Neural correlates of music perception in cochlear implant users using functional neuroimaging

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Abstract

Despite significant advances in cochlear implants (CI), music perception in CI recipients remains generally poor. Studies suggest that an enormous variability exists in CI users' ability to perceive and enjoy music through an implant, and the factors that contribute to this wide variation in individual outcomes following cochlear implantation are diverse and not completely understood. The purpose of this thesis was to examine, with the aid of neuroimaging, the neural basis underlying the wide variability in music perception outcomes following implantation.

The first part of this thesis reviewed applications and limitations of current neuroimaging modalities, including functional near-infrared spectroscopy (fNIRS), in the CI population. This review summarized the existing literature on the use of fNIRS neuroimaging in adult and pediatric CI recipients and outlined possible directions for future research, as well as clinical applications using this promising technique. The results of this review revealed that fNIRS is the imaging modality of choice in CI users because it is non-invasive, compatible with CI devices, and not subject to electrical artifacts.

The second part of this thesis started the examination of the correlation between behavioral measures of music perception and auditory cortical activation in CI users using functional near-infrared spectroscopy (fNIRS), and attempted to identify patient-related factors that modulate this relationship. This prospective case-control study reported on 27 CI recipients and 25 normal-hearing controls. Behavioral music performance was assessed by the Montreal Battery for the Evaluation of Amusia (MBEA). fNIRS neuroimaging of the auditory cortex was recorded during music, rhythm and pitch perception. Results of this study revealed that reliable auditory cortical responses were obtained in all participants with fNIRS. Findings also suggested

that larger areas of auditory cortical hemodynamic responses activations may be linked to improved performance on behavioral tasks.

Taken together, the findings from the present thesis provide evidence that fNIRS is a safe, reliable neuroimaging modality that can provide an objective brain-based measure of music perception in CI users that is correlated with behavioral outcomes. Ultimately, this data will contribute toward the advancement of strategies aimed at improving the overall musical experience in CI users.

Résumé

Malgré les avancées significatives dans les implants cochléaires, la perception musicale chez les patients implantés demeure généralement faible. Les études suggèrent qu'une énorme variabilité existe chez les patients implantés quant à leurs habiletés à pouvoir percevoir et apprécier la musique à travers leurs implants. De plus, les facteurs qui contribuent à cette vaste variabilité de performance après l'implantation cochléaire sont divers et peu explorés. L'objectif de cette thèse était donc d'examiner les fondements neurologiques qui expliquent cette variabilité dans la perception musicale après l'implantation en utilisant la neuro-imagerie.

La première étude a exploré les applications et les limitations des techniques courantes de neuroimagerie, incluant la « near-infrared spectroscopy » (fNIRS), chez les patients implantés. Cette étude a résumé la littérature existante de la neuroimagerie fNIRS dans les récipients cochléaires adultes et pédiatriques et a fourni de futures directions pour des applications potentielles cliniques ou scientifiques de cette technologie prometteuse.

La deuxième étude a examiné la corrélation entre les mesures comportementales de la perception musicale et l'activation du cortex auditif chez les patients implantés en utilisant la fNIRS, et a tenté d'identifier les facteurs spécifiques aux patients qui modulent cette relation. Cette étude cas-contrôle prospective a inclus 27 patients avec implants cochléaires et 25 contrôles avec une audition normale. La perception musicale a été évaluée avec un outil comportemental, la « Montreal Battery for the Evaluation of Amusia » (MBEA). La neuroimagerie fNIRS du cortex auditif a été mesurée lors de la perception musicale, rythmique et spectrale. Les résultats de cette

étude ont démontré que des mesures fiables ont été enregistrées avec la fNIRS chez tous les patients recrutés. Les résultats ont également suggéré que des régions d'activation corticale plus larges pourraient être liées à une meilleure performance sur les tâches comportementales.

Somme toute, les résultats de cette thèse fournissent les arguments qui appuient la fNIRS en tant que technologie sécuritaire et fiable permettant une examen neurologique objectif de la perception musicale qui est associé à la performance comportementale chez les patients avec un implant cochléaire. Ultimement, ces données vont contribuer à l'avancement des stratégies visant l'amélioration de l'expérience musicale globale chez les patients implantés.

Contribution of authors

This thesis consists of two multi-authored manuscripts. The first manuscript “Functional near-infrared spectroscopy for neuroimaging in cochlear implant recipients”, by J Saliba, H Bortfeld, DJ Levitin, and JS Oghalai is presented in Chapter 3. The second manuscript, “Auditory cortical activity during cochlear implant-mediated perception of music using functional near-infrared spectroscopy” by J Saliba, JS Oghalai, H Abaya, H Bortfeld, DJ Levitin, and A Lehmann is presented in Chapter 4. As lead author of both studies, Dr Saliba planned and performed all data analyses, wrote the manuscripts and responded to reviewers following submission of the first manuscript. Dr Oghalai provided guidance and support for all studies with respect to study design, data analysis, manuscript preparation and revisions. Dr. Alexandre Lehmann provided guidance and support for the second study’s design, data analysis, manuscript preparation and revisions. Drs. Bortfeld and Levitin assisted with study design and manuscript writing for both studies. Mr. Abaya assisted with data collection for the second study. Data collection for the second manuscript was conducted in the Oghalai Lab at Stanford University (California, USA).

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Chapter 1: Introduction

Rationale

While music perception in cochlear implant recipients is generally poor, an enormous variability exists in their ability to perceive and enjoy musical stimuli [1,2]. Studies suggest that CI users tend to perform poorly on pitch recognition tasks, whereas rhythmic perception remains relatively intact after implantation [3,4]. Positron emission tomography (PET) and functional magnetic resonance imagery (fMRI) studies of music perception have provided the basis for a model of functional musical processing in the brains of normal-hearing (NH) individuals. Together, they revealed preferential activity in response to music over noise and speech in association areas of the superior temporal gyrus. They also revealed differences in hemispheric lateralization for the processing of spectral (right association auditory cortex) and temporal (left primary auditory cortex) information and stimulation of the limbic system during music-induced emotion [5-7]. However, the neuroanatomical basis for music processing in CI users remains poorly understood due to a paucity of imaging studies in that population. This is likely related to the inherent limitations of various neuroimaging modalities in addressing this patient population.

Functional near-infrared spectroscopy (fNIRS) is an emerging optical neuroimaging modality that offers benefits in the cochlear implant population because it is safe, non-invasive and compatible with a CI device. As such, fNIRS has the potential to provide insight into the cortical changes that take place in patients with cochlear implants. However, its use in the field of CI research has been limited by practical and technological constraints and by lack of awareness within the scientific community.

In view of the above issues, the goal of this thesis is to better clarify the neural basis underlying the wide variability in music perception outcomes following implantation. This will be achieved by obtaining objective brain-based measures of music perception in CI users using fNIRS, a reliable and safe neuroimaging technique.

Specific objectives

The objectives of this thesis are:

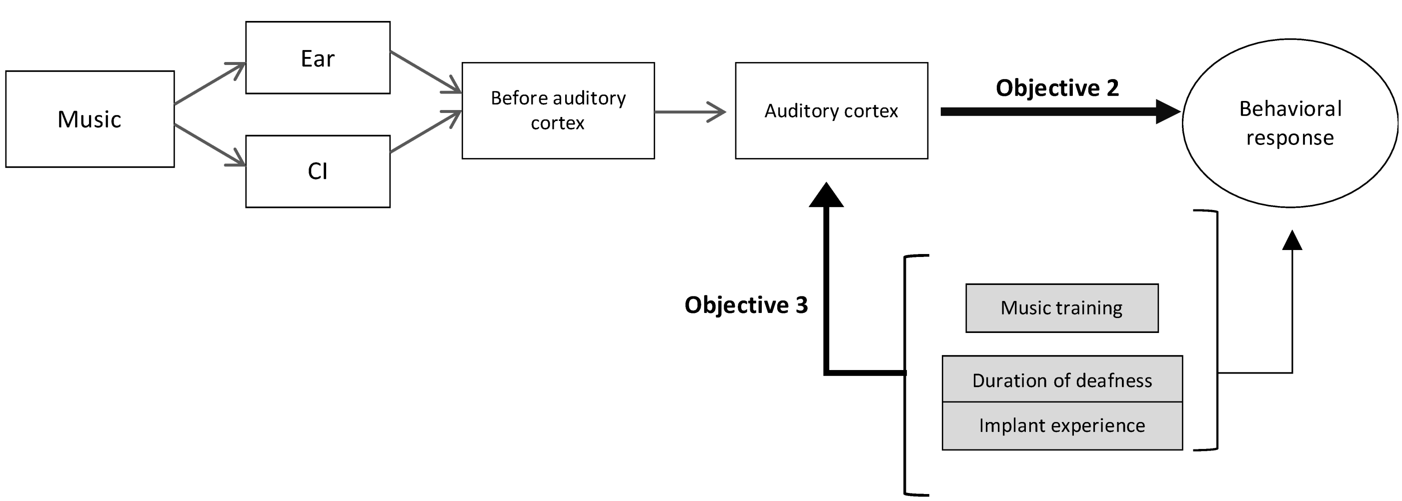
(1) To review the applications and limitations of fNIRS in the CI population, comparing it with traditional neuroimaging methods.

(2) To test the hypothesis that behavioral measures of music perception in CI users correlate with auditory cortical hemodynamic response areas measured with fNIRS.

(3) To determine the patient-related factors that influence music perception outcomes in CI users and to examine the moderating role of these factors on the relationship between music perception and cortical activation.

These objectives are shown schematically in the following diagram:

Model for music processing in CI users



Chapter 2: Literature review

Sound processing through a cochlear implant

CIs are surgically implanted devices designed to restore hearing in some patients with sensorineural hearing loss. They replace the function of the cochlea by converting sound into an electric signal that stimulates the cochlear nerve directly. The external component of the device consists of a microphone, processor and transmitter. The internal surgically implanted device is composed of a receiver-stimulator (which directly underlies the transmitter via magnetics), an inductive link and an electrode array. In short, sound reaches the outer microphone and is then processed and converted into electrical signals by the external processor. This information is subsequently sent to the transmitter which conveys this information transcutaneously via a radiofrequency signal to the antenna of the internal receiver-stimulator. The latter decodes the electric signal which is then relayed through the inductive link towards the electrode array located in the scala tympani chamber of the cochlea. The electrodes located on the array directly stimulate the cochlear nerve fibers which then transmit the signal through the central auditory processing pathways to ultimately generate the perception of sound.

A multichannel device is the current standard for CIs, delivering electric signals to different locations of the cochlea following a tonotopic organization. This frequency-to-place coding improves delivery of spectral cue information, as stimulation of different electrodes along the array elicits different pitch percepts in implant recipients. While some CI models offer electrode arrays of up to 22 electrodes, only eight to ten are functionally utilized at any one time to avoid interaction between the electrical fields of adjacent electrodes [8]. This phenomenon, termed channel interaction, is responsible for the degradation of the output electrical signal. Temporal coding strategies such Continuous Interleaved Sampling have been designed by manufacturers as a mean to reduce channel interaction [9]. This processing paradigm delivers sequential bipolar currents to the electrodes with timing offsets in order to avoid simultaneous stimulation of adjacent electrodes. Manufacturers have also pioneered various spectral emphasis strategies in an effort to improve the spectral resolution of the implants which, until recently, was limited by the number of stimulating electrodes [8]. Spectral Peak Extraction (SPEAK) and Advanced Combination Encoder (ACE) are examples of such advances in spectral coding: the largest spectral peaks of the input signal are selected, and the corresponding electrodes (typically between 6-8) are stimulated at a low frequency in a sequential manner from the cochlear base to the apex [10]. This improved spectral resolution allows for better pitch perception that may cater to music listeners.

Recent trends in cochlear implantation involve atraumatic electrode insertion techniques in an effort to preserve hearing [11]. Studies have shown that in patients with profound high frequency hearing loss with preserved low-frequency hearing, combining electric and acoustic stimulation improved performance, particularly in noisy environments and during music perception [12]. Such hybrid (or electroacoustic) devices have a shorter electrode array that preserves the native acoustic function of the apical cochlea responsible for low frequency hearing, while delivering electrical stimulation to the basal cochlea most sensitive to high frequency sounds. It is likely that future CI candidacy will consider the findings of these studies and include patients with residual low-frequency hearing preimplantation.

