UNIVERSITY OF TURKU

Functional Near-Infrared Spectroscopy Experiment to Investigate Functional Plasticity in the Auditory Cortex

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Master's Thesis

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The aim of this thesis was to develop a functional near-infrared spectroscopy (fNIRS) experiment to measure normal hearing adult participants (N = 9) to find whether stimulus-dependent and attention-related activation could be detected in the auditory cortex. The motivation for conducting the present study is to shed light on the effectiveness of using fNIRS to investigate functional plasticity in different patient groups treated for hearing deficits. This would provide a better understanding of functional plasticity in the auditory cortex during hearing impairment and the recovery of hearing.

Results revealed a significant intermodal attention effect (stronger activation to sounds during auditory than visual attention), but no significant stimulus-dependent activation (activation to sounds in the absence of auditory attention) nor contralateral attention effects (stronger activation to attended ear sounds in the contralateral hemisphere) in the auditory cortex. This is surprising as based on previous fMRI studies all these effects should be relatively strong and therefore further research is needed to develop experimental designs to reliably detect these effects with fNIRS.

Key words: functional near-infrared spectroscopy; auditory cortex; functional plasticity; attention-related activation; stimulus-dependent activation; intermodal attention effect; contralateral attention effect.

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1. Introduction

Hearing loss affects an increasing number of people (Pichora-Fuller, Mick & Reed, 2015). Current estimations approximate the percentage of the world's population affected by some form of hearing loss sits at roughly 6.1% (Davis & Hoffman, 2019) and with aging populations, this figure can be expected to keep growing worldwide (Roth, Hanebuth & Probst, 2011; Shargorodsky et. al., 2010). In high-income countries, it has been estimated that adult-onset hearing loss will be among the top 10 causes of total disability by 2030 (Pichora-Fuller, Mick & Reed, 2015). Hearing loss affects daily life with common challenges involving psychological well-being, self-efficacy, increased risk for dementia and social withdrawal, making it a significant growing societal problem (Davis et al., 2016; Lin & Albert, 2014; Lin, Niparko & Ferrucci, 2011; Olusanya, Neumann & Saunders, 2014).

Therefore, a vital key for promoting overall well-being would be to target audiologic rehabilitation and hearing care (Olusanya, Neumann & Saunders, 2014). Although an important area of research, the prevailing brain imaging tools (i.e. fMRI, EEG, PET) are not well suited for systematic studies in different patient groups treated for hearing deficits. For example, fMRI interferes with cochlear implant devices and thus cannot be used to study cochlear implant listeners (Basura et al., 2018). Additionally, PET does not allow multiple measures (Anderson et al., 2019) which makes it unsuitable for plasticity studies. Recently, functional near-infrared spectroscopy (fNIRS) has evoked considerable interest among hearing researchers (Chen et al., 2020). This is due to fNIRS not interfering with electronics (such as hearing devices or computers), allowing cochlear implants to be used normally during fNIRS measurements. Also, the measurements can be done in a standard listening room and multiple measurements are possible (Basura et al., 2018; Chen, 2015).

The present study was designed to investigate the use of fNIRS on normal hearing (NH) participants in the hopes it can shed light on the effectiveness of using this imaging modality in future brain auditory research on functional plasticity in different patient groups treated for hearing deficits. This brain imaging method seems ideal, as it encompasses several key features for auditory research: it can be used in multiple patient groups, it can be used in standard listening rooms and it allows multiple measurements. However, fNIRS is relatively new and systematic experimental studies of activation in the auditory cortex are still rare. The present study is one of the initial steps in a long-term research project aiming to better understand the operations and functional plasticity in the adult auditory cortex during hearing impairment and the recovery of hearing.

1.1 Previous Earplugging Studies on Functional Plasticity in Animals

The auditory cortex has been shown to be highly malleable (Ryugo, 2015). When the auditory cortex is presented with major changes in incoming inputs, it can cause significant auditory system reorganizations (Firszt et al., 2013; Kurioka et al., 2020). Studies on functional deprivation highlight the importance that neural activity plays on the maintenance of brain structures (Munro et al., 2009). In animal studies, when a fully developed adult has been subjected to hearing loss, some noted changes in the central pathways of the auditory system include the atrophy of dendrites (Benes et al., 1977), somatic shrinkage (Saada et al., 1996) and chromatolysis (Ryugo, 2015; Tirko & Ryugo, 2012). Conversely, stimulation paradigms seem to produce heightened sensitivity specific to conditioned frequencies as well as expanded representations of those neural regions (Suga et al., 2002). Taken together, increased or decreased auditory stimulation may result in physical changes in the auditory system of adult animal brains.

Kurioka and colleagues (2020) examined the plasticity of auditory neurons following conductive hearing loss in mice. In their study, adult mice had earplugs inserted bilaterally for

four weeks. The auditory brainstem response (ABR) was measured before, after and four weeks post-removal of the earplugs to determine the cochlear function of these mice. The researchers found a significant elevation of the ABR threshold on all tested frequencies after the insertion of the earplugs. However, once earplugs were removed, the thresholds fully transferred back to what they originally had been. When examined closer, some adverse effects were found namely in the decrease in the size of the auditory neurons as well as damage occurring at the synapses and myelin. The researchers concluded that to maintain peripheral auditory synapses and myelination, auditory activities (meaning activation in the auditory cortex) are required in adults. Thus, it seems that unilateral conductive hearing loss results in both structural and functional changes inside the auditory system.

A study by Clarkson and colleagues (2016) investigated this hypothesis in more detail using adult rats (N = 20). They wanted to examine structural, functional, and molecular changes in the auditory nerve brainstem and synapses after non-permanent conductive hearing loss induced by earplugging for 10 days. Their results suggest that after sound levels are restored, certain hearing deficits persist. During their recorded 10-day recovery period after the earplugs were removed, hearing thresholds remained increased for frequencies and clicks above 8 kHz. They concluded that sound deprivation can result in long-lasting changes.

Another well-known earplugging study was conducted by Knudsen and colleagues (1984) which studied the effects of early abnormal auditory experiences in barn owls and their later auditory recovery. Young owls had one of their ears blocked with ear plugging at various ages, which resulted in their altered localization abilities. When the earplug was removed, the owls had difficulties when trying to localize sounds, but their ability to localize sounds was recovered after spending a few weeks completely earplug free. This ability to recover their localization skills depended on whether they had a brief exposure to normal adult cues early in the critical period. This suggests that if you have unilateral conductive hearing loss and have

had the experience of normal hearing for even a brief period of time during the critical period of the auditory system development, there is a high chance for the recovery of accurate localization later in life. This could also potentially be extended into other auditory skills, whereby if there was exposure to normal hearing during the critical stage of development, then despite sound blockage later in life these areas could experience enough plasticity to mould back into the pre-blockage state. This would allow these auditory abilities to be regained later in life, as was the case for sound localization in the owls, despite sound deprivation and the resulting auditory cortex changes that followed.

1.2 Studying Functional Plasticity in Humans

Functional plasticity and transient hearing loss are less studied in human subjects due to the difficulties in their naturally occurring incidents. Despite the amount of animal studies available, caution should be used before generalizing the results onto the human population. However, stapedotomy patients, cochlear implant listeners and aging-related hearing loss all can provide a window of opportunity to study functional plasticity in humans.

1.2.1 Stapedotomy Patients

One window of opportunity to examine the effects of auditory deprivation, recovery from deprivation, and the changes that take place within the brain during this process are with patients that suffer from hearing loss caused by otosclerosis. This is a unique opportunity as patients with otosclerosis often initially become unilaterally deaf during adulthood (meaning they already have a fully developed auditory system), with the mean age of onset being the third decade. If there is no intervention, in about 70–85% of cases the unilateral form of hearing loss further develops asymmetrically and bilaterally whereby hearing loss is first experienced in one ear before progressing to the other (Crompton et al., 2019; Tecchio et al., 2000).

However, hearing loss caused by otosclerosis is unique in that it can be surgically cured by replacing the fixed stapes with an implant in a process known as stapedotomy. During this procedure, the fixed stapes is replaced with a prosthetic implant by drilling a hole through the footplate of the stapes (Danesh, Shahnaz & Hall, 2018). The implant is then inserted into the ear. This will result in the two middle ear bones, together with the prosthetic implant, to regain movement. This enables the ossicles to vibrate, which often results in patients recovering from their hearing loss (Fisch, 2009). Despite a small portion of patients suffering from inner ear damage, a majority of patients undergoing this procedure recover their hearing to normal or near-normal levels immediately after surgery.

