



Research paper

Cortical cross-modal plasticity following deafness measured using functional near-infrared spectroscopy

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ABSTRACT

Evidence from functional neuroimaging studies suggests that the auditory cortex can become more responsive to visual and somatosensory stimulation following deafness, and that this occurs predominantly in the right hemisphere. Extensive cross-modal plasticity in prospective cochlear implant recipients is correlated with poor speech outcomes following implantation, highlighting the potential impact of central auditory plasticity on subsequent aural rehabilitation. Conversely, the effects of hearing restoration with a cochlear implant on cortical plasticity are less well understood, since the use of most neuroimaging techniques in CI recipients is either unsafe or problematic due to the electromagnetic artefacts generated by CI stimulation. Additionally, techniques such as functional magnetic resonance imaging (fMRI) are confounded by acoustic noise produced by the scanner that will be perceived more by hearing than by deaf individuals. Subsequently it is conceivable that auditory responses to acoustic noise produced by the MR scanner may mask auditory cortical responses to non-auditory stimulation, and render inter-group comparisons less significant. Uniquely, functional near-infrared spectroscopy (fNIRS) is a silent neuroimaging technique that is non-invasive and completely unaffected by the presence of a CI. Here, we used fNIRS to study temporal-lobe responses to auditory, visual and somatosensory stimuli in thirty profoundly-deaf participants and thirty normally-hearing controls. Compared with silence, acoustic noise stimuli elicited a significant group fNIRS response in the temporal region of normally-hearing individuals, which was not seen in profoundly-deaf participants. Visual motion elicited a larger group response within the right temporal lobe of profoundly-deaf participants, compared with normally-hearing controls. However, bilateral temporal lobe fNIRS activation to somatosensory stimulation was comparable in both groups. Using fNIRS these results confirm that auditory deprivation is associated with cross-modal plasticity of visual inputs to auditory cortex. Although we found no evidence for plasticity of somatosensory inputs, it is possible that our recordings may have included activation of somatosensory cortex that masked any group differences in auditory cortical responses due to the limited spatial resolution associated with fNIRS.

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1. Introduction

The loss of one sensory modality can lead to neural plasticity of cortical areas associated with the remaining modalities. There is

mounting evidence from human imaging studies to suggest that auditory and tactile stimulation can activate visual cortex in blind subjects (Kujala et al., 1995; Sadato et al., 1996; Cohen et al., 1997; Roder et al., 1997; Weeks et al., 2000). Also studies have investigated plasticity in the auditory cortex of deaf individuals using functional magnetic resonance imaging (fMRI; Finney et al., 2001; Auer et al., 2007; Karns et al., 2012; Vachon et al., 2013) and magnetoencephalography (MEG; Finney et al., 2003). One such study (Finney et al., 2001) found visual motion evoked activity in the right auditory cortex of early-deaf individuals. This predominantly right-sided activation of auditory cortex in response to moving visual and/or tactile stimulation has been confirmed in

Abbreviations: CI, cochlear implant; fNIRS, functional near infrared spectroscopy; HbO, oxygenated haemoglobin; HbR, deoxygenated haemoglobin

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other fMRI studies (Sadato et al., 1996; Auer et al., 2007; Vachon et al., 2013). Together, these studies suggest that deafness is associated with cross-modal plasticity within auditory cortex, predominately on the right side, however, Karns et al. (2012) found bilateral activation of auditory cortex to visual and tactile stimulation in deaf individuals. Unlike previous studies that used bilateral stimulus presentation (Sadato et al., 1996; Finney et al., 2001; Auer et al., 2007; Vachon et al., 2013), Karns et al. (2012) presented visual and somatosensory stimuli to the right eye only, which may partially account for the inconsistency of results across studies.