Neural mechanisms of music perception in normal hearing listeners

In order to better appreciate the difficulties of music perception through cochlear implants, an understanding of how the brains of NH listeners process music is first required. In recent decades, studies in cognitive neuroscience have attempted to clarify the neural correlates of musicality. Two alternate views have emerged. In the first view, a large number of neuroimaging studies favor a significant neural overlap between music and speech processing, based on the hypothesis that those two complex auditory stimuli share common properties[13,14]. An fMRI study by Abrams et al. (2011) revealed an overlap in the activation of bilateral prefrontal and temporal regions during music and language processing, although the pattern of neural activation was distinct between music and speech [15]. In another example of this shared neuronal circuitry, Levitin and Menon (2003) found Broadmann area 47 to be associated with the processing of both linguistic and musical structures [16]. In the second view, investigators believe that a functional segregation exists for music and speech processing within the temporal lobe. This view is supported by the observation from lesion studies that speech and music can be affected in a selective manner by certain auditory cortical deficits: while losing their ability to understand speech, some patients will still appreciate music, and vice-versa [17]. Various neuroimaging studies also point towards a neural network specific to music processing. Several fMRI studies revealed a region in the anterior portion of the superior temporal gyrus (planum polare) that showed preferential activity in response to musical stimuli [18,19]. The authors also hypothesize that the planum polare is involved in higher-order music analyses such as extraction of melodic information[18]. Using a novel technique of signal analysis – fMRI adaptation paradigm – Armony and colleagues not only point toward the existence of a region in the anterior superior temporal gyrus that responds more strongly to music than voice, but their results also provide strong support for the presence of “music-preferring” neurons in this area [20]. Rogalsky’s results also highlight the existence of overlapping yet distinct networks for music and speech processing within the same cortical areas: although both stimuli activated bilateral superior temporal gyri, speech elicited more ventrolateral areas, whereas music elicited more dorsomedial regions extending into the parietal lobe[19]. In summary, the existing body of evidence supports both hypotheses of substantial neural overlap between music and speech processing, with areas of segregation for music-specific responses among those regions[21].

Although the debate on the relation between music and language processing is still controversial, most neuroscientists agree that a distinct pattern of music processing can be observed in the temporal lobe: while the activity of the primary auditory cortex is modulated by basic acoustic attributes, regions distal to the primary auditory cortex – auditory association areas such as the planum polare and planum temporale – are involved in higher-order acoustic analyses[22]. For instance, neuroimaging studies have shown that the right secondary auditory areas in the superior temporal gyrus (surrounding Heschl's gyrus) are key to the processing of pitch information[6,23]. Temporal information, related to rhythm perception, is preferentially processed by left-sided primary (core) auditory areas[7]. Lesion studies have reinforced the concept that pitch and rhythm processing involve the recruitment of separate neural subsystems: cortical damage can interfere with pitch discrimination without affecting rhythm performance, and vice-versa[24,25]. The effects of musical training on brain plasticity reinforce this hierarchical division of labor in the auditory cortex. Several fMRI studies have demonstrated distinct patterns of neural activity in auditory association areas related to musical training. Ohnishi et al. (2001) reported a significant difference in the degree of activation between musician and non-musicians of the bilateral planum temporale and left posterior dorsolateral prefrontal cortex on fMRI. Interestingly, the degree of activation in those areas was also correlated with the age of onset of musical training [26]. A study of absolute-pitch musicians showed a correlation between gray matter volume of the right Heschl's gyrus and absolute pitch proficiency, as well as the activation of a distinct neural network in the right planum temporale [27]. Overall, evidence is suggesting that musicians may not only recruit more neural tissue than non-musicians, but that they also use it more efficiently than do nonmusicians[5].

Neural mechanisms of music perception in cochlear implant recipients

While music and language processing in NH subjects have been substantially examined, that literature in CI user is still very scarce. This is likely related to the inherent limitations of various neuroimaging modalities in addressing that patient population. For instance, although fMRI boasts an excellent spatial resolution and is the neuroimaging technology of choice in healthy subjects, its magnetic field is incompatible with most cochlear implant devices. Therefore, most investigators rely on other imaging modalities such as PET scanning and electroencephalography (EEG). A PET study by Wong (1999) has shown that speech processing elicited a greater number of more robust foci of activation in the auditory cortex of postlingually deafened cochlear implant, when compared to NH subjects[28]. Recent PET studies by Naito (speech stimulus) and Limb (speech and music stimuli) have not only replicated these findings, but have also shown that CI users recruit brain areas not traditionally utilized for auditory processing, such as the bilateral inferior frontal gyri, the supplementary motor area and the anterior cingulate gyrus[29,30]. The authors hypothesize that the increased recruitment of cortical areas reflects the supplemental effort required to by the brain to process the degraded speech information relayed by the CI device[31]. This may partly be explained by the changes that occur in the brain as a result of cortical plasticity. Conversely, studies have shown that in individuals with long-standing deafness, cross-modal reorganization occurs in which there is a "take-over" of the auditory cortex by visual perception tasks. To date, it is unclear whether a complete reversal of this maladaptive process is possible by reinstating sound input to this auditory cortex with cochlear implantation [32,33].

The neural correlates behind cochlear-implant mediated perception of music have been the subject of even fewer reviews. In fact, Limb et al. (2010) reported the first – and only – neuroimaging study addressing this topic[30]. In that paper, PET was used to compare cortical responses between CI users and NH subjects during language, rhythm and melody stimulation [30]. For both music stimuli, CI users showed greater extent and intensity of auditory cortical activation compared to control subjects. Extratemporal activations were even recorded in CI users during music stimulation in bilateral post-central gyri (rhythm) and inferior frontal gyri (melody). The weakest between-group differences were seen in the melody perception. During behavioral music perception tests, CI recipients performed significantly worse in the melody task, whereas rhythm and language scores were similar between the two groups. The authors concluded that CI recipients may require greater extent and intensity of activation than normal hearing listeners to achieve similar behavior results. The inability of CI recipients to process pitch information accurately could therefore be a reflection of their limited cortical activation[30]. In that sense, a relation between behavioral music performance and degree of auditory cortical activation in CI users could be hypothesized.

A growing body of psychophysical studies in the recent years has better defined the limitations of music enjoyment and perception in CI users. Behavioral measures such as the MBEA (Montreal Battery for the Evaluation of Amusia) and the PMMA (Primary Measures of Music Audiation) have shown that CI users perform poorly on pitch recognition tasks, whereas rhythmic perception remains relatively normal after implantation[1,3,4]. Music perception and enjoyment are significantly affected by this limitation in pitch recognition, since pitch relationships comprise the basis for melodic and harmonic relationships in music[31]. Studies have shown that appraisal ratings are significantly lower after implantation, with some CI users even describing music as "aversive"[34-36]. Listening habits are also affected post-implantation, as listing time decreases and preference of musical styles changes [35,37]. The challenges CI users face in processing a complex auditory stimuli such as music can be explained by a number of technological, acoustical and biological constraints [2,31]. While many of these constraints have been previously addressed in the literature, the neural mechanisms underlying music processing through a CI have been under-investigated and therefore remain poorly understood.

Preface to Chapter 3

The neural mechanisms underlying music processing through a CI have been under-investigated and remain poorly understood. In order to better understand the factors influencing outcomes following implantation, it is necessary to examine the neural substrates involved in the perception of auditory stimuli with a CI. This knowledge could potentially allow clinicians and researchers to predict the expected results for an individual CI patient prior to implantation. Functional neuroimaging technologies can provide an insight into the cortical changes that take place in patients with CIs and are the ideal tools to undertake such a task. However, measuring cortical responses in CI recipients has been challenging, as currently available modalities are not well suited to research involving CI users because technologies employing strong magnetic fields cannot be used with most CIs that contain ferric materials. Clearly, an alternative neuroimaging method was required to facilitate studies of auditory processing in CI recipients. The next chapter will review the currently available neuroimaging modalities that can be used in the CI population and will summarize the existing literature on the use of fNIRS neuroimaging in adult and pediatric CI recipients.

Chapter 3: Functional near-infrared spectroscopy for neuroimaging in cochlear implant recipients

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Abstract

Functional neuroimaging can provide insight into the neurobiological factors that contribute to the variations in individual hearing outcomes following cochlear implantation. To date, measuring neural activity within the auditory cortex of cochlear implant (CI) recipients has been challenging, primarily because the use of traditional neuroimaging techniques is limited in people with CIs. Functional near-infrared spectroscopy (fNIRS) is an emerging technology that offers benefits in this population because it is non-invasive, compatible with CI devices, and not subject to electrical artifacts. However, there are important considerations to be made when using fNIRS to maximize the signal to noise ratio and to best identify meaningful cortical responses. This review considers these issues, the current data, and future directions for using fNIRS as a clinical application in individuals with CIs.

Keywords: fNIRS, cochlear implant, hearing loss, neuroimaging, speech

1. Introduction

Cochlear implants (CI) have restored hearing to over 90,000 individuals in the United States in the past 30 years [38]. Significant advances in speech processor design, signal processing and surgical techniques have resulted in progressively enhanced performance (Rubinstein, 2004; Roland et al., 2006; Srinivasan et al., 2013). As a result, cochlear implantation has become a highly successful prosthetic solution to replace the function of a sensory organ. Intervention with deaf children has been particularly successful: many children who would otherwise have been placed in schools for the deaf and taught sign language are now learning alongside mainstream peers in a regular classroom environment. The primary goal of cochlear implantation is now open-set auditory-only speech understanding in everyday listening environments. However, while the majority of implant recipients achieve this goal, many still perform poorly [39,40].

The factors that contribute to the wide variations in individual outcomes following cochlear implantation are diverse and not completely understood [41,42]. Numerous reports have identified age of implantation as a strong predictor of better CI outcome (e.g., the younger, the better) [43-45]. Investigators have also demonstrated that children who communicate orally achieve better speech perception skills than children who use visual sign communication [46,47]. Finally, family income predicted language outcomes in pediatric CI recipients [48]. In order to more fully understand how such neurobiological, cognitive, and societal factors influence language outcomes post-implantation, it may be beneficial to examine the neural processing during the perception of auditory stimuli through a cochlear implant. Together with behavioral measures, neurophysiological indicators have the potential to guide post-implant programming in support of deaf patients' speech and language outcomes and, eventually, even predict results for an individual CI patient before implantation occurs.

Functional near-infrared spectroscopy has already been shown to be a reliable neuroimaging modality in both adult and pediatric populations [49-51]. Generally, reviews of this literature have focused on the use of fNIRS in research on language development and language processing in healthy populations [50,52-55]. More recently, an emerging body of reviews addresses the imaging instrumentation and methodology, as well as approaches to statistical analysis of fNIRS data [56-59]. However, most relevant to CI research is the fact that fNIRS is compatible with these devices. This review explores applications and limitations of fNIRS in the CI population, comparing it with traditional neuroimaging methods. We summarize the existing literature on the use of fNIRS in adult and pediatric CI recipients, and conclude by outlining possible directions for future research and clinical applications using this promising imaging technique in the CI population.

2. Neuroimaging options in cochlear implant users

Because auditory perception occurs within and beyond the auditory cortex, neuroimaging has the potential to provide an additional clinical measure for assessing whether the electrical stimulation of the cochlea by the CI is reaching and stimulating auditory-specific cortical regions of the brain similar to normal-hearing subjects [60,61]. Such information can supplement behavioral tests, which are often limited in young CI users [62-68]. However, there are inherent limitations in the use of all of the currently available neuroimaging modalities in CI recipients, as outlined below and summarized in Table 3-1.

Functional neuroimaging attempts to identify the brain systems responsible for different behaviors by comparing brain activity during contrasting states [52,69]. The logic is that neurons in different areas of the brain associated with specific cognitive processing tasks generate electrical signals when they are active. As a result of this activation, the metabolic needs of neurons change: increased oxygen demand results in increased cerebral blood flow and thus oxygen delivery to that area, with a consequent decrease in deoxygenated hemoglobin (HbR) [70]. Certain neuroimaging modalities, such as EEG, measure this neural activation directly by recording the average electric field potential at different regions of the scalp. In contrast, metabolic neuroimaging methods, such as fMRI, PET, and fNIRS, are indirect, surrogate measures of neuronal activity [71-73].

Although functional neuroimaging technologies have the potential to provide insight into the cortical changes that take place in patients with cochlear implants, obtaining meaningful measurements of cortical responses in CI recipients has proven challenging. This is primarily because the traditional imaging methods have limitations when used in implanted patients, and so alternative neuroimaging strategies have been sought. In this context, functional near-infrared spectroscopy (fNIRS) has been a welcome addition to a limited choice of neuroimaging modalities suitable for use in CI recipients. Here we outline the primary techniques and assess their appropriateness for use in combination with CIs. Because it is important understand the benefits and downsides to each technique when selecting an imaging modality, we briefly

Table 3-1. Characteristics of the functional neuroimaging techniques currently available for research involving cochlear implant users. See explanations in text, Sections 2.1-2.3.

Technique	**Spatial resolution**	**Temporal resolution**	**Cochlear implant compatibility**	**Flexibility in auditory stimuli paradigm**	**Potential for use in infants**	**Comments**
fNIRS	+ + +	+ + +	Yes	Yes	Yes	
fMRI	+ + + + +	+ +	No*	No**	No	* Structural imaging possible ** Loud background noise
PET	+ + + +	+	Yes	No*	No	* Limited to block design paradigms
EEG	+	+ + + + +	Yes	No*	Yes	*Limited to sound bursts/clicks
MEG	+ +	+ + + + +	No*	No**	Yes	* Requires use of magnet-less implant and simultaneous radio frequency head shield ** Limited to sound bursts/clicks

fNIRS: functional near-infrared spectroscopy, fMRI: functional magnetic resonance imaging, PET: position emission tomography, EEG: electroencephalography, MEG: magnetoencephalography review several commonly-used techniques including fMRI, PET, EEG, and MEG, before moving on to an in depth explanation of fNIRS.