A study conducted by De Campora and colleagues (2003), investigated the tonotopic reorganization of the primary auditory cortex in ten recovered otosclerosis patients using magnetoencephalographic recordings. In hearing deficits and deafness induced by otosclerosis, damaged or destroyed neuronal functions can be substituted by other groups of neurons, leading to functional plasticity changes due to hearing loss. In the study, acoustic stimulation was delivered by means of tone-bursts with frequency octaves between 250 and 2000 Hz. This was done before and after surgery to determine the characteristics of auditory cortex activation and compared against healthy controls. The researchers concluded that it seems that the patients' auditory system had re-organized to looking close to identical to subjects with no hearing impairment history. Based on their results, the researchers note that this process usually takes up to several weeks to be completed. This suggests that the auditory system can retain some level of plasticity even when experiencing periods of total deafness and re-organize itself to how it was before auditory damage had occurred.

Firszt and colleagues (2013) investigated monaural hearing by examining congenital bilateral auditory deprivation followed by hearing recovery and the resulting auditory system reorganization that followed. In their case study, the participant completed a series of hearing

tasks before and after a stapedotomy at age 41. The hearing tasks were presented randomly from 10 loudspeakers placed along a horizontal plane and 140° arc. After surgery, the participant experienced source localization improvements and hearing normalization, with the largest detected improved differences seen between the tests post-surgery and the 3-month mark. Based on these results, the authors noted that auditory system connections could re-activate once conductive hearing problems were eliminated. This is despite being physiologically latent past any probable critical developmental period of the auditory system. This supports the findings in owls found by Knudsen (1984), whereby if the auditory system has normally developed before the hearing loss, in this case at least on one side, then there is potential for the auditory system to reorganize following recovery to resemble that of someone who has never had auditory deprivation. This suggests that the auditory system does have great potential for plastic changes once normal hearing input is regained.

Overall, despite the interesting information that studying stapedotomy patients could provide, studies are still lacking in this area. Further studying this patient group could therefore provide additional information about auditory cortical processes associated with hearing impairments, the recovery of hearing and the cortical processes related to normal hearing. Focusing on stapedotomy recovery can therefore provide a targeted window to examine the functional plasticity involved in hearing loss and the recovery of hearing.

1.2.2. Cochlear Implant Patients

Cochlear implant (CI) patients provide another window of opportunity to study plastic changes that take place after the recovery of hearing loss. Cochlear implant listener (CIL) patients have severe-to-profound hearing loss before the surgical operation of getting the CI device. Once patients have the CI device, they are able to regain their ability to hear based on the artificial input of the CI device (Miyagawa et al., 2016). The CI replaces damaged sensory cells in the inner ear and thus the ability to produce and send electrical signals to the auditory

nerve is restored, resulting in the regained ability to hear. However, the input from the CI device is quite different and inferior to the input from a healthy cochlea. Yet with time, most CILs show improved hearing (Anderson et al., 2019; Stropahl, Chen & Debener, 2017).

It has been noted that functional plasticity plays a crucial role in the success of CIs to facilitate and develop spoken language in profoundly deaf individuals (Fallon et al., 2008; McKay, 2018). A review paper conducted by Fallon and colleagues (2008) investigated research involving CIs and functional plasticity. They noted that improvements in speech perception in CILs are usually underlined by changes within the auditory system. They remarked that for prelingual CILs, genetic cues are often sufficient to build a basic framework of rudimentary pathways in the absence of auditory experience. However, for postlingual CILs, previous auditory experience plays a significant role in the plasticity of the organizational structures of the central auditory system. Despite the abnormal input provided by the CI, functional plasticity facilitates the success of many postlingual CILs in achieving near-normal speech perception.

This was further studied by Olds and colleagues (2016) who investigated speech perception in CI patients using fNIRS. Auditory cortex activity in CILs were contrasted against NH listeners during responses to different speech stimuli of varying intelligibility (normal, channelized, and scrambled speech) and environmental sounds (control). CILs with good speech perception were observed to have similar cortical activation patterns (in the lateral temporal lobe and superior temporal gyrus) as NH listeners. These results indicate that there is a capacity for plasticity in the adult auditory system as a result of changes in afferent input.

However, the specific brain mechanisms underlying improved hearing performance in CILs are not well understood. This is at least partly, because the prevailing non-invasive brain

imaging tools (i.e. fMRI, EEG and MEG) interfere with the CI device (Saliba et al., 2016) and are thus not well suited for studies with CILs.

1.2.3. Aging-Related Hearing Loss

Finally, aging-related hearing loss provides a third interesting window of opportunity to study plastic changes associated with challenged hearing. As humans age, hearing naturally declines and speech intelligibility becomes increasingly difficult (Cardin, 2016; Glyde et al., 2013), especially in the presence of background noise (Glyde et al., 2011; Parbery-Clark et al., 2011). One way that older adults get around age-related decrements is by employing higher-order cognitive mechanisms and compensatory processes for losses in sensory function (Gordon-Salant & Fitzgibbons, 1997; Schieber, 2003). These compensatory processes are not well understood. Further, it might be possible to support or enhance functional plasticity in the auditory system by means of training programs. Systematic training could help for example spatial hearing in listeners with age-related hearing loss.

A review article by Anderson and Kraus (2013) explored the possibility of developing functional plasticity in aging brains by various training programs. The study noted that plasticity-based training therapies offer promising opportunities to reduce the deficits in perceptual and physiological central processing which is associated with hearing loss due to aging. So far, research has relied predominately on fMRI studies. However, certain aspects of fMRI imaging can be disadvantageous when studying hearing, such as the excessive noise produced by the fMRI machine during imaging sessions. When the target is to study auditory processes, it is especially important that external noise can be blocked out, otherwise it can disrupt the results obtained from the study (Gaab, Babrieli & Glover, 2007). This disadvantage is heightened in populations that already have difficulties with hearing. Furthermore, fMRI studies are not practical for longitudinal studies involving functional plasticity and hearing research conducted in standard listening rooms would be more advantageous.

1.3 Functional Near-Infrared Spectroscopy (fNIRS)

Functional near-infrared spectroscopy (fNIRS) is an optical imaging technique that was first developed 30 years ago (Ferrari & Quaresima, 2012). The absorption properties of near-infrared light are used by fNIRS to detect metabolic changes in cerebral blood flow by means of oxygenated (HbO) and deoxygenated haemoglobin (HbR) concentrations (Chen et al., 2015) which act as an indirect measure for neural activation (Basura et al., 2018). In this way, fNIRS is similar to fMRI as they both measure neural activity indirectly using cerebral blood flow (Wang & Chen 2020).

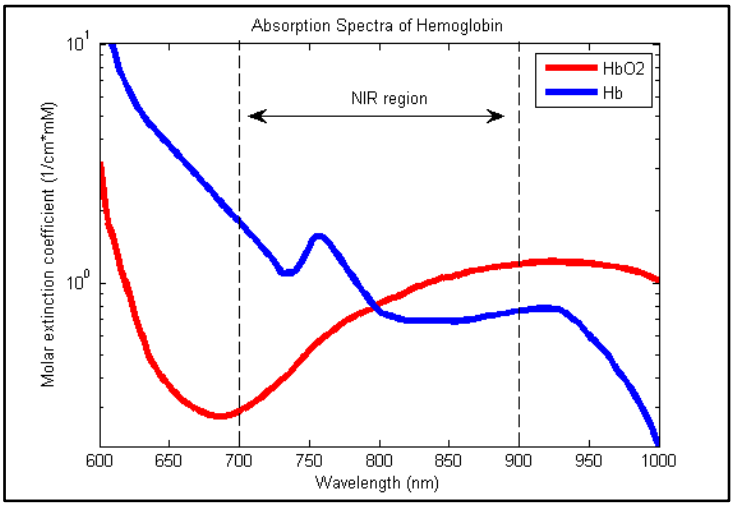

Figure 1. Absorption spectra of haemoglobin in the near-infrared region. Light intensity changes at two wavelengths (690 and 830 nm) which allows the calculation of de- and oxygenated haemoglobin from the intrinsic absorption properties of haemoglobin. Figure by Abtahi et al. (2017).