Evidence suggests that cross-modal plasticity in auditory brain regions following deafness may be an important factor in understanding and predicting how much benefit an individual might subsequently receive from a cochlear implant (CI; Lee et al., 2001; Giraud and Lee, 2007; Lee et al., 2007; Strelnikov et al., 2013; Sandmann et al., 2015; Song et al., 2015; Strelnikov et al., 2015). However, we currently have limited techniques for assessing the effects of CIs on neural plasticity, since testing with positron emission tomography (PET) is restricted (Johnsrude et al., 2002) due to cumulative effects of radionuclide exposure. Furthermore, fMRI is not safe to perform in these individuals and brain recordings using electroencephalography (EEG) and magnetoencephalography (MEG) are often distorted by electrical artefacts associated with CI stimulation. It is also important to consider the potential confounding effect of background acoustic noise associated with fMRI that cannot be matched between deaf and hearing participants, and the effect of techniques such as sparse sampling (Hall et al., 1999) on the resulting temporal signal to noise ratio of functional images due to the acquisition of fewer samples/reduction of temporal resolution. Specifically, acoustic noise from the gradient coils will be perceived more by hearing than by deaf participants. Therefore it is conceivable that any group differences in responses to non-auditory stimulation will be confounded by the differences in sensory experience during stimulation of all sensory modalities.

Functional near-infrared spectroscopy (fNIRS) non-invasively measures changes in cortical concentration of oxy-haemoglobin (HbO) and deoxy-haemoglobin (HbR), from which neuronal activity can be inferred. Also fNIRS provides silent recordings that are free from magnetic and electrical artefacts, and thus is highly suited to auditory research and is safe for repeated use in CI recipients (Sevy et al., 2010). Further, it is possible to measure functional responses to auditory stimulation in auditory cortex using fNIRS (Ohnishi et al., 1997; Minagawa-Kawai et al., 2002; Remijn and Kojima, 2010; Sevy et al., 2010; Plichta et al., 2011).

To our knowledge, the current study is the first to use fNIRS to assess auditory cortex responses to auditory and non-auditory stimulation in profoundly-deaf participants and normally-hearing controls. The primary aim of this study was to determine whether high-contrast moving visual stimuli and vibrotactile stimulation of the palms and fingers of both hands induced responses consistent with cross-modal plasticity in profoundly-deaf individuals using fNIRS. We predicted that the right temporal lobe of profoundly-deaf individuals would exhibit greater responses to non-auditory sensory stimulation, compared with normally-hearing controls.

2. Materials and methods

2.1. Participants

Profoundly-deaf volunteers ($n = 30$; 12 male and 18 female) were recruited to the study *via* local deaf clubs and audiology departments. Although inclusion criteria for participants in this group were based on current CI candidacy criteria within the UK (NICE,

2009), namely unaided pure-tone air-conduction thresholds of ≥ 90 dB SPL at 2 and 4 kHz in both ears, pure-tone air conduction thresholds were measured across four frequencies in both ears (0.5, 1, 2 and 4 kHz in both ears; pure-tone audiometry was performed in accordance with BS EN ISO 8253-1). Of the 30 deaf participants, 27 had pure-tone averages (PTAs) of ≥ 90 dB SPL at 0.5 and 1 kHz and the three remaining participants had thresholds ranging from 15 to 90 dB SPL at these two frequencies. Thus some participants may have perceived the broadband auditory stimuli that were used in our study, particularly those with residual low frequency hearing. Aside from meeting the UK audiometric criteria for CI candidacy, the participant group was intentionally heterogeneous, since subjects were not screened for inclusion based on any particular aetiology of hearing loss. Profoundly-deaf participants were asked about their deafness, including the aetiology of deafness, age at onset and duration of deafness and hearing aid experience (Table 1). Onset of deafness ranged from birth to 29 years of age, and duration of deafness ranged from 20 to 59 years. Unless otherwise stated, all measures of dispersion are reported as standard deviation of the mean. The mean age at onset of deafness was 2 ± 5 years and the mean duration of deafness was 39 ± 12 years. Hearing aid use also varied widely across the group, ranging from none at all to full-time bilateral aiding. Mean duration of hearing aid experience was 31 ± 17 years. All testing was performed unaided and no participant had a CI at the time of testing.

Normally-hearing volunteers ($n = 30$; 12 male and 18 female) were recruited *via* posters around the University of Nottingham. Normally-hearing individuals had pure-tone air conduction thresholds of ≤ 20 dB SPL at 0.5, 1, 2 and 4 kHz in both ears. Profoundly-deaf and normally-hearing participants had no known cognitive or psycho-motor impairments and none reported any active external or middle ear disease.