2.1 Functional MRI

Functional MRI provides high spatial resolution and is often the neuroimaging technology of choice in unimplanted subjects. However, conventional CIs are incompatible with fMRI for several reasons. The primary reason is that CIs contain internal magnets and ferromagnetic components, including a coil used to transcutaneously relay data from the external processor to the surgically implanted components [74-76]. Such ferromagnetic implants exposed to electromagnetic fields or radiofrequency energy may heat, induce a current, or become dislocated [77-79]. Thus, the most important concern in using fMRI to study a subject with a CI is patient safety. Furthermore, the magnet and coil interact with the electromagnetic fields found in MRI scanners, producing interference that can disturb data transfer, and malfunction of the implant can occur due to demagnetization of the CI internal magnet via the imaging magnet [75,80]. Finally, CIs produce considerable artifacts on the MR image, obscuring cortical regions proximal to the internal magnet [81]. Thus, these signal-void areas can compromise accurate diagnosis of certain medical conditions when used for medical imaging and make it nearly impossible to measure activity within the ipsilateral temporal lobe when used for functional imaging.

In response to these limitations, certain manufacturers have designed CIs with removable internal magnets. Unfortunately, large artifacts often remain on the MRI even after the internal magnet is removed [82]. Other models of CI have MRI-conditional internal magnets that do not need to be removed prior to scanning. Regardless of the status of the internal magnet, the external processors for all CI devices are MRI unsafe [79] and the radiofrequency fields generated by the MRI interfere with the transcutaneous radiofrequency link between the external and internal coils [83,84]. Auditory stimulation by the implant during imaging is therefore generally precluded, though anatomical images can be acquired for medical purposes [49,85-87].

The limitations of using fMRI with the CI population extend beyond equipment incompatibility issues. MRI is subject to movement artifacts [50], requiring subjects to remain completely still and to avoid overt vocalizations while in the scanner. In infants, this translates into the need for restraints and even sedation and/or anesthesia. Sedatives and anesthetics, of course, alter brain activity and therefore change cortical responses to auditory stimuli [88]. Such circumstances considerably restrict the use of fMRI in this age group.

It is also important to consider that fMRI is a noisy imaging modality, which introduces a potential confounding effect as the background noise cannot be matched between deaf and hearing participants [89]. Moreover, the acoustic noise associated with fMRI creates an intrusive testing environment for younger children and disturbs the presentation of auditory stimuli relevant to CI users [55]. Finally, the BOLD (Blood Oxygenation Level Dependent) signals obtained using fMRI relate to changes in HbR only and do not directly convey information about HbO.

2.2 PET scan

Nuclear functional imaging techniques such as PET scans have more frequently been used in studies involving CI users. Previous investigators employed PET scans to examine various auditory cognitive processes in the CI population [28-30], and several dedicated reports have even been published for reviewing the use of PET scans in language processing research on CI recipients [46,49]. Several factors account for the popularity of this neuroimaging modality for use with CIs among the scientific community. First, PET is fully compatible with CIs. It also has good spatial resolution and, as with MRI, it can image activity in deep, subcortical structures [56]. Because PET is a relatively quiet imaging modality, it is suitable for studies involving auditory stimuli. Finally, it is tolerant to subtle subject movements thanks to rapid image acquisition times, a significant advantage over fMRI (Crosson et al., 2011).

The significant drawback of using this imaging modality is the exposure of the research subjects to radiation and the necessary limitation in the number of scans that this implies. The radioactive tracers or carrier substances need to be injected into the blood stream, which many subjects find aversive. For these reasons, PET is rarely used in research studies involving children. Though understandable, this is unfortunate because children are a demographically important age group within the CI population. The use of PET to study neuroplasticity post-implantation is also ethically challenging, as measuring such changes would require sequential longitudinal testing in the same subject [49]. Limited temporal resolution, or the accuracy on a temporal scale with which a neural event can be characterized [52], is another shortcoming of PET. This is because PET's ability to resolve neural events is on the order of tens of seconds compared to only a few seconds for fMRI [56]. Such limited temporal resolution requires averaging over long blocks of events; higher sampling rates are generally preferred in functional studies because they allow the use of event-related paradigms, which offer greater flexibility and more precision in experimental inquiry [69].

2.3 EEG and MEG

Unlike fMRI and PET, EEG and MEG directly measure the electrophysiological response of neural activation. The resulting advantage of this technique is an unrivaled temporal resolution in the sub-millisecond range [70], however at the expense of spatial resolution (Posner and Levitin, 1997). Studies have shown that auditory evoked potentials recorded in EEG provide a useful objective metric of performance in CI patients [71,72]. It is therefore not surprising that the EEG literature in CI users is abundant and, indeed, has greatly contributed to the understanding of auditory processing in this population [90,91]. In addition, the combination of the high temporal resolution and an excellent safety profile make EEG and MEG ideally suited for follow-up studies requiring several successive assessments, such as those investigating cortical plasticity following implantation [74,76]. Finally, EEG is tolerant to subtle movements and can even be used with fully awake infants.

On the other hand, as mentioned, EEG and MEG offer relatively poor spatial resolution due to the inverse Poisson problem: the location of activity within a sphere is ambiguous when measuring from the surface of that sphere (Posner and Levitin, 1997). While the reconstruction of brain responses to specific cortical regions is possible (Ferree et al., 2001; Song et al, 2015), the accuracy of this localization remains inferior to other modalities such as fMRI or PET [80].

Data corruption by the electrical components of the implant is another major limiting factor for the use of EEG in combination with CIs. To minimize the electrical artifacts produced in EEG recordings, only short auditory stimuli such as tone bursts or clicks can be employed in CI studies, which significantly limits the flexibility of the experimental paradigm [74]. Despite the various techniques that have been described to filter this artifact, the interpretation of auditory evoked potentials in EEG remains challenging [71,92]. Additionally, MEG measures very weak magnetic fields that can only be recorded in magnetically shielded rooms equipped with detectors that are highly sensitive to minute changes in magnetic signals [52]. Similar to fMRI, MEG instrumentation interacts with the internal magnet of most CI models, precluding any useful recording. To successfully monitor neural activity in CI users using MEG, certain conditions must be fulfilled. This unique experimental setup is described by Pantev [93], who reported the only MEG study involving CI users. The basis for the methodological success of this study is twofold. First, the two participants enrolled were recipients of Clarion (Advanced Bionics, Valencia, CA) magnet-less implants – now withdrawn from the market. Second, a unique radio frequency shield was applied between the head of the patients and the MEG device, preventing interference from radio frequency signals transmitted by the CI. Such setups, however, are very rare and extremely costly.

3. fNIRS

Before fNIRS was adapted for use in people with CIs, PET was reported to be the only technique suitable for measuring brain responses in the CI population for all of the reasons outlined above [49,94]. Because the concepts, features, and instrumentation of fNIRS have been described in substantial detail in previous reports [50,53-55], we will only briefly address them in this review. Here we focus primarily on the characteristics of fNIRS that are relevant to its use with the CI population.

3.1 General principles

fNIRS is an optical imaging technique: it uses near-infrared (NIR) light to detect changes in cerebral blood flow as a proxy for neural activation. When a beam of light is directed onto tissue, three factors can interfere with its undisturbed propagation (i.e. transmission) through it: reflection/refraction, absorption and scattering (Niemz, 2002). The contribution of reflection/refraction can essentially be ignored in opaque media such as the skull. The intensity of the transmitted light therefore depends on the amount of non-absorbed and non-scattered photons[55]. Biological tissues preferentially absorb light in the visible spectrum, while being relatively transparent to light in the NIR wavelengths (650-1000 nm) [95]. As a result, NIR light can penetrate through superficial biological layers, enabling sampling of deeper tissue structures. For neuroimaging, this means that fNIRS can effectively probe the surface of an adult brain to a depth of up to 1.5 cm [53].

fNIRS is capable of measuring changes in cerebral blood flow because hemoglobin is the main pigmented molecule in human tissues that is present in clinically significant quantities to exhibit oxygenation-dependent absorption of light in the NIR spectrum (Delpy and Cope, 1997). In tissues, hemoglobin exists in an oxidized (oxygenated hemoglobin, HbO) and reduced (HbR) form, each characterized by a unique absorption spectrum. The aim of NIRS neuroimaging is to quantify the concentrations of these two hemoglobin chromophores in the tissues traversed by NIR light. This is possible using the Beer-Lambert Law, an equation that describes the light absorbance (A) at a given wavelength (λ) in a medium [52]:

$$A = -\log\left(\frac{I}{I_o}\right) = c \,.\, \varepsilon_\lambda \,.\, l$$

Shining light of an appropriate wavelength at a given intensity (incident light, I) on the head, and measuring the intensity of the light that leaves the tissues (transmitted light, I_o) allows for the calculation of the concentration of the medium, "c" (i.e. the concentration of HbR, HbO and total hemoglobin). This concept assumes that the molar extinction coefficient of the medium at that specific wavelenght (ε_λ) and the optical pathlength "l" in the tissues (the path the light travels between the source and the detector) are known.

The application of this physical principle forms the basis of fNIRS neuroimaging. Of course, other factors need to be considered. Light scattering caused by skin, hair and skull, also contributes to light attenuation in tissues, resulting in an unknown light loss that needs to be accounted for (Delpy and Cope, 1997). Furthermore, light does not travel through biological tissue in a straight line. The Beer-Lambert Law was therefore modified to take into account the scatter and the non-linear trajectory of light in tissues, referred to as the differential pathlength factor (Cope et al., 1988). These two factors cannot be measured directly using continuous-wave NIRS systems (see below), therefore only changes in HbO and HbR concentrations, as opposed to absolute values, can be obtained. A detailed description of the mathematical model underlying light absorption in scattering media can be found elsewhere (Gervain et al., 2011; Hoshi, 2003; Sassaroli and Fantini, 2004).

Practically speaking, fNIRS is performed on human subjects by placing a light source and a light detector adjacent to each other above the brain area to be measured. This source-detector pair is called a channel. A convex banana-shaped tissue region is sampled, corresponding to the light path through the tissue between the source and detector. The depth of penetration of the NIR light in brain tissue is approximately half of the source-detector distance. To reach a clinically relevant depth of cortical area, the source-detector distance should be 2-3 cm in infants and 3-5 cm in adults [50]. The choice of the wavelength pair is also important, as it affects the quality of the fNIRS signals. Ideally, one wavelength should be sensitive to HbO; the other to HbR. This is possible because HbO and HbR demonstrate differential absorption in the NIR spectral range (except at the isosbestic point, where the extinction coefficients of these two chromophores are equal). Generally, wavelengths below the isosbestic point are used to measure HbR responses (below 760–770 nm), whereas longer wavelengths are more sensitive to HbO (up to 920 nm) (Boas et al., 2004). Theoretical models also revealed that the highest signal-to-noise ratios were obtained if one wavelength was below 720 nm, and the other higher than 730 nm (Uludag et al., 2004). The 690 nm and 830 nm pair is commonly reported in fNIRS literature, but a variety of other systems capitalizing on different wavelength contrasts are commercially available [54].

Three different fNIRS instrumentation techniques are currently available, and they vary in the type of illumination employed [96]. The first modality, continuous wave (CW) light, is the most commonly used and the least costly. It is based on constant tissue illumination and simply measures changes in light attenuation as it passes through the head. This technique does not allow calculation of light scattering or optical path length in tissues and, as a result, can only determine relative changes in HbO, HbR and total hemoglobin concentrations [58]. However, relative values of hemodynamic parameters are usually sufficient in functional brain studies. The last two techniques, time-domain (TD) and frequency-domain (FD), are equivalent in that they both measure the time needed by light to travel through tissues (i.e. time of flight) to determine optical path length (Wolf et al., 2007). They differ in their approach to time of flight measurements, and in the resulting instrumentation that this implies. TD systems emit extremely short pulses of light into tissue, and directly measure the arrival times of the scattered photons that emerge (Torricelli et al., 2014). Such recordings require very sensitive photon-counting detectors. The time of flight multiplied by the speed of light in the tissue provides optical path length. In contrast, FD technique uses intensity-modulated light to illuminate the brain at very high frequencies, and measures both the attenuation and the phase delay of the emerging light (Wolf et al., 2007). Time of flight is then obtained by Fourier analysis of the phase delay, and can be used to calculate optical path length. The resulting advantage of TD and FD imaging is that knowledge of optical path length allows calculation of absolute values of HbO, HbR and total hemoglobin concentrations. On the other hand, such systems are associated with higher costs, bulky instrumentation, and slower acquisition times. The characteristics of the different fNIRS technique have been described in much greater detail in recent reviews [58,97].