In fNIRS, optodes (sources or detectors) are placed on the scalp above the brain area of interest 3 to 5 cm adjacent to each other. The source optode emits light allowing photons to propagate and the detector optode quantifies the received light. Most of the photons from the light source get refracted, scattered, and absorbed by the tissue, and only a small portion form a banana shaped light path back to the detector near the source (Figure 2; Saliba et al., 2016; Wang & Chen, 2020). Human tissue is relatively transparent to light in the near-infrared range. In practice, fNIRS can be used to measure signals from superficial cortical regions up to a depth

of 1.5 cm (from the surface of the cortex) in adult human brains (Elwell and Cooper, 2011; Dang et al., 2016; Saliba et al., 2016; Wang & Chen, 2020).

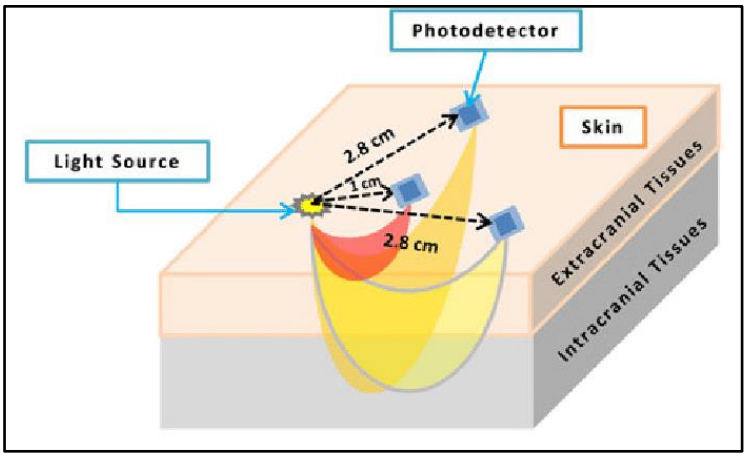

Figure 2. A schematic diagram showing an example of a fNIRS probe configuration. From the light source, photons travel to a photodetector along a banana shaped pathway. Figure by Barati et al. (2013).

In contrast to other brain imaging modalities such as fMRI, fNIRS measurements can be done in a standard listening room and there is no interference with electronics (such as computers or hearing devices). A CI device does not affect the measured signal and it can be normally used during fNIRS measurements (Basura et al., 2018; Saliba et al., 2016). fNIRS is also fully non-invasive (Chen et al., 2015). Positron emission tomography (PET), which has been seen as one potential imaging alternative for CI patients, has the disadvantage of not allowing multiple measurements, unlike fNIRS (Anderson et al., 2019; Chen et al., 2016; Olds et al., 2016). Additionally, fNIRS is significantly cheaper than either PET or fMRI (Dang et al, 2016). Due to these factors, fNIRS could be a promising alternative for flexible, more cost-efficient long-term research, as it allows the easy imaging of all potential patient groups, even CILs.

The main downside of fNIRS is that it can only measure outer cortical activities near or at the surface of the brain (Basura et al., 2018). The signals obtained are also relatively low

in spatial resolution and in practice the signal-to-noise ratio tends to be low. Further, despite the numerous advantages provided by fNIRS, it is still not widespread in clinical use (Obrig, 2014).

1.4 Functional Indices of the Status of the Auditory Cortex

This study is based on the idea that stimulus-dependent and attention related activation patterns can be used as indices of the functional status of the auditory cortex. It is assumed that these indices make it possible to follow the changes in auditory cortex operations during recovery of hearing after stapedotomy, CI switch on or plasticity-based auditory training programs in normal aging. Stimulus-dependent and attention-related contrasts are associated with relatively strong effects in fMRI (Alho et al., 2014; Häkkinen et al., 2015; Rinne, 2010; Rinne et al., 2005, 2008, 2012) but it is still unknown whether these effects can be seen using fNIRS.

Stimulus-dependent activation. Stimulus-dependent activation in the auditory cortex can be measured by contrasting activation during a visual task (i.e., in the absence of auditory attention) with auditory stimuli and activation during a visual task with no auditory stimuli (or a rest condition; see Häkkinen et al., 2015). Stimulus-dependent activation is typically observed in regions in or near the Heschl's gyrus (approximate anatomical marker for primary auditory regions).

Intermodal attention effect. An fMRI study conducted by Rinne (2010) contrasted auditory cortex activation to identical sounds presented during either a demanding auditory task or a visual task. The results showed stronger auditory cortex activation during auditory tasks compared to visual tasks in wide auditory cortex regions extending from the anterior to posterior superior temporal gyrus, including the Heschl's gyrus. This indicates that auditory cortex activation is enhanced during attention-engaging auditory tasks. This effect is called the intermodal attention effect.

Contralateral attention effect. In an fMRI study conducted by Rinne (2008), participants selectively attended to asynchronous auditory stimuli in either the right or left ear. The results showed that auditory cortex activation in the human inferior colliculus was stronger in the hemisphere contralateral to the attended ear. This effect is called the contralateral attention effect.

Currently it is not known whether stimulus-dependent activation, intermodal attention effects and contralateral attention effects can be measured using fNIRS. If this is possible, then these effects could be potentially used as functional indices to follow, for example, how sensitivity and specificity of auditory cortical operations change as a function of time after the CI onset and after stapedotomy. Furthermore, these indices could be used to track the potential changes in auditory cortical activation during hearing rehabilitation programs developed to improve hearing in the older population.

Based on our initial pilots (not reported), the signal-to-noise ratio of auditory cortical activation measured with fNIRS is relatively low. Because of this, the present study focused on a minimal number of experimental conditions in order to be able to increase the number of repetitions per condition.

1.5 Aims of the Present Thesis

The purpose of this study is to shed light on the effectiveness of using fNIRS as a brain imaging modality in future brain auditory research on functional plasticity in different patient groups treated for hearing deficits. This would provide a better understanding of functional plasticity in the auditory cortex during hearing impairment and the recovery of hearing.

The specific aims of this study are to answer the following questions:

1. Are we able to detect stimulus-dependent activation in the auditory cortex in adult NH participants?
2. Are we able to detect intermodal attention effects (auditory vs visual condition with identical stimuli)?
3. Are we able to detect contralateral attention effects (attend left vs right ear sounds with identical stimuli) in the auditory cortex?
4. How does increasing the number of repetitions per task condition impact the quality of data?

2. Methods

2.1 Participants

The participants for this study were healthy volunteers from The University of Turku and the surrounding community. Data acquisition took place from February to March 2021. Initially, 14 participants were recruited. However, two participants had to be discarded due excessive movement of the fNIRS cap during the experiment. Thus, the final sample comprised of 12 individuals (10 women) aged 23–51 (M = 28.1, SD = 7.66) with one participant identifying as being left-handed. The subjects were all healthy, normal hearing adults with normal or corrected-to-normal vision. All participants provided informed consent before participating. The ethical protocol was approved by the ethics Committee for Human Science at the University of Turku.

2.2 Stimuli

Auditory stimuli. During the fNIRS measurement, auditory stimuli were presented in 15 s blocks. In each block, 30 pairs of narrow pass filtered noise bursts (sampling rate 44100 Hz) were presented in asynchronous left and right ear streams. The sounds in one sequence

were either low or high frequency bursts (left and right ear sounds were of different frequency to facilitate selective attention). Low (filter limits: low 447 Hz, centre 500 Hz and high 562 Hz) and high (filter limits: low 3548 Hz, centre 4000 Hz and high 4467 Hz) frequency bursts were created using third octave bands. The bursts were either long (250 ms) or short (150 ms) in duration. The auditory stimuli started earliest at two and latest at 12 s from block onset. The noise bursts of a pair were separated by a between burst gap ranging from 40–60 ms. The pairs were presented in a sequence so that a temporal pattern (i.e.: long, short, long, short, …) was created. This temporal pattern was interrupted 1 – 3 times during a 15 s block, so that a long duration sound burst was followed by another long duration sound burst (i.e.: long, short, long, short, long, *long,* short, …) or by two consecutive short sound bursts (i.e.: long, short, long, short, *short,* long). The auditory stimuli were delivered using insert earbuds (Sennheiser IE 40 PRO earbuds).