All participants included in the study were aged between 18 and 60 years old. The profoundly-deaf group were aged 41 ± 11 years, ranging from 20 to 59 years, while the normally-hearing control group were aged 34 ± 13 years, with a range of 18–60 years. There was small but statistically-significant difference in age between the two groups ($p = 0.02$). However, preliminary data analysis showed no significant correlation between the age of our normally-hearing participants and their auditory cortical response to visual stimulation ($p = 0.89$, $R^2 = 0.0006$; data not shown). Therefore there was no evidence to suggest that the small difference in mean age between the groups would influence our results. All participants were able to understand instructions in spoken or written English and/or British Sign Language (BSL) and reported normal or corrected-to-normal vision. BSL interpreters were used as and when requested by the participant, particularly when obtaining written informed consent, with 23 out of the 30 profoundly-deaf participants using BSL as a preferred communication method (see Table 1). The majority of participants in the normally-hearing and profoundly-deaf groups were right handed. Although there were 4 left-handed individuals in the profoundly-deaf group and none in the normally-hearing group, there were no significant group differences in handedness quotient scores. Neuroimaging data from all participants were analysed in the same way, regardless of handedness, as we had no basis for a handedness-dependent hypothesis. The study was approved by the National Research Ethics Service Nottingham Committee (Ref: 12/EM/0016).

2.2. Stimuli

The paradigm consisted of recording responses to auditory, visual and somatosensory stimulation separately. In each sensory modality, responses to two, separately presented stimuli were compared to a common baseline condition. The common baseline

Table 1

Aetiology and duration of hearing loss, hearing aid experience and audiometric thresholds (pure tone average over 0.5, 1, 2 and 4 kHz), by subject. The final column indicates each participant's preferred communication method.

I.D	Aetiology of hearing loss	Age at onset of hearing loss (yrs.)	Duration of hearing loss (yrs.)	Hearing aid experience	Duration of hearing aid use (yrs.)	PTA left ear (dB HL)	PTA right ear (dB HL)	Preferred communication method
1	Otosclerosis/auditory neuropathy damage	29 years	20	Bilateral	18	111.25	111.25	English
2	Congenital/hereditary	Birth	26	Bilateral	26	107.5	100.75	Sign supported English
3	Head injury	Childhood	Unknown	Unilateral (L)	25	91.25	87.5	Sign supported English
4	Viral/unknown	1 year	40	Bilateral	36	95	95	BSL
5	Unknown	2 weeks	52	Bilateral occasional use	49	95	95	BSL
6	Rubella	Birth	40	Bilateral	37	95	95	BSL
7	Rubella/head injury	Birth	56	Bilateral occasional use	54	95	95	BSL
8	Meningitis	3 years	44	None	N/A	95	95	BSL
9	Congenital/hereditary	Childhood	Unknown	Unilateral (R)	45	95	95	BSL
10	Congenital/hereditary	Birth	23	Bilateral occasional use	18	56.25	53.75	English
11	Unknown	Birth	28	Bilateral	27	92.5	90	English
12	Viral/unknown	6 months	53	Bilateral occasional use	53	95	91.25	Sign supported English
13	Congenital/hereditary	Birth	35	None	N/A	95	95	BSL
14	Rubella	Birth	54	Bilateral occasional use	52	95	95	BSL
15	Unknown	Birth	46	None	N/A	95	95	BSL
16	Unknown	Birth	41	Bilateral	40	92.5	91.25	BSL
17	Pendred syndrome	Birth	39	Bilateral occasional use	32	91.25	92.5	BSL
18	Meningitis	1 year	37	Bilateral from 2 to 16 y/o	14	95	95	BSL
19	Congenital/hereditary	Birth	20	Bilateral	17	106.25	107.5	BSL
20	Congenital/hereditary	Birth	48	Unilateral (R)	47	95	95	BSL & English
21	Rubella	Birth	44	Bilateral	42	91.25	91.25	English
22	Congenital/hereditary	Birth	57	Bilateral	52	97.5	113.75	English
23	Congenital/hereditary	Birth	59	None	N/A	95	95	BSL
24	Congenital/hereditary	Birth	51	Bilateral	49	95	95	BSL
25	Congenital/hereditary	5 years	29	Bilateral	28	115	115	English
26	Congenital/hereditary	Birth	29.5	Bilateral	29.5	88.75	88.75	BSL
27	Congenital/hereditary	4 years	25	Bilateral occasional use	25	95	95	BSL
28	Congenital/hereditary	Birth	21	Unilateral (R), occasional bilateral use	19	95	90	BSL
29	Meningitis	Childhood	Unknown	Bilateral	33	93.75	95	BSL
30	Congenital/maternal Rubella	Birth	49	Bilateral from 1 to 13 y/o, unilateral 13 y/o-present (R)	48	95	92.5	BSL & English