3.2 Advantages, limitations and considerations for using fNIRS with CIs

Compared to other techniques, fNIRS has several clear advantages that encourage its use in CI research. One of its most appealing features is its full compatibility with CI devices.

Owing to the optical nature of the technology, fNIRS data are not corrupted by the electronic or ferromagnetic components of the CI device during acquisition. PET is the only other neuroimaging modality that provides a matching level of compatibility. However, unlike PET, fNIRS does not require injection of tracer substances in the blood stream and does not expose individuals to radiation. The number of examinations is therefore not restricted, and repeat assessments through longitudinal studies can be performed. fNIRS is also ideally suited for research involving young infants. Measurements can be recorded without the need for sedation or restraints because it is robust to motion artifacts. In fact, recording during overt speech in even possible [50]. This is of great significance for CI investigators, as a large field of CI research involves the pediatric population.

Good research tools are safe, but also practical. To carry NIR light, fNIRS uses optic fibers that are light, flexible, and therefore suitable for a range of head positions and postures. Some centers replaced the plastic optic fibers with glass optic fibers and have reported reduced weight of the optic bundles on the headgear [54]. Furthermore, fNIRS requires only a compact measurement system. The setup typically consists of a mobile cart carrying a computer tower and monitor, an optical NIRS module and the optical fibers connected to that module. This increases portability and allows for measurements in non-intrusive environments and even in clinical settings. PET scans, on the other hand, can only be performed in a radiation-proof radiological suite and require the presence of a radiochemist and a cyclotron for the production of radioisotopes [52]. Advances in optical technology have even allowed the production of a wireless, completely wearable, multi-channel fNIRS system suitable for use in unrestrained settings [57]. Cost is another important factor to consider when choosing a research instrument.

fNIRS is among the most affordable neuroimaging modalities, after EEG. There are no disposables and minimal maintenance is required. In comparison, the instrumentation and maintenance fees associated with MRI, PET and MEG are on the order of millions of dollars [56].

The temporal resolution of fNIRS is the highest among the hemodynamic neuroimaging techniques, reaching up to 100 Hertz (Hz) with CW systems [98]. Although inferior to EEG and MEG by one order of magnitude, this fine temporal resolution allows the use of event-related paradigms and allows for nuanced examination of the temporal dynamics of cortical blood flow. The spatial resolution of optical topography is typically estimated at 1 cm [96], enabling the localization of brain responses to specific cortical regions with reasonable precision. The spatial resolution is dependent on the arrangement of source-detector fibers on the scalp. Increasing the density of channels, among other things, achieves finer sampling of the cortex [99]. At our institution, we transitioned from a four channel system to a 140 channel system, allowing us to generate topographic activation maps of the auditory cortex [100,101]. It is even possible to generate three-dimensional images of the optical properties of the brain given a sufficient number of sources and detectors placed around the head [99]. This technique, called optical tomography, is costly and is usually restricted to young infants, as adults' larger heads usually result in too much light attenuation [102]. Another advantage of fNIRS is that it offers quantitative monitoring of HbO, HbR, and total hemoglobin, generating a more complete evaluation of the cortical hemodynamic response than the fMRI BOLD response which tracks HbR [58]. Lastly, the fNIRS hardware is silent, which makes it ideal for the presentation of accurate auditory stimuli in an acoustically-quiet environment, and artifact-free response measurement.

The major spatial limitation of NIRS is that it only probes a thin top layer of the cortex, up to 1.5 cm deep [103]. This is a considerable drawback for cognitive studies that aim to investigate deep regions such as the brainstem, basal ganglia, or amygdala [99]. However, a substantial amount of research can be done probing the upper layers of the auditory, visual, somatosensory or frontal cortices in CI research. Depth resolution is also highly dependent on the age of the subjects and varies somewhat from region to region even within a particular age group [104]. In adults, thicker scalp soft tissues and skulls significantly restrict NIR light penetration, impacting the accuracy of the recording. Deeper neural activity can be probed by increasing the source-detector distance, although at the cost of lower signal-to-noise ratio due to a reduction in the number of transmitted photons.

Good contact between the optodes and the skin of the scalp is also critical for a high signal-to-noise ratio (SNR) and a good quality recording. Hair is a nuisance in fNIRS recordings because (1) it interferes with this contact and (2) hair pigments significantly scatter and absorb NIR light and therefore attenuate the detected signal. In subjects with thick, dark hair, a researcher can spend a considerable amount of time trying to optimize the positions of the optodes to maximize the SNR. The use of gel can help to keep hair pushed out of the way. Nevertheless, the best recordings often come from subjects who are bald or have thin, blond hair — this makes fNIRS particularly suitable for work with infants.

Another drawback to fNIRS is the need to separate signals of cerebral origin from those of extra-cerebral tissues. For instance, blood volume changes in the scalp and within the muscles beneath the optical probes create noise in the fNIRS recordings and must be filtered during data analysis. Physiologic noise originating from heart rate and changes in respiratory effort may also be a source of confounding cerebral blood flow signals and must be accounted for during analysis [105]. To remove the noise component from the raw data, analytical strategies must be adopted. While some institutions use their own custom software, others turn to freely available software packages. However to date, there is a lack of a standard method for data analysis in fNIRS [59].

Similar to EEG, MEG and PET, the raw fNIRS data not provide an anatomic image upon which neural activity can be superimposed. Therefore, to localize brain activity to known anatomical locations, the optodes must be carefully positioned according to a standard for the recordings. The 10-20 (EEG) system is often used (Minagawa-Kawai et al., 2008). Once this is done, the optode layout is precisely aligned, and therefore the functional data obtained with fNIRS can be overlaid onto structural MRI images or anatomical atlases, if desired [52].

Certain considerations must be taken into account when acquiring fNIRS data from CI users. Depending on the probe layout and the size of the headset, the external magnet of the CI device can interfere with headset placement over the temporal area. In such circumstances, we simply place the headset over the magnet (Figure 3-1). While this obstructs the scalp contact of certain channels, the remaining channels can still be used. In our experience, however, the external magnet is generally posterior and inferior enough so as not to interfere with headset placement that permits the measurement of responses within the regions of interest, such as primary auditory cortex. Of course, care must be taken not to displace the magnet, as the implant would turn off. Gentle manipulation is also required when placing the headset in the

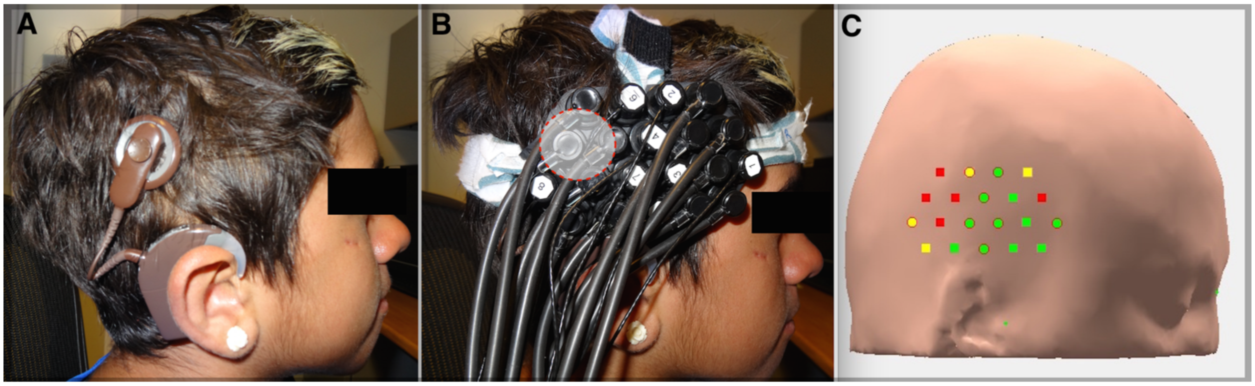

Figure 3-1. fNIRS headset placement over a cochlear implant device. A) The location of the cochlear implant's external magnet and coil interferes with headset placement over the temporal area. B) The fNIRS headset is simply apposed over the magnet (shaded area). C) Diagrammatic representation depicting the quality of scalp contact of the optode array, obtained from custom analytic software using real-time fNIRS recordings. The optodes obstructed by the magnet postero-superiorly lose their scalp contact (red), while the remaining optodes are unaffected and can still be used (green). The status of scalp contact was indeterminate for certain optodes (yellow).

crease between the pinna and the temporal skin to avoid repeated contact with the CI microphone and the resultant unpleasant noise for the CI user.

In an attempt to facilitate recording in the CI population, we designed a custom probe layout and headset at our institution. This arrangement features six light sources clustered in the center of the headpiece and an additional source anteriorly and posteriorly. Detectors are positioned in between (Figure 3-2D). The center-to-center distance between adjacent optodes was 15 mm. Moving away from the checkerboard pattern described in our previous work (Figure 3-2C;[101], this new honeycomb-shaped design allows for a denser configuration of probes, while maintaining an equal number of channels. The result is a smaller and more convenient headpiece suitable for both adult and pediatric subjects, without compromising

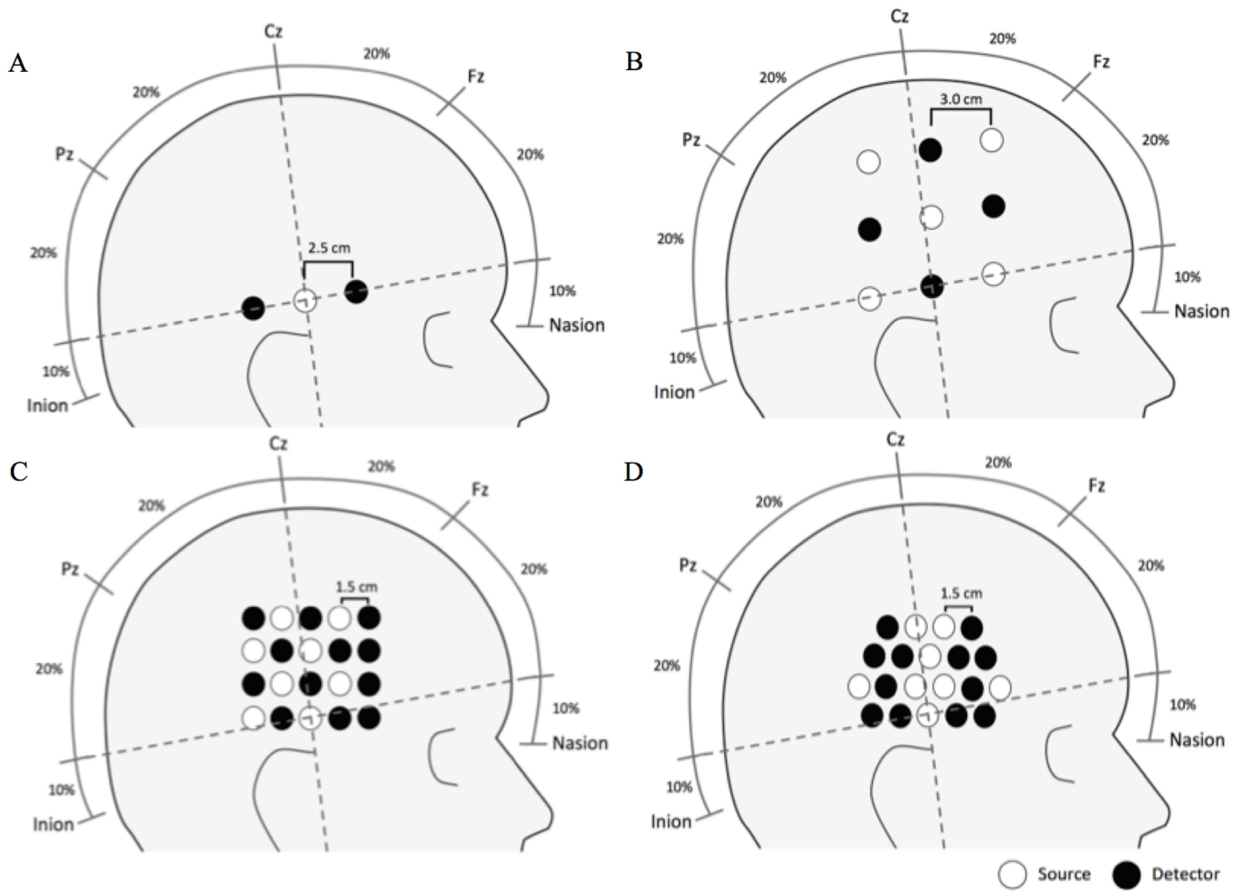

Figure 3-2. Comparison between fNIRS probe layouts previously reported for CI use. A, Sevy (2010); B, Dewey (2015); C, Pollonini (2014); D, Our new honeycomb-shaped headpiece. The optode arrangement in all headsets is based on the International 10/20 system: A is centered at the T3/T4 position; the optode located in the middle of the bottom horizontal line in B, C and D is aligned with the T3/T4 position.

resolution. This dense multi-array headset allows spatial oversampling of a defined cortical area through adjacent channels that cross each other.