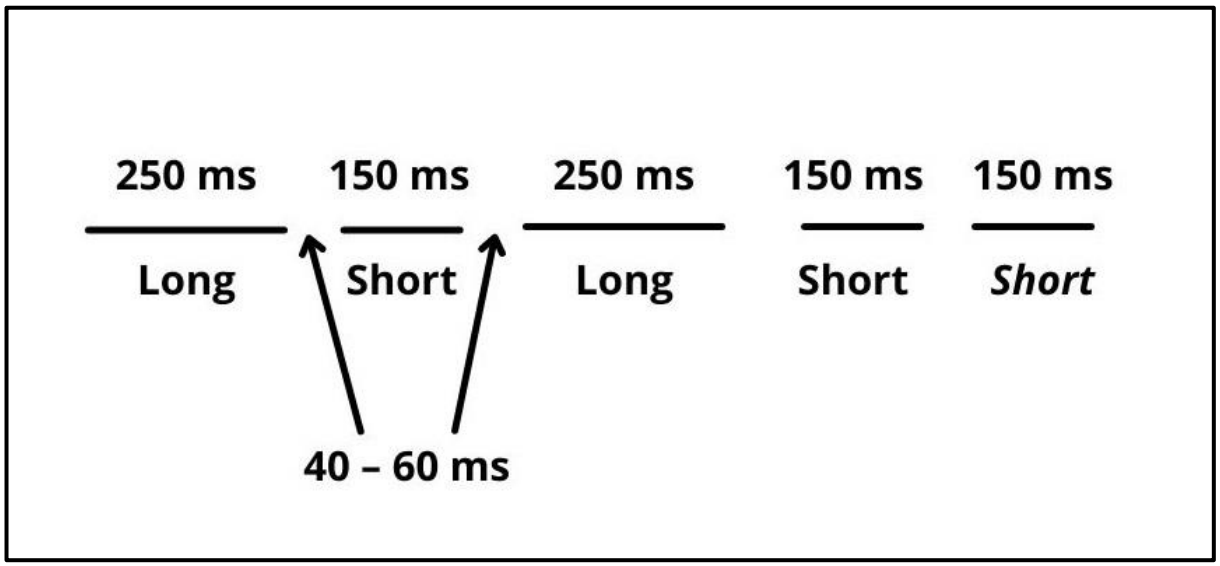

Figure 3. Sound streams alternated between long (250 ms) and short (150 ms) duration sound bursts. There was a between-stimulus gap that varied in duration from 40 to 60 ms. The gap duration remained between 40 to 60 ms between all sound pairs both long and short. Occasionally, the temporal pattern was interrupted so that either the short or the long sound was repeated.

Visual stimuli. The visual stimuli was a flickering Gabor patch presented in the middle of a Dell monitor (refresh rate 60 Hz) approximately 1 m in front of the participant. The flickering was achieved by reducing the spatial frequency to zero on every sixth screen refresh rate (i.e., on 5× 16.67 ms = 83 ms, off 1 × 16.67 ms). Orientation of the Gabor changed (by 3.5 or 4°) 1–3 times during a block. The orientation change happened earliest at two and latest at 12 s from block onset.

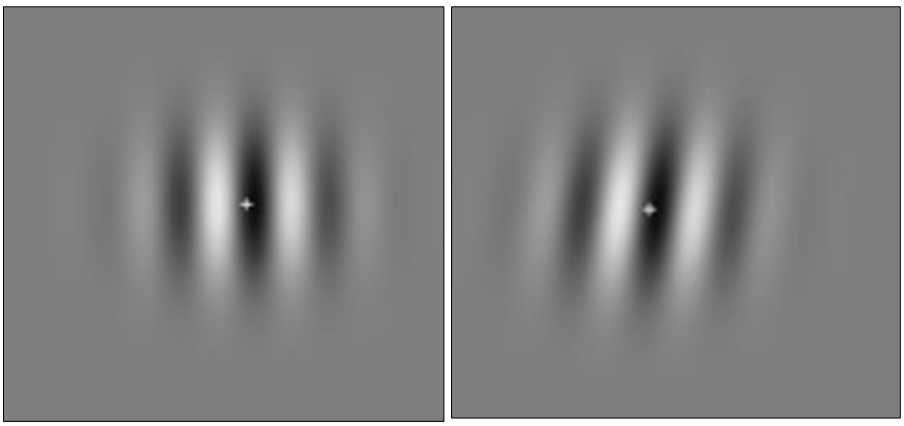

Figure 4. Orientation change of the Gabor patch.

2.3 Experimental Design and Procedure

The duration of the experiment was 48 minutes, which comprised of 12 runs consisting of 8 task blocks (15 s) each. Four conditions (two auditory and two visual) were presented twice per run totalling 24 times per condition. The experimental design is visually illustrated in Figure 5 and a summary of the experimental design and conditions are given in Table 1.

The design of the experiment was balanced, meaning half the participants started with an auditory condition and the other half started with a visual condition. Each task block was followed by a rest block during which subjects focused on a fixation mark (+) presented in the middle of the screen. The rest block durations varied between 12 and 26 s to avoid temporal adjustment.

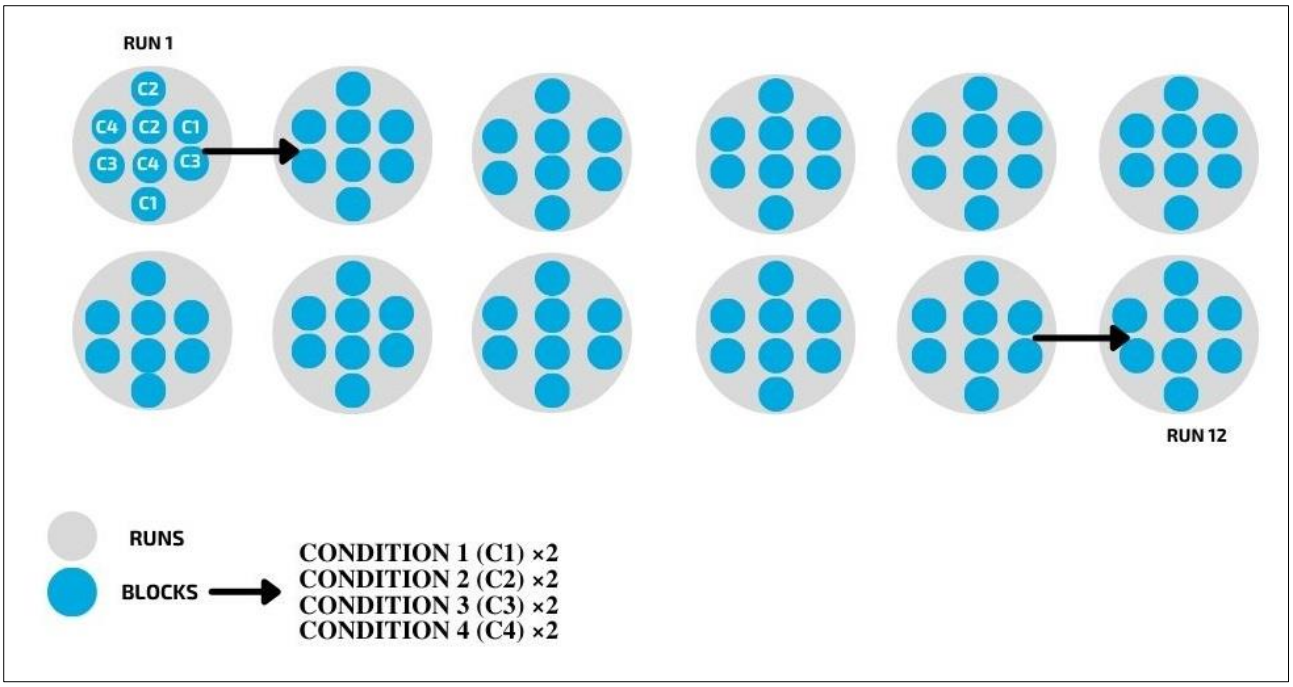

Figure 5. Experimental design and the structure of the stimuli presentation. Total number of runs was 12 (grey circles) and within each run there were 8 task blocks (blue circles). There were four types of conditions, each presented two times per run in random order. Each condition was thus presented 24 times.

Table 1. Summary of Experimental Design and Conditions.

