comprises channel overlaying secondary and tertiary auditory areas, also known as belt and parabelt fields (Kaas & Hackett, 2000), (the primary auditory cortex, core field, is not reachable by fNIRS). It is further known from fMRI studies that greater contralaterality effects are found in core fields than in lateral belt and parabelt fields (Woods et al., 2010, 2011). There is further evidence that different regions are specialized for processing different types of auditory information. For example, it is known that the posterior part of the STG of the dominant hemisphere (Wernicke's area) is responsible for processing specific characteristics of speech. In contrast, the same area on the nondominant hemisphere is known to play a fundamental role in the processing of nonverbal (complex) sounds. Thus, in both cases, related sound information from ipsilateral and contralateral ear has to be processed (hemispheric asymmetries) in these regions. Therefore, information has to be transferred via the CC to the responsible areas. We investigated this possibility by comparing the hemodynamic responses in ROI2, a subregion of ROI1, which comprises only channel overlaying the posterior parts of BA 22 and lateral parts of BA 42. We expected that our monaural presented sound stimuli will induce stronger right-side activation independent from the stimulated ear as this area is responsible for processing non-speech-related sounds. Evidence therefore might be seen in the "HIGH-MonR" condition which induces a clear deactivation pattern on the left hemisphere. However, the stimulus does not induce the expected significant stronger right-side activation although a difference can be found. Furthermore, during "HIGH-MonL" stimulus presentation comparable activation patterns can be seen in both hemispheres in these ROIs. A similar outcome was found in the work of Jäncke et al. (2002) using speech stimuli. They concluded that each auditory cortex processes the stimuli-related information directly without the support of the other hemisphere (direct-access model).

We found novel and very promising results but it is essential discussing also the following limitations and recommendations for future studies.

One limitation of this study was a possible but unknown influence of selective attention between the different conditions (Sigalovsky & Melcher, 2006). This study was designed to determine cortical activation during passive listening. We did not evaluate to which type of stimuli subjects draw their attention to. Therefore, in further studies, this information has to be collected for example using a questionnaire. A further possibility might be to use tasks promoting stronger but equal attention to all the different sounds. This would also additionally increase the measured activity induced by the stimulus (Grady et al., 1997; Jäncke et al., 1999). Another point which has to be mentioned is the comparatively low sound intensity in our high condition compared to the different fMRI studies discussed. These studies used higher intensity stimuli, up to 100 dB SPL (Neuner et al., 2014), whereas our highest intensity was 70 dB for binaural and loudness matched 79 dB for monaural presentation, respectively. It can thus be assumed that by using higher intensities, and further increasing also the differences between "HIGH-" and "LOW-" conditions, more significant differences will occur. Another limitation of this study was the limited spatial resolution over both hemispheres. By reducing the areas under investigation and increasing the number of channels overlaying the temporal regions, more detailed investigations of auditory induced activity in secondary and tertiary auditory areas are possible. Further masking effects of cortical patterns in subregions of ROI1 could be investigated in more detail. An interesting point which should be mentioned is the different time to peaks of responses in different regions. As it can be seen in the group data (Figure 2) but also in single subjects (Figure 5), there exist differences in the ROI-related hemodynamic patterns. Such variability in the timing (up to the order of seconds), shape, and or magnitude of the hemodynamic responses across subjects and brain regions (Kamran, Jeong, Malik, & Mannan, 2015; Kamran, Mannan, & Jeong, 2016) may arise from multiple factors and can also be found in fMRI BOLD responses (Buckner, 1998; Buckner et al., 1998a; Handwerker, Ollinger, & D'Esposito, 2004). Possible reasons are delays in underlying neural activity and network dynamics, vasculature differences, pulse or respiration differences, and low-frequency fluctuations (~0.01–0.1 Hz) in cerebral blood flow, influences due to the type of task or due to consciously/unconsciously processing of several tasks at the same instant of time (Erdoğan, Tong, Hocke, Lindsey, & deB Frederick, 2016; Handwerker et al., 2004; Jasdzewski et al., 2003; Kamran et al., 2015, 2016; Rosen, Buckner, & Dale, 1998). Which of these points (or a combination) could be the reason of the ROI related differences in our study can only be speculated and must therefore be investigated in more detail in further studies. A further point which has to be mentioned is the used optode placement and the definition of ROIs. Due to the characteristics of the recording method the underlying cortical areas of a specific recording channel are not easy to define and might differ between subjects. Also with a reliable optode placement by probabilistic cranio-cerebral correlation, as done in this study, group analyses are not easy to perform. Especially with a large number of used channels the placement is less reproducible because of variability in shape and size of the subject's heads (Tsuzuki & Dan, 2014). Therefore, we used an approach (as done in previous studies; e.g., Bauernfeind et al., 2014; Kaiser et al., 2014; Pfurtscheller et al., 2010;

Wriessnegger et al., 2012) which integrates multichannel data into a macro-anatomical region of interest (ROI). However, in future studies, especially when using also speech perception tasks, the use of functional localizers (Berman et al., 2010; Fedorenko, Hsieh, Nieto-Castañón, Whitfield-Gabrieli, & Kanwisher, 2010; Fedorenko & Kanwisher, 2009; Nieto-Castañón & Fedorenko, 2012) might also be a promising approach. Functional localization would enable the summarization of data over multiple subjects from corresponding functional, rather than macro-anatomical, ROIs which seems to increase sensitivity and functional resolution (Nieto-Castañón & Fedorenko, 2012), but this has to be investigated in more detail in upcoming studies. Finally we received statistically significant effects but the rather small sample size of 10 subjects should be increased in future studies to strengthen our findings.

5 | CONCLUSION

We found, as expected, pronounced cortical activation patterns (increases in [oxy-Hb]) in the temporal region of both hemispheres. We also found additional activation patterns in frontal areas. In contrast to these activation patterns, we found strong decreases in [oxy-Hb] in central and parietal regions of both hemispheres which can be seen to reflect noninvolvement or deactivation of a particular cortical region. We further found significant differences for stimulus presentation in different cortical areas with different sound intensities in both hemispheres. Although the sample size is not very high, our findings point clearly toward a relationship between the hemodynamic signal and stimulus intensity. These findings are further in line with previous fMRI studies which also found a systematic change of activation in these areas with increasing sound intensity. Although we do not found clear evidence for contralaterality effects and hemispheric asymmetries in the group data, these effects were partially visible on the single-subject level. Concluding, fNIRS is sensitive enough to capture the brain responses in different cortical regions due to sound processing. Furthermore, fNIRS is also sensitive enough to capture differences in the brain responses to stimuli presentation with different sound intensities. Therefore, fNIRS is a promising, noninvasive, and easy-to-use method for future use in central auditory diagnostics and hearing research.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interests.

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