3.3 What region(s) of the central nervous system should be studied?

To understand the neural substrates involved in auditory processing through cochlear implants, it is necessary to observe activity within the brain when a sound stimulus is presented [90,106]. Ideally, one would track activity all the way from the level of the auditory nerve, through the ascending auditory pathways in the brainstem to the auditory and auditory-associated cortical regions. However, given its depth limitations, such whole-brain imaging is not possible with fNIRS. Because fNIRS is not a whole-brain technique, choices must be made about what portion of the cortex to record from in order to get the information most relevant to understanding auditory processing through a CI. A substantial body of fMRI data highlights the lateral temporal lobe and superior temporal gyrus (LTL/STG) as foundational to auditory processing at the cortical level.

Several studies have revealed preferential activity for the processing of acoustic parameters such as pitch, noise and spatiotemporal fluctuations in the LTL/STG [107,108]. Selective responses to species-specific vocalizations were demonstrated in the LTL/STG of humans and other mammals [109]. In addition, studies using fMRI and implanted recording electrodes have shown localized responses within the left LTL/STG to phonemes, words, and phrases [110,111]. Of particular relevance to understanding hearing through a CI, Smalt et al. [112] demonstrated rapid neural adaptations in normal-hearing participants exposed to degraded sound, similar to what a CI user experiences.

While fNIRS does not provide whole-brain imaging, it can be used to dissociate music and language processing within constrained cortical regions such as the left and right LTL/STG thanks to stimulus specific processing differences across the cerebral hemispheres.

Neuroimaging studies in normal-hearing subjects using PET and fMRI have previously shown that the left temporal lobe is primarily involved in speech and language processing, while the right temporal lobe preferentially responds to music (Hickok and Poeppel, 2007; Price, 2000; Belin et al., 1998). Furthermore, reports have demonstrated that secondary auditory areas in the right STG (surrounding Heschl's gyrus) are key to the processing of pitch information (Zatorre, 1998; Tramo et al., 2002). Temporal information, on the other hand, is preferentially processed by left-lateralized primary (core) auditory areas (Zatorre and Belin, 2001). Evidence also points toward a functional segregation between music and speech processing within the temporal lobes [15,16]. Armony and colleagues not only revealed the existence of a region in the anterior STG (planum polare) that responds more strongly to music than voice, but their results also provide strong support for the presence of "music-preferring" neurons in this area [20]. Moreover, several fMRI studies have demonstrated that the anterior portion of the STG is involved in higher-order music analyses such as extraction of melodic information [19]. Lesion studies have reinforced the idea that pitch and rhythm processing recruit separate neural subsystems within the auditory cortex: cortical damage can interfere with pitch discrimination without affecting rhythm performance, and vice-versa (Di Pietro et al., 2004; Ayotte et al., 2000). These and other findings indicate that the LTL/STG are the most clinically relevant regions of the cortex to focus on when imaging different classes of auditory perception in CI recipients using fNIRS.

3.4 Data analysis techniques in multi-array fNIRS headsets

A comprehensive review of analysis techniques available for use with fNIRS data is beyond the scope of this paper, and this topic has been extensively reviewed recently [59]. Rather, in the following section we summarize current strategies to analyze recordings from dense multi-array headsets, as they are the most suitable for CI research. As with fMRI, signal pre-processing is initially performed to remove motion artifacts and physiologic noise. The first step requires identification of channels with good scalp contact. At our institution, we filter channels with excessive noise according to their scalp-coupling index [101]. In brief, this technique relies on the fact that adequate scalp contact is characterized by a synchronous cardiac pulse signal recorded by both wavelengths of light emitted from a single probe. While a perfect correlation between each wavelength's cardiac signals is ideal (coefficient of 1), channels with an index threshold above 0.70 are reliable and can be retained.

The next step is motion artifact correction. Relative to hemodynamic-related changes, head movements will cause rapid changes, sharp spikes, and increases in the magnitude of the recorded signals [59]. Previous reports have described the use of external accelerometers to estimate and correct baseline motion artifacts, but this requires additional instrumentation with its related cost and complexity [113]. Many approaches to remove these artifacts without the need for motion sensors have also been described [114,115]. Our preferred technique consists of identifying start and stop times of motion artifacts by bandpass filtering each channel between 0.1-3.0 Hz to remove slow signal drift and by normalizing the intensity of the highest peak of the entire time course. We define peaks in the signal exceeding 20% of the maximum peak intensity as motion artifacts. These are then removed from the raw data by performing linear interpolation between the start and stop time points. Once motion artifacts are corrected, physiologic noise can be removed from the hemodynamic signal. This is usually accomplished by bandpass filtering between 0.016-0.25 Hz. The modified Beer-Lambert law is then used to calculate the relative concentrations of HbO and HbR for each channel and time point (see Section 3.1).

Once signal processing is complete, brain activation can be detected by performing inferential statistics on the fNIRS data. For each channel, all the trials of each stimulus first need to be averaged, a process called block-averaging [58]. The resulting block-averaged hemodynamic response is then compared to a predicted hemodynamic response. Predicted fNIRS responses can be modeled in a manner similar to the analysis of fMRI data [101]. In such models, the HbO concentration rapidly rises after stimulus exposure, reaching a peak in a few seconds. The response then plateaus pending stimulus discontinuation, following which it slopes down until baseline HbO concentration is reached. Physiologically, this corresponds to an augmented blood supply required by the neuronal activation. Conversely, HbR concentration changes in a similar but opposite direction, decreasing during stimulus presentation. The quality of fit is determined by linear regression analysis of the measured and predicted responses,resulting in a T-statistic for each channel. Thus, each source-detector pair (channel) in the headset can be represented by a single number that describes the goodness of the fit. Thes T-statistics are then arranged in a spatial grid representing the position of the channel they derive from within the source-detector array. Multi-array fNIRS headsets provide spatial oversampling in the cortex since many channels cross each other at a given location. The resulting benefit is a reduction of noise in overlapping channels. A topographic (2 dimensional) activation map for each stimulus condition can then be generated by color-coding the T-statistic spatial grid. Alternatively, it is possible to project this colored T-statistic distribution map onto a standard brain image to create cortical activation maps that are easier to visualize and interpret.

4. Review of fNIRS neuroimaging studies in CI recipients

In 2013, fNIRS celebrated its 20th anniversary as a human neuroimaging modality. Jöbsis (1977) was the first to demonstrate the possibility of detecting changes of cortical oxygenation by transilluminating the cranium of anesthetized cats with NIR light [116]. However, it was not until 1993 that this emerging technology was first applied to human brains. That year, four research groups independently published the first single-site fNIRS human adult studies [117-120]. fNIRS has since rapidly gained popularity among the neuroscience and clinical communities. If the number of annual publications reflects scientific enthusiasm, fNIRS has definitely emerged as one of the most popular research fields in the past 20 years: its publications have doubled every 3.5 years and have now reached over 200 per year [121]. Despite this growing interest, the literature reporting the use of fNIRS in the CI population remains sparse. A comprehensive review across multiple databases of published articles mentioning fNIRS and cochlear implantation yielded four papers (Sevy et al., 2010; Pollonini et al., 2014; Dewey and Hartley, 2015; Lawler et al., 2015) and one conference abstract [122].

Sevy and colleagues report the first research application of fNIRS in CI users [100]. The authors used fNIRS to measure speech-evoked cortical responses within four subject cohorts: normal-hearing adults, normal-hearing children, deaf children who had over 4 months experience hearing through a cochlear implant, and deaf children who were tested on the day of initial CI activation. The speech stimuli consisted of digital recordings from children's stories in English. A four channel NIRS 2CE system (TechEn, Inc., Milford, MA) with 2 emitters mounted on a custom headframe was used to sample bilateral auditory cortices (Figure 3-2A). The authors report successfully recording auditory cortical activity using this fNIRS setup in 100% of normal-hearing adults, 82% of normal-hearing children, 78% of deaf children who have used a CI for at least four months and 78% of deaf children on the day of CI initial activation. Interestingly, Sevy et al. had validated their NIRS experimental paradigm with fMRI in 3 normal-hearing adults. They showed that similar speech-evoked superior temporal gyrus responses were obtained with both fNIRS and fMRI. Such results were encouraging as they demonstrated that fNIRS was a feasible neuroimaging technique in CI users and that reliable hemodynamic cortical responses to speech could be recorded in these patients.

The same group later evaluated whether fNIRS was sensitive enough to detect differences in cortical activation evoked by different quality levels of speech in normal-hearing individuals [101]. The investigators used a 140 channel fNIRS system (NIRScout, NIRx Medical Technologies LLC, Glen Head, NY) in a tight array to provide spatial oversampling, and permit averaging between channels to improve the SNR (Figure 3-2C). By increasing the number of channels, the authors were able to generate topographic maps and measure the area of activation and center of mass. They also designed their own custom analytic software and developed novel data analysis techniques to filter channels with poor scalp contact or high SNR. The experimental paradigm consisted of four different stimuli: normal speech, channelized (vocoded) speech, scrambled speech and environmental noise (for previous use of these stimuli as cross-controls see, for example, Abrams et al., 2011; Humphries et al., 2001; Levitin et al., 2003). Their results revealed that speech intelligibility correlated with the pattern of auditory cortical activation measured with fNIRS: normal speech evoked the strongest responses, distorted speech produced less region-specific activation and environmental sounds evoked the least response. Again, the investigators validated their stimulus paradigm with fMRI on a single participant. Such results demonstrated that in normal-hearing individuals, fNIRS can detect differences in the response of the auditory cortex to variations in speech intelligibility. The conclusions of this study raise implications for the CI population. If fNIRS can provide an objective measure of whether a normal-hearing subject is hearing normal or distorted speech, then it has the potential to be used to assess how well speech information activates the brain in subjects hearing through a CI.

While Pollonini's study did not involve CI subjects, subjects hearing through a CI were studied with a similar technique [122]. Olds' study used an experimental paradigm and fNIRS instrumentation comparable to that of Pollonini, but expanded the approach to participants with CI. Specifically, the authors aimed to better understand the variability in speech perception outcomes in CI using fNIRS. A NIRScout 1624 instrument (NIRx Medical Technologies, LLC, Glen Head, NY) with 140 channels was used to record the auditory cortical response of 32 post-lingually deaf adults hearing through a CI and 35 normal-hearing adults. Again, four auditory stimuli with varying degrees of speech intelligibility were employed: normal speech, channelized speech, scrambled speech and environmental noise. Speech reception thresholds (SRT), monosyllabic consonant-nucleus-consonant word (CNC Words) scores and AzBio sentence recognition scores were used as behavioral measures of speech perception. Results from this study demonstrated that the cortical activation pattern in implanted adults with good speech perception was similar to that of controls. In those two groups, less cortical activation was noted as the speech stimuli became less intelligible. In contrast, CI users with poor speech perception displayed large, indistinguishable cortical activations across all four stimuli. As the authors had hypothesized, the findings of this study demonstrated that activation patterns in the auditory cortex of CI recipients correlate with the quality of speech perception. Importantly, when the fNIRS measurements were repeated with the implant turned off, reduced cortical activations in all CI recipients were noted. This suggests that sound information is conveyed to the auditory cortex of CI users with poor speech perception, but that these subjects are unable to discriminate speech from the information that gets to the cortex.

To our knowledge, Lawler and colleagues are the only other research group actively using fNIRS neuroimaging in auditory processing studies in deaf individuals and CI recipients; to date, they have published two articles on that topic [89,123]. While this group's long-term aim is to examine cortical reorganization associated with deafness and cochlear implantation using fNIRS, none of these articles enrolled CI users thus far. The first report discusses maladaptive cross-modal plasticity in CI subjects and its role as a potential factor underlying poor performance following implantation [123]. Through this article, the authors describe their long-term research goals and introduce their plans for future fNIRS studies with deaf individuals and CI recipients. Later that year, Dewey and Hartley published a study on the use of fNIRS to detect visual and vibrotactile cross-modal plasticity changes in profoundly deaf but non-implanted individuals [89]. Their setup consisted of a Hitachi ETG4000 (Hitachi Medical Corporation, Tokyo, Japan) optical topography system with 12 recording channels over each hemisphere (Figure 3-2B). The authors reported that auditory deprivation is associated with cross-modal plasticity of visual inputs to auditory cortex. Practically speaking, such results highlight the ability of fNIRS to accurately record cortical changes associated with neural plasticity in profoundly deaf individuals. The application of these findings to the CI population is very promising, as they demonstrate the potential of fNIRS as an objective neuroimaging tool to detect and monitor cross-modal plasticity both prior to and following cochlear implantation.