condition always consisted of the presentation of a black background on the computer monitor without auditory or somatosensory stimulation. The choice of two stimuli in each sensory modality also permitted parametric comparisons between unisensory responses.

Auditory stimuli consisted of (i) 10-Hz amplitude-modulated (AM) broadband noise at 100% modulation depth or (ii) unmodulated broadband-noise. Unmodulated and AM broadband noise have previously been reported to cause intense stimulation of auditory cortex (Nelken et al., 1999; Giraud et al., 2000). The stimulus duration of 20 s included a 500-ms cosine squared onset-offset gating envelope occurring at the beginning and the end of the stimulus period. Thus the duration of the steady-state portion of the stimulus was 19 s. Diotic stimuli were presented free-field at 80 dB SPL through left and right Logitech LS11 PC speakers placed 115 cm above the ground, 60 cm from the participant at angular displacements of $\pm 15^\circ$ from midline.

Visual stimuli were 1000 white dots, each 2.7 mm wide, on a black background. Dots were either (i) coherently swirling clockwise at a speed of 15° per second or (ii) randomly appearing and disappearing. Coherently moving white dots on a black background (Finney et al., 2001; Vachon et al., 2013) and other coherently moving high-contrast visual stimuli (Finney et al., 2003; Lomber et al., 2010; Sandmann et al., 2012) have been shown to evoke responses in auditory cortex of deaf individuals. Stimuli were presented on a 19-inch computer monitor at a distance of 60 cm from the participant. The mean \pm standard error luminance of the white dots were 169 ± 5 cd m^{-2} compared to a black background luminance of 0.23 ± 0.04 cd m^{-2} .

Somatosensory stimuli consisted of sinusoidal tone vibrations presented to the palms and fingers of both hands through a

custom-built horizontal vibrating plate and propagated across a thin plastic sheet. Palms and fingers of both hands were in contact with the plate for the duration of the neuroimaging experiment. Vibrations were presented at frequencies of (i) 20 Hz and (ii) 10 Hz. Vibrations were perceptually inaudible. The noise level in the room was measured at the position of the participant's ear with and without vibration. The sound level averaged over three measurements was 35.5 ± 2.2 dB SPL(A) RMS during vibration, and 35.3 ± 0.8 dB SPL(A) RMS without the stimulus. This difference is not statistically significant ($p = 0.4$). Vibration amplitude was measured using a displacement transducer and found to be in the order of 0.1 mm. As with the auditory stimulus, the 20 s duration of vibration included a 500-ms cosine squared gating envelope occurring at the beginning and the end of the stimulus period to prevent sound distortions occurring at the onset and end of the stimulus, thus making the duration of the steady-state stimulus 19 s. Sinusoidal vibrations have been shown to elicit highly salient cortical responses, with the peak response occurring at about 20 Hz vibrational frequency (Golaszewski et al., 2002; Valaparla et al., 2012).

Each of the six different stimuli ($2 \times$ auditory, $2 \times$ visual and $2 \times$ somatosensory) were presented five times for a duration of 20 s each, in a pseudo-random order, interleaved with rest periods of pseudo-randomised duration (25 – 45 s in 5 s intervals) in which the common baseline condition was presented. Functional NIRS recordings took place in a quiet darkened room. Prior to the start of the experiment, participants were briefed on the paradigm. Participants were asked to place their hands, palms downward, on the vibrotactile stimulator, and to keep their head as still as possible while fixating on the centre of the computer monitor.