Experiment	
Conditions	4 (each condition repeated twice in a run) Condition 1: Auditory attend right (C1) Condition 2: Auditory attend left (C2) Condition 3: Visual with sounds (C3) Condition 4: Visual silent (C4)
Blocks per run	8
Number of runs	12
Run duration	4 min (8 × 15 s task blocks + 8 × 15 s rest blocks)
Rest duration	15 s
Duration of experiment	48 min

Conditions. The experiment consisted of four conditions: auditory attend right (C1), auditory attend left (C2), visual with sounds (C3) and visual silent (C4). The auditory and visual conditions alternated. Otherwise, the conditions were presented randomly within each block (e.g., auditory (C1), visual (C4), auditory (C2), visual (C4), auditory (C2), ….). Each condition was presented twice in each run. In the auditory conditions (C1 or C2), the participants had to direct their attention to either the left or right ear streams, respond to targets in the attended stream and ignore the sounds presented to the other ear. The sounds in one stream were either low or high frequency bursts (left and right ear sounds were of different frequency to facilitate selective attention). In the visual conditions (C3 or C4), the participants had to direct their attention to the orientation change of the Gabor patch presented on the screen. In the case of C3, participants would also have to ignore the sound streams being played. The task was indicated to participants before the beginning of a task block using graphic task instruction symbols (Figure 6).

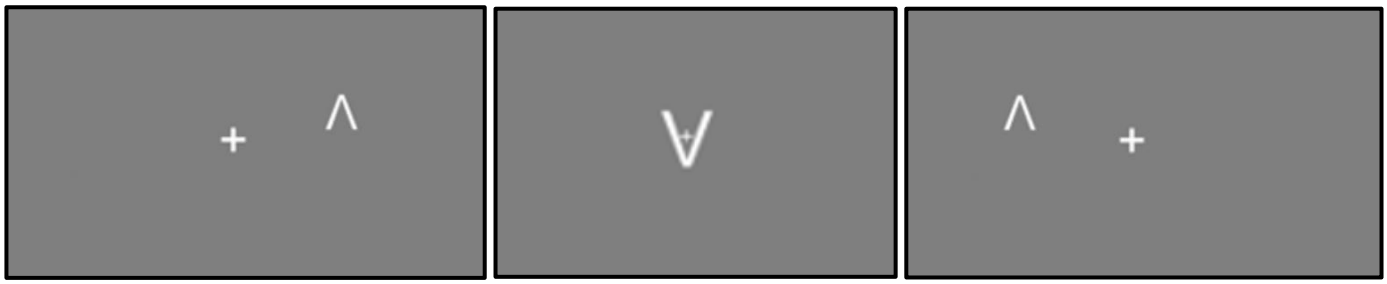

Figure 6. Instruction symbol for auditory and visual tasks. **Left:** An example of instructions that would be displayed on the screen for condition C1. **Middle:** An example of the instructions that would be displayed on the screen for conditions C3 and C4. **Right:** An example of instructions that would be displayed on the screen for condition C2.

Procedure. A high-resolution T1-weighted anatomical MRI image (Philips Ingenia Ambition 1.5T X, 1 × 1 × 1 mm^3 resolution) was acquired for each subject before the fNIRS. This anatomical MRI was used to define coordinates of anatomical landmarks for each participant (the left and right preauricular point, the nasion, a single point approximating the anterior and posterior parts of the Sylvian fissure as well as the left and right ocular point) in order to align the optode patch with the Sylvian fissure (Figure 7).

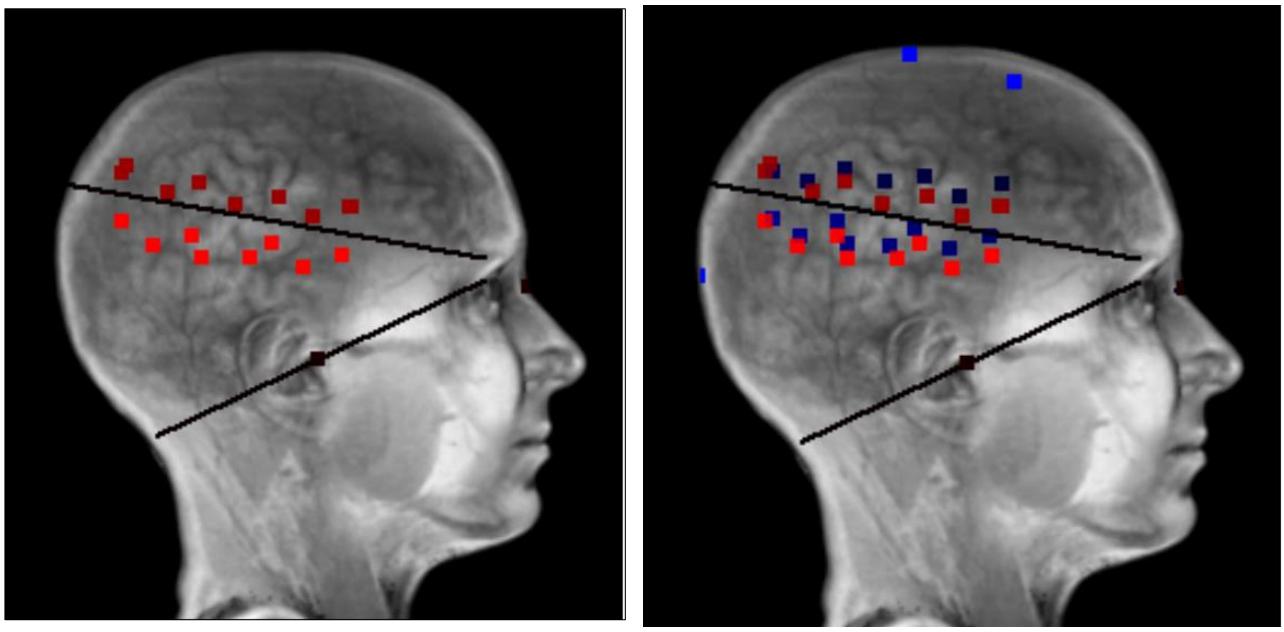

Figure 7. Target optode placement and digitized optode placement. **Left:** The red dots visualize the placement of the detectors (upper row of dots) and the placement of the sources (lower row of dots). The upper black line shows the approximate location of the Sylvian fissure. The lower line connects the right cantus with the right preauricular point. The black dots mark the nasion point and the right preauricular point. **Right:** Dark blue dots show the digitized actual location of the optodes. Bright blue dots are the digitized scalp locations.

In the beginning of the fNIRS session, the loudness of the sounds was first adjusted for each participant. The auditory stimuli were presented at a comfortable level. Then, a practice run (or two if needed) was performed to get the participant acquainted with the task. The optode grid was placed as accurately as possible on the participant's scalp. The location of the optodes was digitized and compared with the target location (Figure 7). If needed, the optode placement

was repeated until the optode placement was acceptable. After this, the sources and detectors were attached on the scalp. The signal from each detector was checked to make sure there was at least one (ideally two or more) source pairs that had a signal with AC values reaching a magnitude of at least 100. The actual experiment was conducted in a dark room to minimize light interference with the fNIRS data recording.

2.4 fNIRS Data Acquisition, Data Processing and Analysis Strategy

For the fNIRS data acquisition, a multichannel system (Imagent^{TM}, ISS Inc., Champaign, USA) was used. In this experiment, 14 photonmultiplier tube-based detectors and 16 source pairs were used (seven detectors and eight source-pairs per side). The data analysis pipeline used in this study corresponds to a typical fNIRS data analysis pipeline used in Homer.

Data processing. In-house Python scripts were used to process the data. AC levels were checked in order to exclude channels with bad signal quality (mean AC values below 100). Then, the data were converted into optical density before a motion artifact correction (kurtosis-based wavelet filter) was applied. Next, the data were filtered before it was converted to oxygenated and de-oxygenated Hb concentrations. Epoching, averaging and baseline corrections were also applied, before the signal from all participants were averaged across subjects.

Analysis strategy. A limited set of channels were chosen for statistical analysis. The selected channels had good signal quality (mean AC values above 100 and a clear pulse). Channels 20 and 52 from the left hemisphere as well as channels 130 and 164 from the right hemisphere were selected for analysis.

3. Results

3.1 Pulse Signal

Pulse signal was investigated in order to ensure the optodes had a good connection to the scalp. In order to do this, raw AC intensity signal was filtered using a bandpass filter of 0.6 to 2.0 Hz. Three participants did not show a clear pulse signal and were therefore excluded from the statistical analysis.