5. Directions for future fNIRS application in CI users

5.1 Clinical applications

A promising future for fNIRS clinical applications includes the implementation of NIRS as a neuroimaging tool to guide post-implant programming in the service of improving deaf patients' speech and language outcomes. CIs need to be reprogrammed frequently to ensure they are accurately conveying the sound information within speech to the auditory nerve and, ultimately, to the auditory cortex. If the language areas of the brain are appropriately activated, then the child has the best chance of learning normal speech and language. Early identification of patients who do poorly is therefore critical, as prompt intervention can prevent delay in linguistic and psychosocial development [45]. Current cochlear implant assessment tools are limited and hard to administer in young infants, whose behavioral responses are difficult to elicit and are often not interpretable. An objective measure of how well speech information is processed within the cortex would provide an ideal tool for monitoring (and possibly predicting) language development in young CI users. Given that the number of imaging sessions is not restricted for fNIRS, repeat assessments through longitudinal studies can be performed to monitor rapid cortical modifications resulting from poor implant programming. In doing so, fNIRS studies may allow early identification of children on poor language development trajectories. If this can be achieved while the child is still within the critical time period when significant language development occurs (i.e. age 1-4 years), prompt intervention can be started. Ultimately, this type of early intervention could prevent delays in a child's psychosocial development, a process highly dependent on hearing [124]. Using fNIRS to supplement our current clinical practice of CI programming and speech and language therapy is an exciting possibility.

5.2 Research applications

The opportunity for safe, repeated testing of CI recipients with fNIRS also provides investigators with the ability to explore the cortical changes associated with neural plasticity in this patient population. For instance, understanding the cortical reorganization that occurs following prolonged auditory deprivation in potential CI recipients may help predict their expected outcome post-implantation. This expectation is based on emerging evidence suggesting that cross-modal plasticity of visual inputs into a sensory-deprived auditory cortex may affect the ability of a CI recipient to process auditory information from their implant effectively [32]. fNIRS may also provide insight into the cortical changes that take place in deaf patients following implantation. An example of such an application is the study of post-implantation training and its effects on brain plasticity. Pantev et al. examined the dynamics of auditory plasticity after implantation through MEG longitudinal imaging, suggesting that CI users would benefit the most from language training within the first 6 months after implantation [93]. As discussed, fNIRS is significantly easier to use in longitudinal studies compared to MEG.

The opportunity to further explore cortical reorganization following hearing restoration has the potential to guide the design of post-implantation training strategies.

The neural basis for CI users' variable experience perceiving music is another interesting topic and one that merits further investigation. Despite advances in CI technology, music perception in CI recipients remains quite poor [1]. A growing body of psychophysical studies has better defined the limitations of music enjoyment and perception in CI users. For example, studies suggest that CI users perform poorly on pitch recognition tasks, whereas rhythmic perception remains relatively intact following implantation [3,4]. Reports have also shown that appraisal ratings and overall listening time are significantly lower following implantation, with some CI users even describing music as "aversive" [34,35]. The challenges that CI users face in processing a complex auditory stimulus such as music can be explained by a number of technological, acoustical and biological constraints [31]. While many of these have been addressed in the literature previously, the neural basis for poor music perception in CI users is under-investigated and poorly understood. This is at least in part due to inherent limitations on the use of most neuroimaging modalities with CI users, as outlined here. fNIRS is quiet and allows the use of event-related paradigms, thus offering greater flexibility in experimental inquiry. It is also relatively low cost, another factor that may have constrained examination of neural mechanisms underlying better or worse music perception in implant users in previous years. These and other features make fNIRS an ideal tool for evaluating music-evoked brain activation in CI recipients, as well as for examining the relationship between behavioral music performance and degree of auditory cortical activation in this patient population. Together, these inquiries would help achieve the long-term goal of higher-level music perception in CI recipients.

6. Conclusion

fNIRS is a safe, reliable neuroimaging technique that is compatible with CI devices. It offers many benefits over other approaches for examining cortical responses in CI recipients, although care must be taken in collecting and analyzing the data. While the existing literature on fNIRS neuroimaging in adult and pediatric CI users is currently limited, the future of this emerging technique is promising and numerous clinical and research applications remain to be explored.

Preface to Chapter 4

The review detailed in study 1 suggested that fNIRS is a safe and non-invasive neuroimaging modality that is compatible with cochlear implant devices. In addition, it highlighted the good spatial and temporal resolutions of fNIRS, with the ability to record reliable hemodynamic responses from the temporal lobes. Given such technological and practical advantages, we believe fNIRS is the neuroimaging modality of choice to study the neural correlates of sound perception CI users. The next study sought to extend the findings of study 1 by examining the music-evoked auditory cortical activation patterns in cochlear implant recipients using fNIRS neuroimaging.

Chapter 4: Auditory cortical activity during cochlear implant-mediated perception of music using functional near-infrared spectroscopy

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Abstract

Objectives : (1) To examine the correlation between behavioral measures of music perception in cochlear implant (CI) users and auditory cortical hemodynamic response areas measured with functional near-infrared spectroscopy (fNIRS). (2) To determine the patient-related factors that influence music perception outcomes in CI users and examine the moderating role of these factors on the relationship between music perception and cortical activation.

Study design: Prospective case-control study conducted in a tertiary referral otology clinic

Methods: Cases consisted of CI users with at least 6 months of implant experience. Controls consisted of age-matched normal-hearing (NH) controls. Behavioral music performance was assessed by the Montreal Battery for the Evaluation of Amusia (MBEA). fNIRS neuroimaging was recorded during music, rhythm and pitch perception (using normal, spectrally-rotated and time-scrambled music, respectively).

Results : A total of 52 subjects were recruited (27 CI users and 25 controls). Reliable auditory cortical oxy- and deoxyhemoglobin responses were obtained in all participants. CI users recruited the largest areas of auditory cortex during rhythm perception, a task in which they performed as well as NH individuals behaviorally (MBEA: 80.1 vs 81.3 respectively, $p=0.5$). In contrast, CI users obtained significantly worse behavioral scores than NH individuals on pitch-related tasks (MBEA scores : 48.9 vs 80.6, respectively, $p<0.001$), and recruited smaller cortical areas during pitch perception. All music stimuli showed a right hemispheric lateralization in NH individuals, but not in CI users.

Conclusion : Behavioral measures of music perception in CI users may be associated with auditory cortical hemodynamic response areas measured with fNIRS.

Keywords: cochlear implant, music, neuroimaging, auditory cortex, fNIRS

Introduction

Cochlear implantation has been tremendously successful in restoring speech comprehension in individuals suffering from profound hearing loss[125]. However, despite advances in in speech processor design, signal processing and surgical techniques, music perception in CI recipients remains poor [1,3,4]. Studies have shown that CI users perform poorly on pitch recognition tasks and that appraisal ratings are significantly lower after implantation [34,36]. Some CI recipients even describe the music as “aversive” [35]. Investigators have also demonstrated that listening habits are affected post-implantation, with decreasing listing time and changing musical style preference [35,37]. In addition, a recent body of evidence suggests that there is an enormous variability in CI users’ ability to perceive and enjoy musical stimuli, with some patients performing close to normal hearing individuals and others unable to distinguish it from noise[2]. The factors affecting this variability in outcomes after implantation are not completely understood, but the challenges CI users face in processing a complex auditory stimuli such as music can be explained by a number of technological, acoustical and biological constraints [2,31].

While many of these constraints have been previously addressed in the literature, the neurobiological basis for music processing in CI users remains poorly investigated due to a paucity of imaging studies in that population. To date, the only study comparing music perception between CI users and NH individuals revealed greater extent of auditory cortical activation in CI users during rhythm perception, a task in which they performed almost as well as controls [30]. Conversely, the least activation in the CI group was noted during melody perception, which was also the most difficult task for CI users. These findings suggest a possible relation between music implant performance and neural activity, a concept that has not yet been addressed. The goals of the present study are to examine the correlation between behavioral measures of music perception and auditory cortical activation in CI users using functional near-infrared spectroscopy (fNIRS), and to identify the patient-related factors that moderate this relationship. This will provide an objective brain-based measure of music perception in CI users and determine the neural basis underlying the wide variability in music perception outcomes following implantation.

Methods

Participants and study design

A prospective case-control study was conducted at a tertiary otology clinic of Stanford University (Stanford, CA). The experimental protocol was approved by the ethics review board of Stanford University, and all subjects signed an informed consent form before participating in the study. Cases consisted of adult CI recipients with post-lingual severe-to-profound hearing loss and at least 6 months of implant experience. Subjects were recruited during a routine appointment to the otology clinic and were excluded from the study if they were not fluent in English or had a nonfunctional CI. Controls consisted of age-matched normal-hearing (NH) adult volunteers with bilateral hearing thresholds of 30 dB HL or better at 500, 1000 and 2000 Hz on a screening hearing test. Patients and controls with a psychiatric condition, a previous traumatic brain injury or an underlying neurodegenerative disorder were excluded from this study.

Prior to testing, all participants were asked to complete a musical background and demographical questionnaire (Queens Modified Questionnaire, see Appendix A) [126,127]. CI users with hearing aids in the unimplanted ear removed their hearing aid before the experiment. Medical information concerning duration of deafness, duration of implantation, CI model and speech perception scores were retrieved from the hospital records of CI participants. All subjects then underwent testing for (1) behavioral music perception and (2) fNIRS neuroimaging during acoustic stimulation.

Behavioral measures of music perception

Behavioral musical perception was evaluated using the online version of the *Montreal Battery for the Evaluation of Amusia (MBEA) (http://www.brams.org/amusia-public)*. All measurements used in this study were obtained on the day of fNIRS testing by a member of the research team. The MBEA is a test battery initially designed to screen for amusia, a condition in which an individual lacks musical perception abilities, but it has since been validated as a reliable tool to measure music perception in cochlear implant users [3,128]. The online version, modified from it's original longer format, consists of three block (25 musical trials in each), each of which is designed to assess different aspects of music perception: pitch perception (blocks one and three) and rhythm perception (block two). The testing method used in blocks one and two involves the presentation of two melodies that are to be compared. The subject must then determine whether the two melodies are the same or different. In block one, they will differ in an aspect of pitch perception, whereas in block two they will differ in their temporal properties. In the last block, only one melody is presented in which one of the notes may be altered to sound "out of tune". The subject must determine whether the melody sounds out of tone or not. Each bock is proceeded by two examples with feedback, but no feedback was given during the test. The assessment was administered on a computer and musical clips were presented using two free field stereo speakers placed directly in front of the listener (see *fNIRS Testing Procedure* section below). The duration of the assessment was approximately 25 minutes, at the end of which scores were obtained for each block and for the entire test. Values below 70 are suggestive of abnormal music perception skills [127,128].

Acoustic stimuli

The song "Panda Nation" (by Melancholy Blues) was selected among an online royalty-free music repertoire (Jamendo, www.jamendo.com) containing songs representative of the Western music tradition but unknown to the general population. This choice was made in an effort to greatly reduce familiarity and memory effects [129]. The song was then manipulated in MATLAB (R2013A; The MathWorks) to generate three types of music stimuli. All stimuli were presented to participants at a comfortable listening volume (60 dB SPL). The first stimulus, *normal music*, consisted of recordings of the song digitally edited into 20 s sequential segments. The second stimulus, *spectrally-rotated music,* was generated using a freely available algorithm and a method previously described to remove all spectral information in an acoustic stimulus without altering the temporal component [129-131]. In short, the file was low-pass filtered at 2400 Hz, multiplied by a 2500 Hz sine wave, and low-pass filtered once more at 2400 Hz to prevent aliasing. The center frequency for spectral rotation was 5512 Hz, which was selected so that the rotated frequencies would be within the frequency response range of CI device. The third stimulus, *time-scrambled music*, was created by randomly drawing 250- to 350-ms variable-sized excerpts from the song and concatenating them with a 30-ms linear cross-fade between excerpts. Contrary to the spectrally-rotated stimulus, this time-scrambled clip is devoid of all temporal cues but maintains its native spectral elements. All the music stimuli were then normalized, amplified, and outputted as wave files (eventually converted to Mp4).

fNIRS testing procedure

All fNIRS testing was performed in a quiet, darkly-lit room equipped with a computer.

The subjects were seated in a chair in front of the computer screen. To minimize head movements and to maintain the subjects' attention, a silent visual stimulus (moving geometric shapes) was displayed on the monitor. The music stimuli were presented to the subjects from two free-field speakers placed directly in front of the listener. Four trials of each sound stimulus were presented in a pseudorandom order, alternating with 20-sec blocks of silence. This event-related paradigm is shown in Figure 4-1. Subjects were asked to press any key on the keyboard whenever a red box randomly appeared on the screen; this was designed as an additional attention task during the testing procedure. Each session took approximately 10 minutes to complete. During data collection, the start and end of auditory stimuli were synchronized with the incoming fNIRS data and recorded in an event file, which recorded the timing of the beginning and end of each stimulus. To control for the subjects' emotional and physiological responses to the musical selection, all stimuli were subjectively rated (10-point likert scale) at the end of the testing procedure on the following parameters: liking, "sounds like music" and "mechanical".