2.3. Procedure

All data were acquired on a Hitachi ETG4000 (Hitachi Medical Corporation, Tokyo, Japan) optical topography system with a total of 18 optodes (10 infrared sources and 8 infrared detectors) which can be arranged in any one of a number of pre-defined rigid holder arrays, always ensuring alternating sources and detectors at fixed separations of 30 mm. The optodes were arranged in two 3×3 arrays, each consisting of five infrared light sources and four detectors, placed over the left and right temporal regions corresponding to 12 nearest-neighbour source–detector pairs on either side of the head. The mid-point of each nearest-neighbour source–detector pair is termed a recording channel (Fig. 1). Thus fNIRS responses were acquired at a total of 24 sites. Infrared light was produced at two wavelengths (695 nm and 830 nm), and sampled with a frequency of 10 Hz. In order to standardise array placement, the optode arrays were placed with the central optode directly above the preauricular point on the line connecting T3/T4 and CZ using the 10–20 system (Niedermeyer and Lopes da Silva, 2005). Despite this, the outer extremes of the optode array varied in their exact placement due to the location of an individual's pinna and jaw. Therefore, the locations of all optodes relative to surface landmarks (left and right tragus, nasion,inion and CZ) were recorded at the beginning of each session using a Polhemus 3D digitiser system (Polhemus, Vermont, USA) for the purpose of estimating channel locations on the cortical surface.

2.4. Data analysis

Anatomical channel locations derived from the 3D digitiser system were averaged across the group and projected onto a standard brain atlas using AtlasViewer from HomER 2 (Tsuzuki et al., 2012). This was done to confirm accuracy of optode placement across the group, as the placement of the peripheral optodes within the 3×3 array varied slightly depending on the position of an individual's pinna and jaw. These measures were also used to facilitate input of optode placement into the AtlasViewer. Subsequently, visual inspection of group average channel locations by two independent raters was used to determine two regions of interest (ROIs). ROIs were defined for the left and right auditory cortices, i.e. Heschl's gyrus and the superior temporal gyrus with respect to known surface landmarks (Morosan et al., 2001). Three channels on the left-hand side formed the left ROI and three channels on the right-hand side formed the right ROI, as shown in Fig. 1. The ROIs are placed relatively near to the inferior/ventral most part of the sensorimotor areas, located in the superior/dorsal temporal lobe but are not at all near to the visual areas, which are located in the occipital lobe. ROIs were then interrogated for changes in HbO and HbR concentration that were time-locked with

stimulus presentation in either group, and for differences between the groups.

Light intensity values were exported from the fNIRS system for pre-processing and analysis in Matlab (version 2012a, The Mathworks, Natick, Massachusetts). Using an approach similar to that of Umeyama and Yamada (2013), channels were assessed for characteristics associated with unstable or weak optode contact, characterised by notably high variance in the signal. Visual inspection of the distribution of the variance in the signal informed the choice of an exclusion threshold at 1.5 standard deviations from the mean. Any channel with a signal variance that exceeded this was excluded from further analysis.

Time course pre-processing and analysis steps were performed using the software HomER 2 (Huppert et al., 2009). Light intensity data were converted to optical density (OD) values separately for each of the two light wavelengths. Motion artefact correction was applied using the wavelet approach in HomER 2 (Molavi and Dumont, 2012). Recordings were band-pass filtered with a lower cut-off frequency of 0.01 Hz and an upper cut-off frequency of 0.5 Hz in order to reduce artefacts from participant motion, signal drift, and physiological processes such as heart rate. OD data were converted into haemoglobin (Hb) concentration for the two chromophores; oxy-haemoglobin (HbO) and deoxy-haemoglobin (HbR) using the modified Beer–Lambert Law (Cope et al., 1988). This fNIRS signal was then separated into functional and systemic components based on their hemodynamic differences using methods developed by Yamada et al. (2012). Their method is founded on the assertion that in functional signals, the HbO and HbR concentrations have a negative linear relationship to each other, whereas HbO and HbR concentrations can be assumed to take on a positive linear relationship in systemic signals (Yamada et al., 2012). Following this, values representing HbO and HbR signals are linearly related, thus statistical analysis was only performed on HbO concentrations.

Functional signals were block averaged across the five repetitions of each stimulus to calculate the average haemodynamic response to each stimulus condition, channel and participant separately. During the stimulus period, the peak amplitude and peak latency of the average HbO response were calculated relative to the onset of the stimulus.