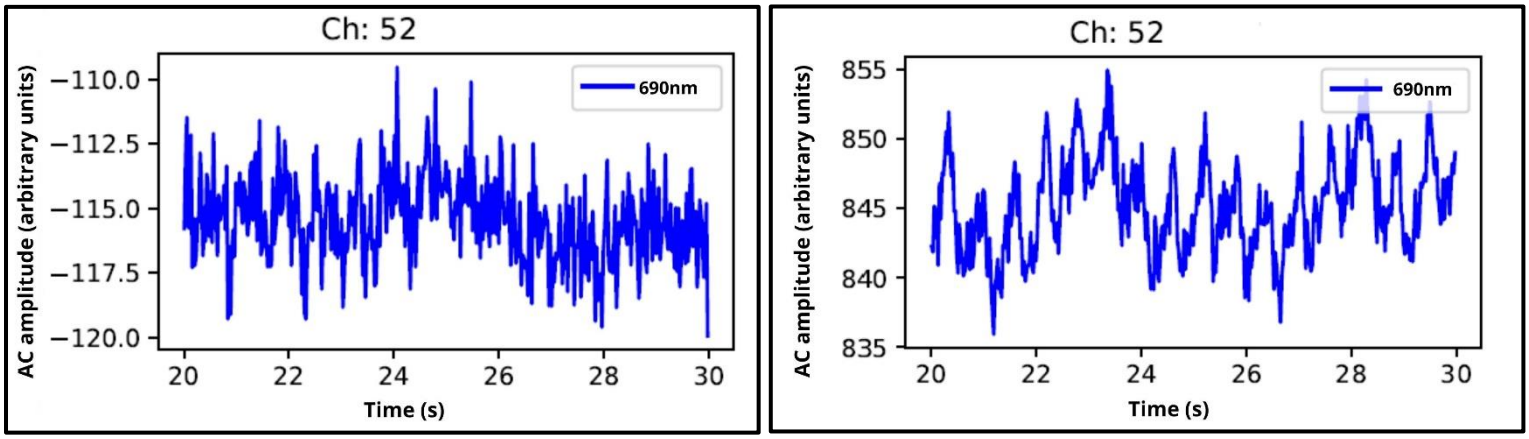

Figure 8. Raw AC intensity data (blue 690 nm) showing the pulse signal from channel 52 (left hemisphere) of two different participants in a randomly selected 10 s sample. **Left:** A noisy signal where the pulse is not clearly visible. This participant was excluded from the analysis. **Right:** A clearer pulse signal is visible, indicating that the optode had a good connection to the scalp.

3.2 Concentration Changes of HbO and HbR

Figures 9 and 10 illustrate the concentration changes of HbO and HbR for different conditions of one sample participant. The concentration changes for each condition were averaged across participants (N = 9) and used for the statistical analysis.

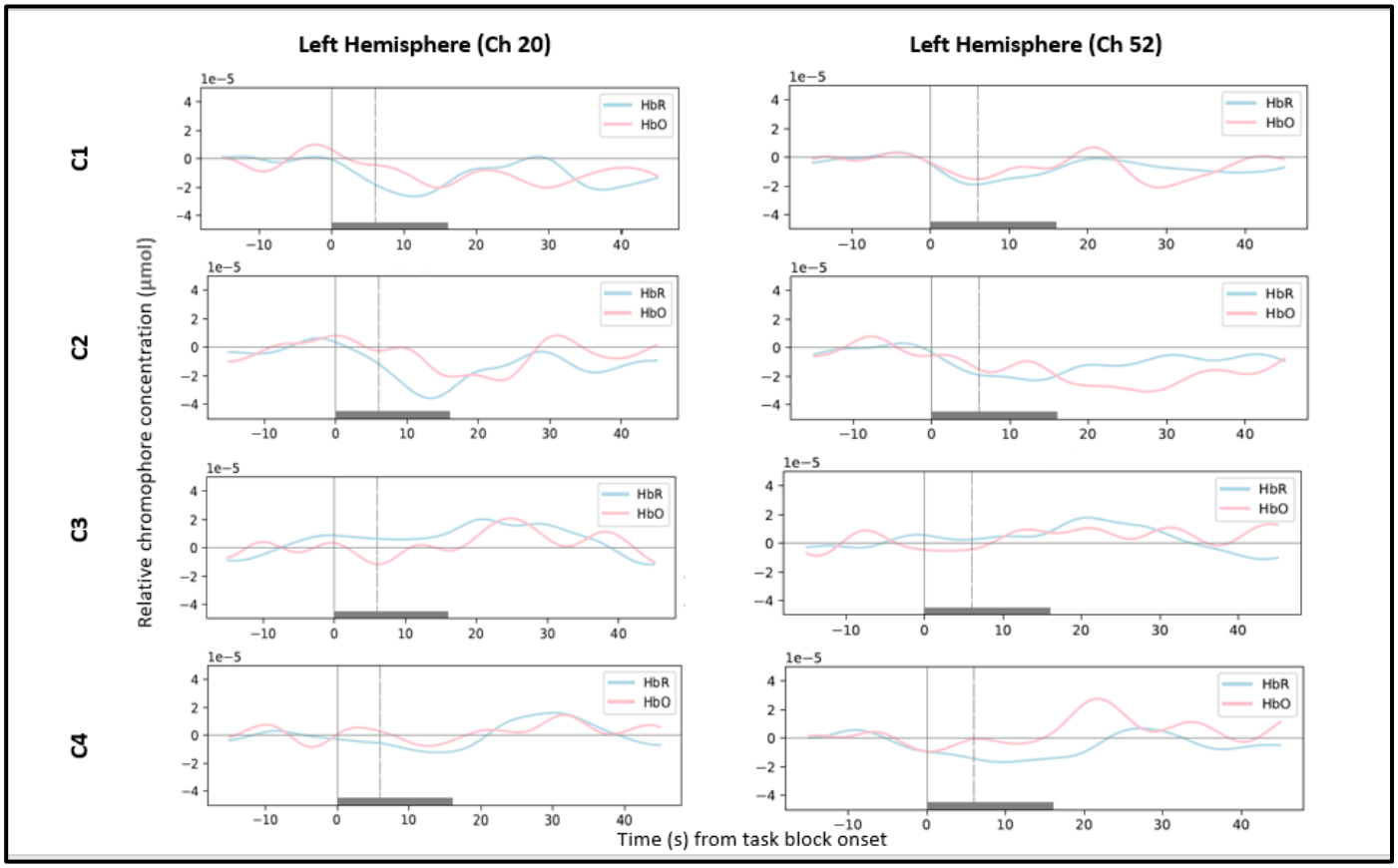

Figure 9. Concentration changes of HbO and HbR for different conditions in channel 20 and 52 in the left hemisphere of one participant. The horizontal bar shows the duration (15 s) of the task block.