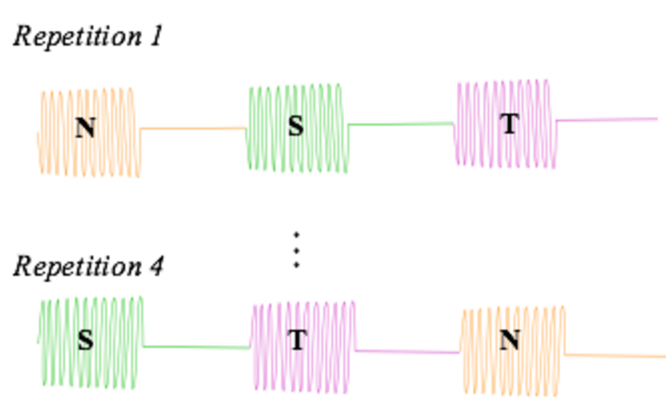

Figure 4-1. Auditory stimuli exposure protocol, illustrating four repetitions of each stimulus in pseudorandom order (N: normal music, S: spectrally-rotated music, T: time-scrambled music)

fNIRS hardware

The fNIRS hardware used in this study is similar to the setup previously reported by Olds et al. [132]. A NIRScout 1624 (NIRx Medical Technologies, LLC, Glen Head, NY) instrument was employed, containing 16 dual-wavelength infrared light sources and 24 detectors. Our fNIRS system along with a computer and monitor were mounted on the same portable cart. Each illumination optode consisted of two light-emitting diodes (LEDs) emitting at 760 and 850 nm in the near-infrared electromagnetic spectrum. The light source was connected to the headpiece with fiber-optic cables. Signals at the two wavelengths were separated by sequentially activating the sources. The fNIRS data was collected from all channels (rate of 6.25 Hz) using the software that shipped with the device.

We designed a custom honeycomb-shaped headpiece to hold the light sources and detectors in place against the participant's scalp. This arrangement featured six light sources clustered in the center of the headpiece and an additional source anteriorly and posteriorly. Detectors were positioned in between. The center-to-center distance between adjacent optodes was 15 mm (Fig. 4-2). The optodes for each hemisphere were secured in a scaffold of flexible black polypropylene by rubber O-rings supplied by the instrument's manufacturer. This arrangement yielded two symmetrical optode holders, one for each hemisphere. The optode holders were connected to one another with Velcro straps, making the headpiece adjustable to the participant's head size and shape.

The headpieces were placed against the scalp centered at the T3/T4 position (according to the international 10-20 system, American Electroencephalographic Society), with the second column of optodes being situated directly superior to the tragus and the bottom of the headset

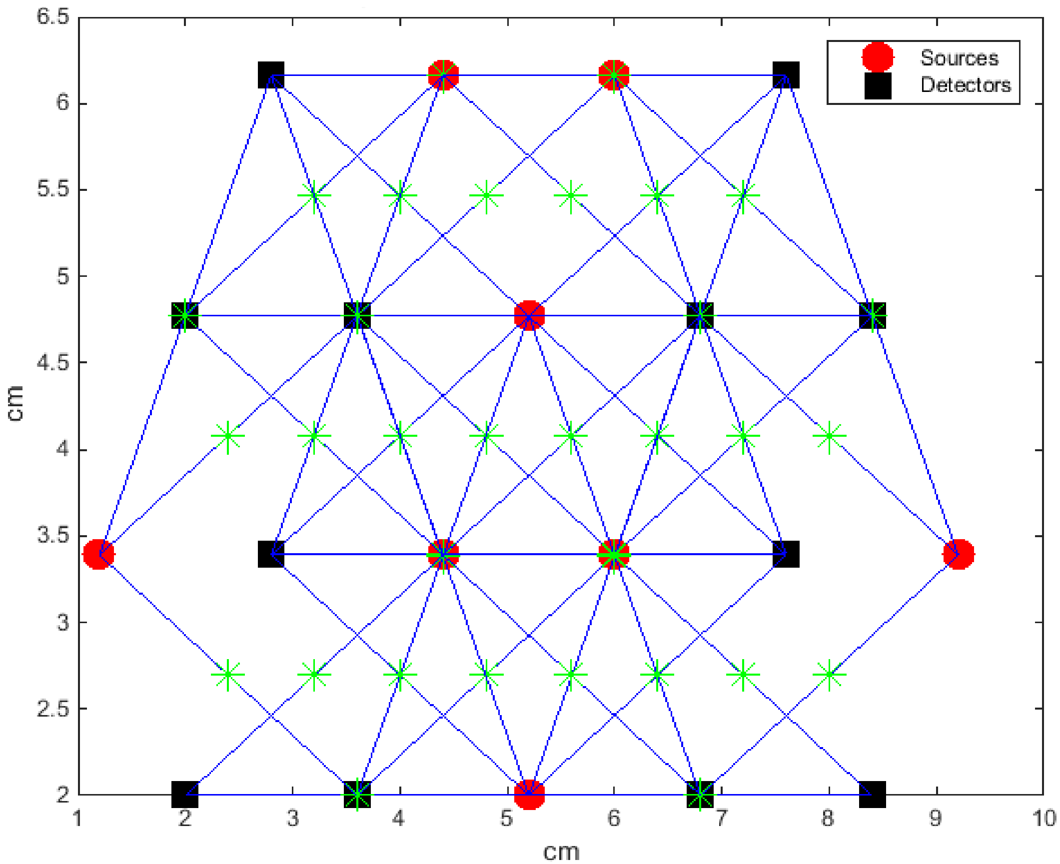

Figure 4-2. Headset optode arrangement: the middle source of the bottom horizontal line was centered at the T3/T4 position

sitting in the sulcus between the pinna and the skull. The external magnet of the CI device would occasionally interfere with headset placement over the temporal area. In such circumstances, the headset was simply placed over the magnet. While this obstructed the scalp contact of certain channels, the remaining channels are still available for use. The light from each source was received by neighboring detectors in the array, giving a potential of 96 source–detector pairings (or channels) on each side of the head. To optimally probe the cortex, we only analyzed channels in which the source–detector distance was 3.0 to 3.3 cm [100,101].

Data analysis

The analysis of the fNIRS data was performed in manner similar to our previous publications [101,132]. In brief, the data was first pre-processed to remove channels with poor contact with the scalp. At our institution, we filter channels with excessive noise according to their scalp-coupling index [101]. The data was then cleared of motion artifacts and band-pass filtered to the time course of the stimuli. The modified Beer-Lambert Law was applied to calculate the changes in oxyhemoglobin and deoxyhemoglobin. For each channel, all the trials of each stimulus were then to be block-averaged. The resulting block-averaged hemodynamic response curve was then compared to a predicted hemodynamic response [98]. The quality of fit is determined by linear regression analysis of the measured and predicted responses, resulting in a T-statistic for each channel. Thus, each channel in the headset can be represented by a single number that describes the goodness of the fit. These T-statistics are then arranged in a spatial grid representing the position of the channel they derive from within the optode array, allowing calculation of the area of cortical activation. As opposed to plotting a 2D square of the fNIRS data (such as a topographic map), this colored T-statistic distribution map was projected onto a standard brain image (obtained from a representative adult's anatomical MRI data) to create cortical activation maps that were easier to visualize and interpret (Fig. 4-3). This strategy is reasonable given previously published work from our group demonstrating that the responses measured with fNIRS derive from the lateral temporal lobe/superior temporal gyrus areas. Using a mathematical model, a report by Huppert et al. first estimated the coverage area of a single optode within our headset[98]. By combining a high number of channels within our headset to an accurate headset positioning (centered at the T3/T4 position), we predicted that adequate coverage of the lateral temporal lobe/superior temporal gyrus was achieved with our array. Subsequent studies confirmed this hypothesis by demonstrating similar response patterns to auditory stimuli within this area by fNIRS and fMRI[100,101].

Statistical analysis

T-tests for independent samples were used to compare CI subjects to controls on continuous descriptive study variables. Chi-square analyses were computed to examine the association between binary variables in our study groups. Independent samples t-tests were also used to compare mean cortical activation areas between study groups and across stimuli. The p level was set at .05. No correlational analyses were performed. All analyses were performed using IBM SPSS statistics version 21.0 (IBM Corp., Armonk, NY).

Results

A total of 27 CI users (mean age: 42.1 years) and 25 NH controls (mean age: 31.0 years) were recruited for this study. Group differences between CI users and controls on all study variables are presented in Table 4-1. There were significant differences between the study groups in mean age (p=0.006), but not in gender, handedness or music training. CIs from all three Food and Drug Administration (FDA)-approved brands (Cochlear, Advanced Bionics, and Med-El) were represented in the participants tested.

Most CI users had one implant (63.0%), whereas 10 subjects had bilateral implants. Participants that were unilaterally implanted all had pure-tone averages and speech reception thresholds in the contralateral ear that were >60 dB HL before their implantation surgery. No participant had been implanted for unilateral sensorineural hearing loss.

Variable	NH (n = 25)	CI (n = 27)	p-value
Age in years, mean % (SD)	31.0 (7.7)	42.1 (19.9)	**0.006***
Gender (% female)	60.0	48.1	0.4
Handedness (% right)	92.0	92.6	0.9
Any music training (% yes)	70.4	50.0	0.3
Duration of severe-profound HL, years (SD)	--	17.0 (12.7)	--
Duration of implant use, months (SD)	--	51.3 (50.3)	--
CI side, n (%)			
Right	--	7 (25.9)	--
Left	--	10 (37.0)	--
Bilateral	--	10 (37.0)	--

Table 4-1. Group demographics

Behavioral music perception scores are shown in Table 4-2. CI users performed significantly worse than NH controls in pitch-related tasks (blocks one and three, $p < 0.001$ for both). Conversely, they performed as well as controls during rhythm perception (block two, $p=0.5$). Results of the rating scales revealed that the normal music stimulus was most liked by the NH group, while the spectrally-rotated stimulus was favored by the CI group. There were no

	NH (n = 25)	CI (n = 27)	p-value
MBEA scores, % (SD)			
Overall	82.4 (9.5)	61.2 (5.8)	**<0.001***
Block 1	84.6 (11.3)	56.0 (9.1)	**<0.001***
Block 2	81.3 (9.1)	80.1 (9.7)	0.5
Block 3	80.6 (13.6)	48.9 (10.6)	**<0.001***
Rating scales, mean (SD)			
Normal music			
Liking	7.8 (1.9)	5.2 (2.2)	**<0.001***
Sounds like music	9.0 (1.6)	7.1 (2.5)	**0.002***
Mechanical	0.7 (1.3)	2.5 (3.1)	**0.01***
Spectrally-rotated music			
Liking	2.6 (2.2)	4.4 (3.0)	**0.02***
Sounds like music	2.3 (2.7)	5.6 (3.6)	**0.004***
Mechanical	7.7 (3.2)	4.5 (3.4)	**0.001***
Time-scrambled music			
Liking	3.5 (2.8)	3.5 (2.4)	0.9
Sounds like music	4.2 (2.9)	4.6 (2.7)	0.08
Mechanical	2.8 (2.2)	3.7 (2.3)	0.3

Table 4-2. Behavioral music perception scores and music enjoyment

differences between the two groups' rating scale parameters for the time-scrambled stimulus. Reliable auditory cortical oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) responses were obtained in all participants. Figure 4-3 illustrates a cortical activation map from a representative CI adult recipient during music perception. The activation maps were obtained by projecting the two dimensional optode array spatial grid onto a standard brain image. The increase in HbO concentration (in yellow) and corresponding decrease in HbR concentration (in blue) are indicative of a cortical activation pattern. Figure 4-4 shows the average hemodynamic response areas for each study group. There were no statistically significant intergroup or intragroup differences in HbO or HbR response areas across stimuli or hemisphere (Figure 4-4). However, CI users tended to recruit the largest areas of auditory cortex during rhythm perception (Stimulus 2), while pitch-related tasks recruited the smallest cortical areas (Stimuli 1 and 3). All music stimuli showed a right hemispheric lateralization in NH individuals, but not in CI users.

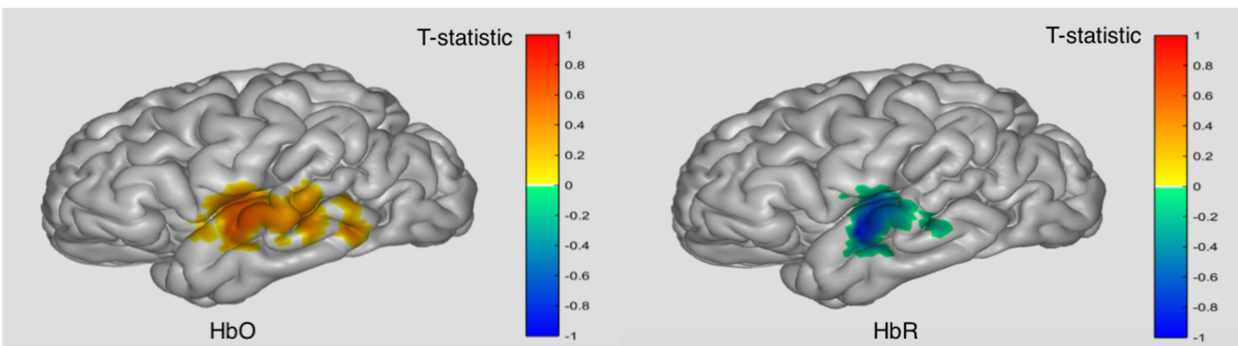

Figure 4-3.
Cortical activation maps (left hemisphere) of a representative CI adult recipient during music perception.