Functional NIRS response time courses were fit to a general linear model (GLM) of the stimulus time-course convolved with a canonical haemodynamic response function implemented in SPM 8 software (Wellcome Trust Centre for Neuroimaging, UCL, UK, 2009), resulting in the calculation of the optimal parameter estimate (beta value) of the contribution of the stimulus to the response. Beta value estimates were calculated for each participant, channel and stimulus separately. Beta values were then averaged across each ROI, providing a measure of each participant's response

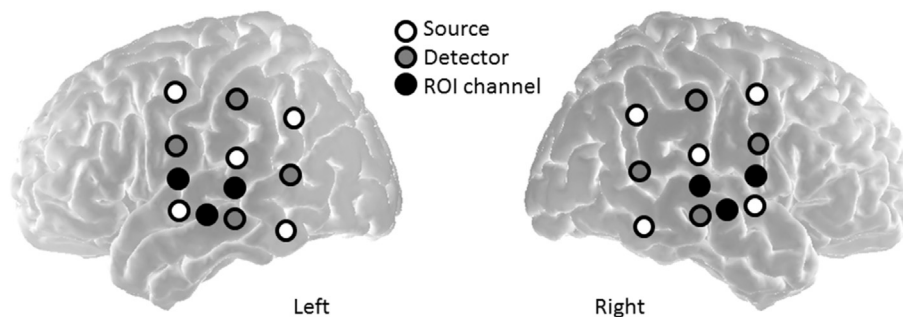


Fig. 1. Cohort grand average optode locations, projected onto a standardised cortical surface using AtlasViewer from HomER 2. Source locations are marked with white dots, while detector locations are marked in grey. Channels that formed the anatomically derived regions of interest based on the probable location of Heschl's gyrus and the superior temporal gyrus are indicated in black.

to each of the six stimuli. Statistical analysis was carried out on the GLM beta values. As the analysis involves multiple outcomes and multiple dependent variables, a multivariate analysis of variance (MANOVA) was performed on the GLM beta estimates of the response. The MANOVA assessed the effects of multiple factors (participant group, stimulus modality and stimulus type within modality) on the GLM beta estimate of the fNIRS response. A Student's T-test was used to compare between individual conditions where multiple comparisons were not being made.

3. Results

The cohort grand average channel locations are shown in Fig. 1, projected onto an anatomical atlas (Tsuzuki et al., 2012), estimating the anatomical locations of the optode arrays on the scalp, and of the left and right ROIs, and also the variation across the group of the optode locations on the scalp. Across all participants, the mean displacement from the median location of the central optode (placed according to the 10–20 procedure) was 9.8 mm. Indeed the mean displacement of all 9 optodes in the 3×3 array from their median location was 12.5 mm. Since the optode separation of the Hitachi ETG4000 is fixed at 30 mm, our results are unlikely to be significantly influenced by this minimal variation in optode placement.

Raw light intensity time courses contained stimulus-driven activity with noise from a variety of sources, including heart beat and motion, which was consistent with published findings (Sevy et al., 2010). A total of 52 channels out of an available 1440 channels (3.6%) met the exclusion criteria outlined in the methods section and thus were removed from further analysis. Of these, 16 out of 360 available ROI channels were excluded (4.4%). Even after this step, a degree of variance is still present in the data, likely derived from occlusion of the optodes by hair follicles, and imperfect light transmission due to poor fitting of the optode array because of variation in the location and size/angle of the pinna and jawbone. Interference from the skull and optical contributions from the scalp and cerebrospinal fluid (CSF) may also contribute to noise in the data. This is evident in the group mean \pm standard error across participants' time courses of ROI HbO and HbR response to each stimulus (Fig. 2).