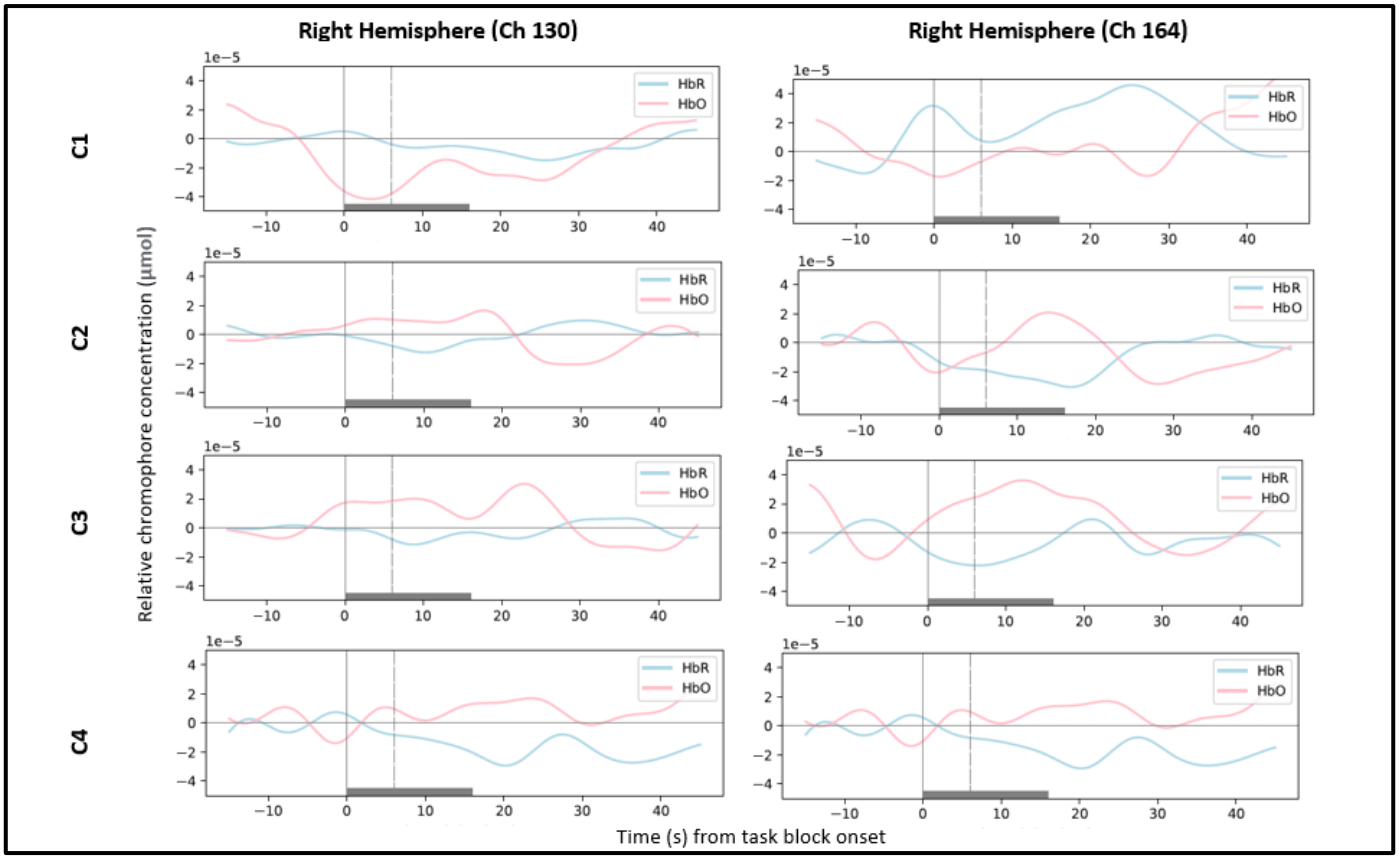

Figure 10. Concentration changes of HbO and HbR for different conditions in channel 130 and 164 in the right hemisphere of one participant. The horizontal bar shows the duration (15 s) of the task block. The waveform during C2 in the right hemisphere (channel 164) shows what the expected haemodynamic response looks like. HbO increases until it reaches a peak a few seconds after task block onset and HbR decreases with a slight delay.

3.3 Task Performance

To ensure participants were following the task, task performance was recorded. An in-house Python script was used to calculate the hit rate (number of hits divided by the number of targets), false alarms (number of FAs divided by the number of non-targets) and d prime (d'). These were calculated for both visual and auditory conditions (Table 2). The overall mean hit rate 64.08% (SD was 11.57%) and the relatively high d' indicates that participants understood and performed the task as instructed.

Table 2. Task performance in auditory and visual conditions. HR = hit rate, FR = false alarm, SD = standard deviation. N = 9.

	HR range	**HR mean (*SD*)**	**FA range**	**FA mean (*SD*)**	**d' range**	**d' mean (*SD*)**
Auditory	35 – 80%	61.88% (15.70%)	0 – 5%	3.22% (1.975%)	1.25 – 3.00	2.25 (0.54)
Visual	58 – 82%	72.33% (6.57%)	0 – 1%	0.11% (0.31%)	2.57 – 4.29	3.63 (0.46)

3.4 Normality Checks

The normality assumption was visually checked in R (version 4.0.5) using a density plot and a quantile-quantile plot (QQPlot) before conducting repeated measure analysis of variance (ANOVA) and Tukey HSD post hoc tests. Despite the density plot having the appearance of a normal distribution, the QQPlot revealed the violation of normality. This was confirmed by the Shapiro-Wilks test. Several extreme outliers were also flagged in the data. Nonetheless, as ANOVAs are relatively robust to non-normally distributed data, these methods were used for the statistical analysis.

3.5 Stimulus-Dependent Activation Effects in the Auditory Cortex

The first aim of this study was to explore whether stimulus-dependent activation effects could be detected in the auditory cortex. A two-way repeated measure ANOVA was performed separately for each hemisphere and measure (left and right hemisphere; HbO and HbR) to test for any global effects. The factors were time (mean windows 0–5, 5–10 and 10–15 s from task block onset) and condition (2 levels, C3 and C4). A Tukey HSD post hoc test was then performed.

Left Hemisphere ANOVA

The repeated two-way measure ANOVA (factors: time and condition) did not produce any significant interaction effects for either HbO or HbR. The post hoc Tukey test did not show any significant effects or trends (all tests $p > .05$).

Right Hemisphere ANOVA

The repeated two-way measure ANOVA (factors: time and condition) did not produce any significant interaction effects at for either HbO or HbR. The Tukey post hoc test did not show any significant effects or trends (all tests $p > .05$).

3.6 Attention-Related Activation Effects in the Auditory Cortex

The second and third aim of this study was to explore whether intermodal or contralateral attention effects could be detected in the auditory cortex.

Intermodal Attention Effects: Three-Way ANOVAs

A three-way repeated measures ANOVA was performed in each hemisphere and measure (left and right hemisphere; HbO and HbR) to test for any global effects. The factors were time (mean windows 0–5, 5–10 and 10–15 s from task block onset), hemisphere (left and right) and condition (4 levels, C1–C4). Then, a Tukey HSD post hoc test was performed.

1. HbO:

   The ANOVA revealed a significant main effect of condition ($F_{(3,680)} = 5.28$, $p < .01$).

   The Tukey HSD post hoc test revealed a significant difference between conditions C1 (auditory attend right) and C4 (visual silent). This combined effect of stimulus-dependent and attention-related activation happens only when both hemispheres are pooled together. When hemispheres are tested separately, the effect does not exist.

   The Tukey HSD post hoc test also revealed a significant difference between conditions C2 (auditory attend left) and C4 (visual silent). The power of both hemispheres combined is needed here too for effects to emerge.

   No significant intermodal attention effects were found (i.e., C1/2 vs C3).

2. HbR:

   The ANOVA revealed a significant main effect of condition ($F_{(3,680)} = 14.99$, $p < .001$).

   The Tukey HSD post hoc test revealed significant intermodal attention effects (Table 3). There was a significant difference between conditions C1 (auditory attend right) and C3 (visual with sounds). There was also significance between conditions C2 (auditory attend left) and C3.

Table 3. Adjusted p-values for Tukey HSD post hoc test for significant intermodal attention effects in HbR.

	p (adjusted)
C1 vs C3	1.437069e-08
C2 vs C3	0.0002832

The Tukey HSD post hoc test also revealed a significant difference between conditions C1/C2 (auditory attend right/left) and C4 (visual silent). This combined effect of stimulus-dependent and attention-related activation happens only when both hemispheres are pooled together. When hemispheres are tested separately, the effect dissapears.

Contralateral Attention Effects: Two-Way ANOVA

A repeated two-way measure ANOVA was performed separately for each hemisphere and measure (left and right hemisphere; HbO and HbR). The factors were time (mean windows 0–5, 5–10 and 10–15 s from task block onset) and condition (2 levels, C1and C2). A Tukey HSD post hoc test was then performed.

The ANOVA did not produce any significant main or interaction effects for either hemisphere in HbO or HbR. The post hoc Tukey test did not show any significance. No contralateral attention effects were found (i.e., C1 vs C2).

3.7 Effect of Increasing the Number of Repetitions Per Condition

The fourth aim of this study was to explore whether increasing the number of repetitions per condition improves fNIRS data quality. As reported above, no significant stimulus-dependent activation effects were detected. Thus, for the contrast C3 vs C4, 24 task condition repetition seems not to be enough. However, significant intermodal attention effects were detected between conditions C1/C2 and C3 in HbR. This suggests that 24 repetitions is enough for the detection of intermodal attention effects. For contralateral attention effects, no significance was detected indicating 24 task condition repetitions is not enough.

For comparison purposes, the above analysis was repeated with only 12 task condition repetitions, which were randomly selected. All the significant effects disappeared, suggesting that increasing the number of repetitions had an effect on at least the significant intermodal attention effect results with HbR.

4. Discussion

4.1 Key Findings

In the present sample of adult NH participants, the first aim was to explore whether stimulus-dependent activation effects (activation to sounds in the absence of auditory attention) could be detected in the auditory cortex. The results yielded no significant stimulus-dependent activation effects or trends (between C3 and C4) with either HbO or HbR in either hemisphere.