Discussion

The present study is the first to examine the correlation between music perception outcomes after cochlear implantation and auditory cortical activation. While our findings are

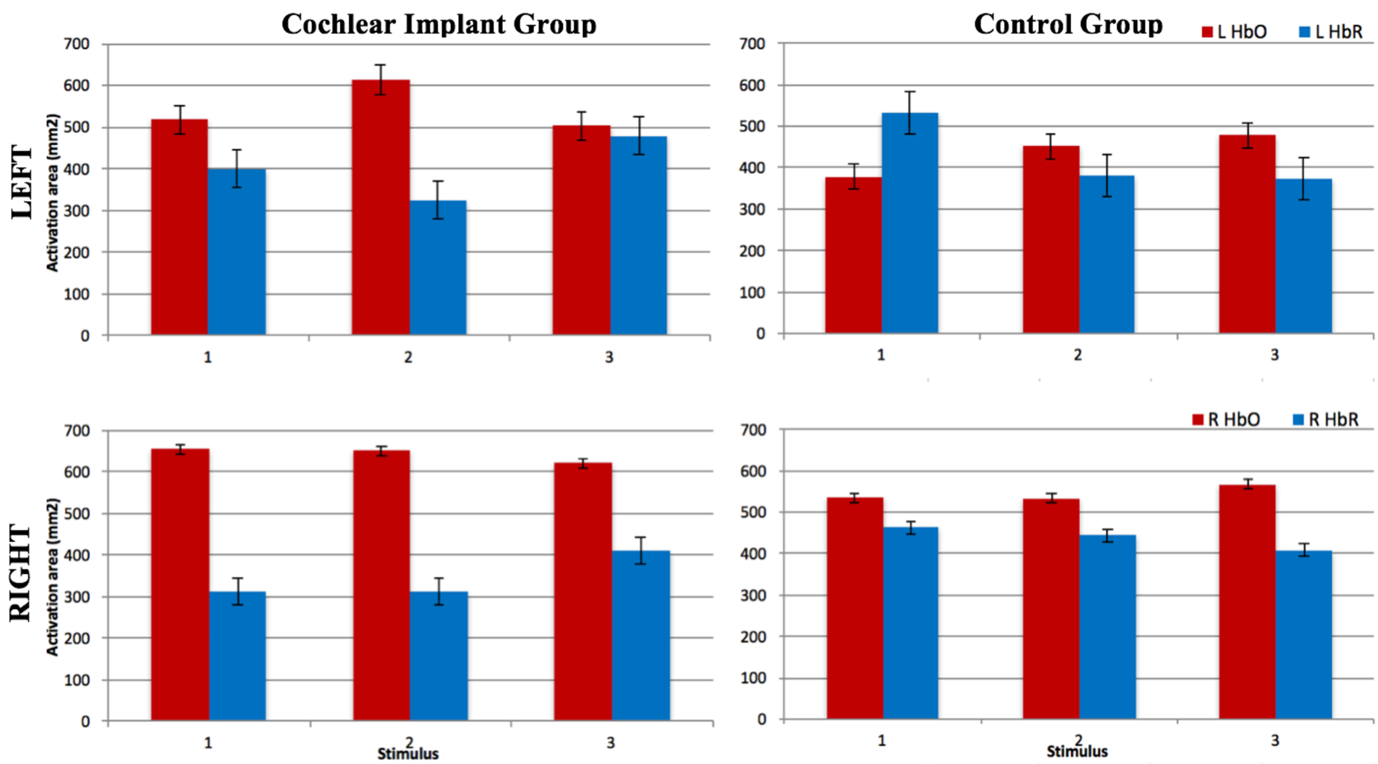

Figure 4-4. Average (with standard errors) hemodynamic response areas according to group and hemisphere (1: normal music, 2: spectrally-rotated music, 3: time-scrambled music). There were no statistically significant intergroup or intragroup differences in HbO or HbR response areas across stimuli or hemisphere

preliminary and not statistically conclusive, the trend of our data supports our first hypothesis that increased area of brain activation may be linked to improved music perception outcomes following implantation.

The neural correlates underlying the wide variability in music perception outcomes following implantation is an interesting topic that merits further investigation. As music and language perception share common neural processing pathways, a review of the speech perception literature in CI users may shed light into to neurobiological factors affecting music perception following implantation. Green et al. have previously demonstrated that there is a correlation between auditory cortical activity measured with PET scan and speech perception scores in CI patients [133]. Likewise, other reports have shown that CI users, in an effort to analyze the degraded information relayed by the device, require greater extent and intensity of activation than NH listeners to achieve similar behavioral speech outcomes [29,134]. Our findings, while not statistically significant, demonstrate a trend that supports this hypothesis: CI users recruited the largest areas of auditory cortex during rhythm perception, a task in which they performed as well as NH individuals behaviorally. In contrast, CI users obtained significantly worse behavioral scores than NH individuals on pitch-related tasks and recruited smaller cortical areas during pitch perception. Such results are not unexpected, as CIs have been shown to relay temporal information reliably but to have poor spectral resolution [2,135]. Our music rating scales corroborate this claim: CI users preferred the spectrally-rotated music, a stimuli with preserved temporal cues but lacking spectral information. These results, however, were obtained from the entire study sample. Further stratifying our subjects into good and poor music performers may strengthen the relationship between behavioral performance and cortical activation. Accordingly, we would expect our future analyses to show that CI users with good music perception, as a function of increased neuronal recruitment during implant-mediated listening, will demonstrate activations of auditory cortex that exceed those of NH controls for normal, spectrally-rotated and time-scrambled music. The weakest activation will be for time-scrambled music, where we also expect CI users to perform the worst behaviorally. We believe CI users with poor music perception scores will have similar overly large areas of cortical activation across all three stimuli, reflecting their inability to discern the pitch and rhythm components of music. While our findings do not currently validate such hypotheses, these correlations will be tested in future analyses.

Our second objective to determine the patient-related factors that influence music perception outcomes in CI users has not been tested in our preliminary analyses. However, there is a basis for believing musical training, duration of deafness and implant experience will influence music perception outcomes [136]. This hypothesis is based on evidence from the speech perception literature, in which studies have shown that duration of deafness and implant experience influence cortical activity in speech perception [134,137]. We expect these findings will extend to music perception in CI users. This process is theorized to occur as a result of plastic reorganization of the auditory cortex: CI subjects with musical training, longer implant experience and shorter duration of deafness will recruit more areas of cortex (such as association areas) to process the information relayed by the auditory nerve [33,49]. We expect users with higher speech perception scores to perform better on pitch-related tasks, which will translate into larger areas of cortical activation. Further analyses are required, however, to support those claims.

There are a number of limitations to this study. First, the results reported in this manuscript were obtained from preliminary analyses. The lack of statistical significance may be due to the large standard deviations, and normalization of our data should be considered in the future. Second, the study sample size was limited. However, similar samples were employed in previous fNIRS studies examining cortical activity in NH subjects and CI user and provided enough power to reveal significant results [101,132]. In addition, the two study groups were significantly different in mean age: the NH group was younger, and this could potentially confound the cortical activation patterns.

Conclusion

This study is the first to examine the correlation between behavioral music outcomes and auditory cortical activation following cochlear implantation. Our results are preliminary and not statistically significant, but they show a trend suggesting that larger areas of brain activation may translate behaviorally into improved music perception outcomes. Further analyses are required to explore this association and to determine the patient-related factors that moderate the relationship between music perception and cortical activation.

Chapter 5: General Discussion

With the expanding indications for cochlear implantation and the technological and surgical advances, expectations for audiological outcomes have steadily increased. There is a growing demand for improved music perception among implant recipients who are increasingly higher performers or music enthusiasts. Because the CI stimulates the cochlear nerve and generates a signal that reaches the central auditory processing centers, functional neuroimaging has the potential to provide additional information on the neurobiological factors that influence music perception: this was the central objective of the present thesis.

The first study reviewed and compared all the traditional neuroimaging techniques available for use in CI users. More importantly, it explored the applications and limitations of an emerging technology, fNIRS, in the CI population. Study 1 revealed that fNIRS combines good spatial and temporal resolutions, while being safe, non-invasive and compatible with CI users. The second study employed fNIRS to explore the neural correlates underlying the wide variability in music perception outcomes following implantation. The preliminary results of that study suggest that behavioral measures of music perception in CI users may be linked with auditory cortical hemodynamic response areas.

As stated in Chapter 4, a number of future analyses are required to further test the hypotheses of study 2. Stratification of the CI group into good and poor music performers may strengthen the relationship between behavioral performance and cortical activation. Regression analyses also need to be performed in order to assess for the potential confounding effects of variables such as age and education on auditory cortical activation. Likewise, the study of the spatial patterns of brain activation would potentially allow for the detection of preferential activation of areas during pitch and rhythm perception. Nonetheless, our preliminary results demonstrate the feasibility of using fNIRS in CI population to objectively detect differences in cortical responses to the various acoustical components of a musical stimulus.

There are a number of considerations that could be implemented in the future to minimize or overcome some of the limitations of Study 2. The stimulus paradigms adopted in this paper was event-related, with 20 second musical excerpts presented in a pseudo-randomized pattern. While such a paradigm has previously been examined with speech stimuli[132], it remains to be validated with music. A comparison between the cortical activation patterns obtained with fMRI and fNIRS in a normal-hearing subject exposed to music using an event-related paradigm should be considered in future studies, as it could validate the fNIRS spatial data obtained with such paradigm. Another consideration would be the use of longer musical excerpts which would more adequately reflect real-life listening conditions. Such "ecological" stimuli would potentially generate more reliable auditory cortical activation patterns, facilitating the analysis of such data. One of the limitations of fNIRS neuroimaging is its dependence on a good contact between the optical optode and the scalp, which reduces light scatter thereby improving signal-to-noise ratio. The use of gel and combs can help to keep hair pushed out of the way, but it is also important to employ a headset that conforms to the convexity of the skull. To this effect, our optode array was secured to a flexible polypropylene film scaffold; nonetheless, we frequently needed to discard channels with poor scalp contact. A headset design with spring-loaded optodes could potentially overcome this problem. Our collaborators were also developing a custom analytic software that uses real-time fNIRS recordings to depict the quality of scalp contact of the optode array in a diagrammatic fashion. This would enable researchers to identify the channels with poor contact prior to initiating the recording and adjust their placement accordingly. However, this software was not available for use at time of writing.

Directions for future fNIRS applications in CI users involve both clinical and research perspectives. From a clinical standpoint, the use of fNIRS to supplement the current clinical practice of CI programming and speech and language therapy is an exciting possibility. CIs are frequently reprogrammed in the months following implantation to ensure the sound is appropriately processed by the device and that a signal is reaching the auditory cortex of the recipient. There are no modalities, however, to assess whether such signal translates behaviorally into comprehensible speech or music. In young children, this process is further complicated by the fact that behavioral responses are difficult to elicit and often not interpretable. An objective measure of how well speech information is processed within the cortex would provide an ideal tool for monitoring and possibly predicting language development in young CI users: if the language areas of the brain are appropriately activated, then the child has the best chance of learning normal speech and language. In that sense, fNIRS could prove to be a promising objective tool to guide the process of post-implant programming, with the ultimate goal of improving CI recipients' auditory outcomes.

From a research perspective, the safety profile of fNIRS allows for repetitive testing that would be perfectly suited to explore the cortical changes that occur in the context of neural plasticity. As such, it would theoretically be possible to monitor the cortical changes that occur after implantation or in the course of rehabilitation. This information could provide the basis for future rehabilitation therapies aimed at improving auditory outcomes, such as visual deprivation [32].

Conclusion

The wide variability in music perception outcomes following implantation remains incompletely understood. While some of the technological and acoustical constraints have been examined, the neurobiological constraints involved in music perception have not been explored mainly due to the limitations and costs of traditional neuroimaging modalities. The results of this thesis have demonstrated that fNIRS combined good spatial and temporal resolutions, while being safe, non-invasive and compatible with CI users. This thesis has also shown that behavioral measures of music perception in CI users correlate with auditory cortical hemodynamic response areas. The potential clinical and research applications of fNIRS in CI recipients are diverse and should be explored in the future. Ultimately, this area of research will contribute toward the advancement of strategies aimed at improving the overall musical experience in CI users.

Abbreviations

CI: cochlear implant

EEG: Electroencephalography

fMRI: Functional magnetic resonance imagery

fNIRS: functional near-infrared spectroscopy

HbO: oxyhemoglobin

HbR: deoxyhemoglobin

MBEA: Montreal Battery for the Evaluation of Amusia

MEG: Magnetoencephalography

NH: Normal hearing

PET: Positron emission tomography

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