Cortical fNIRS activation is typically associated with an increase in HbO and corresponding decrease in HbR which occur following stimulus onset, and typically peak at approximately 5–6 s after the onset of a short stimulus or event. After the change in concentration has peaked, this then returns to undershoot the original baseline level, often reported in fMRI studies as the “post-stimulus undershoot” (Schroeter et al., 2006). Fig. 2 (panels G and S) illustrates that in the normally-hearing group, AM noise was associated with low amplitude fluctuations in both ROIs, where the standard error significantly overlaps zero (i.e. no detectable response). The profoundly-deaf group showed low amplitude deactivation in both ROIs (panels A and M). Unmodulated noise elicited an HbO response in the right ROI of the normally-hearing group (panel H) with a peak amplitude and latency of 6.0 μmol and 7.6 s, respectively. Unmodulated noise elicited a similarly large response in the left ROI (panel T), but as the peak did not occur until after the end of the stimulus presentation period, we are unable to report peak amplitude and latency in this case. The peak amplitude was comparatively smaller (5.3 μmol) and the peak latency was shorter (6.4 s) in the profoundly-deaf group right side ROI (panel B), and once again approximately zero in the left side ROI (panel N).

In the profoundly-deaf group, HbO increased to a peak amplitude of 6.8 μmol in 10.7 s in response to coherent dots in the right ROI (panel C), but the same stimulus only elicited a

peak amplitude of 1.9 μmol in 11.1 s in the left ROI (panel O). The peak amplitude of the responses to random dots (panels D and P) were comparatively small (2.2–2.3 μmol) with fast peak latencies (1–2 s), and with a much larger deactivation following the end of the stimulus period. In the normally-hearing group, responses to both visual stimuli in both ROIs were small and standard errors overlapped with zero, however these responses also demonstrated a substantial post-stimulus undershoot (panels I, J and U, V).

The peak amplitude and peak latency of the response to the 20 Hz vibrotactile stimulus were similar between the two groups in the right ROI (profoundly-deaf, panel E: 5.0 μmol and 10.1 s; normally-hearing, panel K: 5.0 μmol and 8.7 s) but, in normally-hearing individuals the response on the left side had a smaller peak latency and smaller amplitude than that of profoundly-deaf individuals (profoundly-deaf, panel Q: 3.6 μmol and 3.1 s; normally-hearing, panel W: 1.5 μmol and 1.6 s). Responses to the 10 Hz vibrotactile stimulus were only recognisable in the normally-hearing group (4.8 μmol and 8.9 s in the right side ROI, panel L; 5.3 μmol and 9.6 s in the left side ROI, panel X). The deaf group showed deactivation in both ROIs in response to the 10 Hz vibrotactile stimulus, and particularly after the end of the stimulus period (panels F and R). Statistical analysis using MANOVA did not find any significant effect of group, modality or stimulus type within modality.

Within any single sensory modality, no significant differences were found in response to the two stimulus types (i.e. auditory: unmodulated versus AM noise; visual: randomly versus coherently moving dots, nor somatosensory: 10 Hz versus 20 Hz vibrations). Therefore, for all subsequent analyses responses to pairs of unisensory stimuli were averaged.

To assess the goodness of fit of a GLM using multiple linear regression using least squares, it is possible to calculate a statistic for each channel in each participant. This represents the goodness of fit of the GLM to the data. As stated in the analysis section, it was necessary for the GLM to incorporate responses to stimuli in all three modalities. However, the normally-hearing control group were hypothesised to show responses to only one third of stimuli, and the profoundly-deaf group were hypothesised to show responses to at most two thirds of stimuli. Individual subject *p* values for the fit of each channel's timecourse to the GLM did not differ significantly between the two ROIs or between the two participant groups, or between the two ROIs. No individual *p* value for the model exceeded $p < 4 \times 10^{-6}$.

Fig. 3 shows the group mean auditory, visual and somatosensory GLM beta values of the HbO response within the right ROI for the two participant groups. Consistent with expectations, the left and right ROIs responded to auditory stimulation in the normally-hearing group. Specifically, a one-sample Student's T-test on beta estimates of fNIRS responses confirmed that bilateral ROIs responded to unmodulated and AM noise significantly more than to rest (normally-hearing group mean (\pm standard error) beta estimate = 2.19 ± 0.86 ; $p = 0.021$, $T = 2.077$, 58 degrees of freedom). In contrast, as we hypothesised, the profoundly-deaf group did not show a significantly greater response to these sounds compared with rest ($p = 0.46$).