The second aim of this study was to explore whether intermodal attention effects (auditory vs visual condition with identical stimuli) could be detected. In HbO, no significant intermodal attention effects were found. In HbR, systematic significant differences were detected for both C1 vs C3 ($p < .01$) and C2 vs C3 ($p < .01$). This was as expected, given that intermodal attention effects have been previously studied using fMRI and auditory cortex

activations to sounds were found to be higher during auditory than visual tasks in both hemispheres (Rinne, 2010).

The third aim of this study was to see if contralateral attention effects (attend left vs right ear sounds with identical stimuli) could be detected in the auditory cortex. The analysis revealed no significant contralateral attention effects (C1 vs C2) for either hemisphere (left and right) in HbO and HbR.

Finally, the fourth aim of this thesis was to determine whether increasing the number of repetitions per task condition had an impact on the quality of the data. It seems that 24 repetitions is enough for the detection of intermodal attention effects, but not for the other two tests. This was compared against the results of a previous pilot study (not reported) and by repeating the analysis from this thesis data with only 12 repetitions per task condition. Once the repetitions were halved, all significance was lost. This suggests that increasing the number of repetitions per task condition can help decrease task related noise and increase the possibility for detecting intermodal attention effects in the auditory cortex with fNIRS.

The present results seem somewhat in contrast with previous fMRI studies that have been able to measure strong stimulus-dependent activations and contralateral attention effects in human subjects (Alho et al., 2014; Häkkinen et al., 2015; Rinne, 2008). Therefore, it should be possible to detect similar effects when using fNIRS. It seems that there is not enough power or repetitions, particularly when measuring stimulus-dependent activation or contralateral attention effects. Further increasing repetitions per task condition could lead to lower estimation variance and better predictive performance due to the increase in power afforded by having more data points to analyse. Additionally, increasing the sample size and reducing the noise in the data could be explored to see whether this would result in the detection of stimulus-

dependent or attention related activation, perhaps even without further increasing the amount of task condition repetitions.

4.2 Limitations

4.2.1 Design Centred Limitations

One central limitation to this study was the small sample size. Three participants had to be discarded due to insufficient pulse signal and a further two were discarded due to the excessive movement of the fNIRS cap during the experimental trials. Particularly for those participants with longer, sleeker hair (such as East Asian descendants), the cap seemed to shift position very easily and did not hold sturdy. Adjustments should be made to be more inclusive of hair types in the experimental design. Adding an adhesive on the underside which would increase friction without damaging the hair itself could be designed and implemented. It seems though that small movements of the current cap during the experiment is inevitable, resulting in the location shifting slightly by the end of the task. It is thus advised that rigorous documentation should be done before and after the experiment to make sure the effect on the data quality is limited.

Compared to other recent fNIRS studies (Chen et al., 2016 & Weder et al., 2018) the custom-built cap used in this experiment could be individually tailored in alignment with the participant's MRI image. This provided greater flexibility with the adjustment and placement of the cap, allowing more accurate optode placement. However, there was large variability in the success rate of accurate cap placement (1–9 times). This step tended to be time-consuming leading some participants to feel drowsy before even starting the task. For NH healthy participants, this could be acceptable, but when considering the potential implementation for clinical populations, this step could be streamlined to be more efficient. Suggestions would be to have more pilot participants in order to practice cap placement sufficiently, as well as having

an extra set of hands available during cap placement, as this seemed to be a vital component increasing the chance of successful cap placement in the first or second try.

After completing the task, participants noted that the task seemed quite long and mentioned fatigue and drowsiness about halfway through. As the study took place in a dark room, lasted approximately 50 minutes, and only had four conditions (making the task very repetitive) this could have resulted in a decrease in concentration and thus accuracy in the task itself. This was reflected by two of the participants having a HIT rate of under 50%, despite saying they understood the task at hand. Increasing the rest times in between runs or taking a longer mental break about half-way through could potentially improve concentration levels. Additionally, finding an appropriate balance between getting enough condition repetitions to have better quality data and finding a task length that does not significantly decrease participant concentration could be further investigated.

4.2.2 Data Quality Centred Limitations

A further limitation to this study was the noisiness of the data quality overall. One source of noise was physiological noise coming from extracerebral sources. According to Kirilina (2013) there are three main mechanisms that contribute to physiological noise in fNIRS signals. Two of these are induced by global systemic physiology, namely the oscillation of arterial pressure (known as Mayer waves) and respiration. Another contributor would be induced by local blood flow changes in skin tissue. According to Kirilina's study, global processes affect HbO signals more significantly both intra and extra-cerebrally. Perhaps this could partially explain the more apparent significance between conditions and the HbR signal, compared to the HbO signal in the statistical analysis of intermodal attention effects.

Further noise came from environmental factors such as skull thickness, hair density, hair colour (denser, darker hair reduces signal strength by blocking light transmission to the skull) and motion (including head motion during the experiment as well as breathing related

movements) (Chen et al., 2020). Although participants were told to remain as still as possible, movement artifacts could have impacted the data. Additions could be made to limit excessive head movement during the experiment, such as adding a neck cushion around the participant's neck to add stability, as was done in Weder and colleagues' fNIRS study (2018).

Although experimental preparations were done to separate hair follicles during sensor placement (these signals were also checked before the start of the experiment) some noise could have interfered with the signal obtained from the auditory cortex. Furthermore, some participants had to be discarded from the study due to the absence of a pulse signal in their data. This alludes to the optodes not having enough contact with the scalp, making a clear signal difficult to obtain. Participants with thicker, darker hair were more susceptible to this and more rigorous preparations should be made in this case to ensure proper optode contact. The analysis pipeline could additionally be refined to process noise more efficiently as well as further optimizing the optode and cap placement on participants to reduce the amount of noise in the final data.

4.3 Implications and Future Directions

One noteworthy aspect of this study was the significant intermodal attention effects that were found in the auditory cortex. Using fNIRS to study intermodal and contralateral attention effects in the auditory cortex has not been done before. This study therefore followed a novel and challenging path, and the implication of finding significant intermodal attention effects is exciting as it sheds light on this new approach for brain auditory research involving fNRIS.

This also holds implications for future functional plasticity research involving clinical populations, such as stapedotomy patients, CI patients, and patients with aging-related hearing loss. If future studies reveal that indices (like stimulus-dependent and attention-related activation) of the functional status of the auditory cortex can be detected using fNIRS, this opens up a host of opportunities for furthering auditory research involving functional plasticity

in clinical groups. These effects could be used as functional indices to follow how sensitivity and specificity of auditory cortical operations change as a function of time after the CI onset and after stapedotomy. Furthermore, these indices could be used to track the potential changes in auditory cortical activation during hearing rehabilitation programs developed to improve hearing in the older population. Together, these would provide interesting opportunities to learn more about how functional plasticity develops in the auditory cortex during hearing impairment and the recovery of hearing.

As functional indices have a strong theoretical basis in fMRI auditory studies (Häkkinen et al., 2015; Rinne, 2008; Rinne et al., 2010), it remains hopeful that with some fine-tuning of this experiment, stimulus-dependent and attention-related activation effects can be reliably detected in fNIRS research. In order for this to happen, more research needs to be done on reducing noise and improving data quality and analysis pipelines. This could provide more robust results in the future and participants would not have to be discarded due to excessive noise in their data due to methodological issues. These confounds could be further tested in future research so that these tentative results can be built upon. With time and more research, fNIRS seems to be a promising new tool that could add to the literature of studying the functional plasticity in the auditory cortex of patients with various hearing deficits and the subsequent recovery of their hearing.

5. Conclusion

Overall, this study resulted in preliminary data observing that intermodal attention effects can be detected with 24 repetitions per task condition using fNIRS in the auditory cortex. Results revealed no significant stimulus-dependent activation nor contralateral attention effects in the auditory cortex, which is surprising as based on previous fMRI studies all these effects should be relatively strong. Therefore, further research is important with an increased

sample size, reduction of overall noise and modifications to the experimental set up in order to develop experimental designs that reliably detect these effects in fNIRS. Additionally, exploring whether further increasing the repetitions per task condition would result in detectable activations or if reduction of noise and an increase in power would be enough is advisable. The ability to detect these functional indices could lead to applications in studying functional plasticity in the auditory cortex using a novel imaging modality offering flexible, more cost-efficient long-term research in standard listening rooms. This would result in the opportunity to research different clinical groups (such as stapedotomy patients, CILs and patients with aging-related hearing loss) during both hearing loss and recovery.

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