A two-sample t-test was performed to compare the beta estimate of the fNIRS response to moving visual stimulation (combined responses to randomly and coherently moving dots) in the right side ROI between the two participant groups. The response was significantly greater in the profoundly-deaf group compared to the normally-hearing control group (profoundly-deaf group mean (\pm standard error) beta estimate = 2.58 ± 1.43 ; normally-hearing group = -0.35 ± 0.83 ; $p = 0.041$, $T = 1.774$, 58 degrees of freedom). This group difference was not observed in the left side ROI

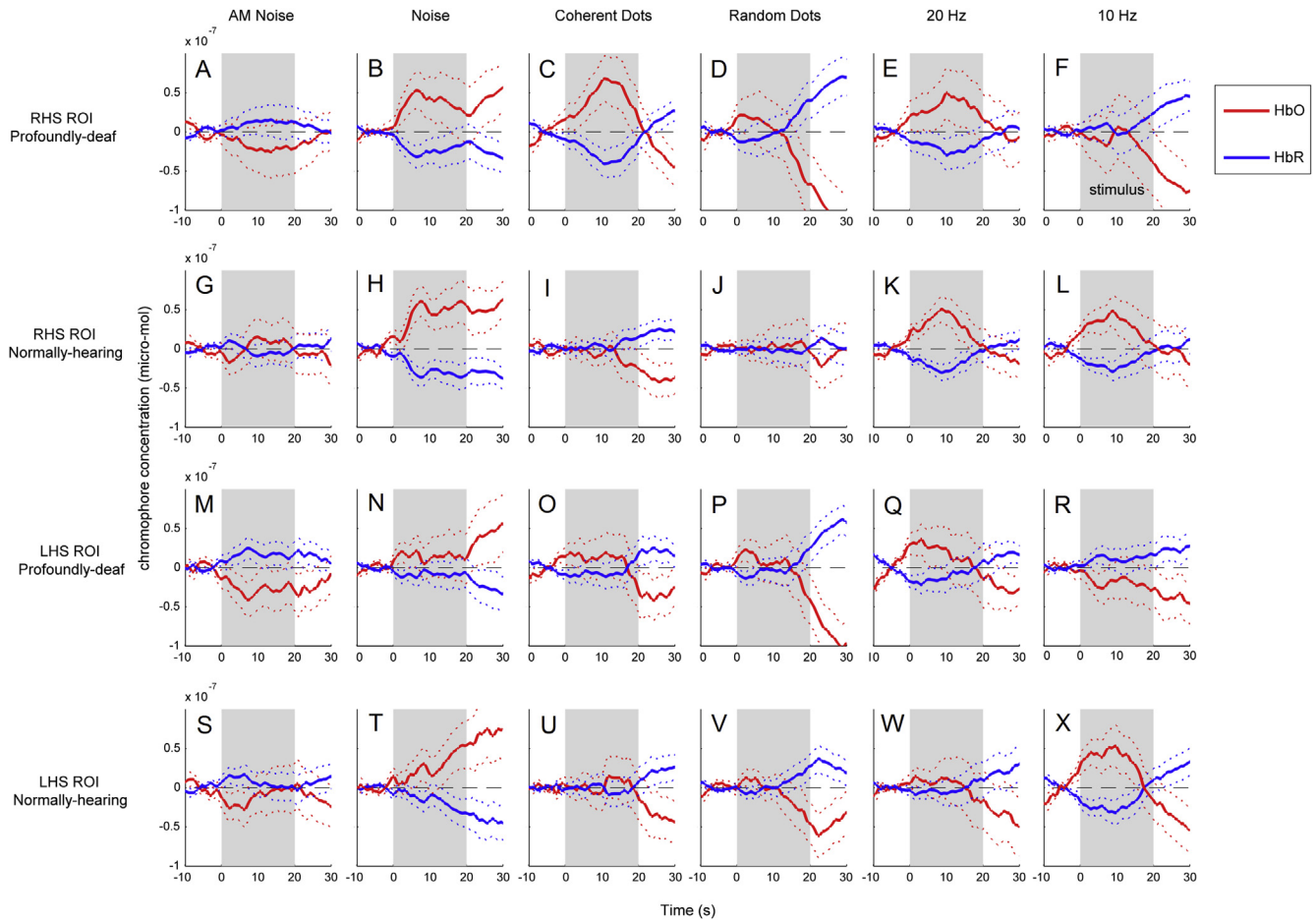


Fig. 2. Left and right ROI group mean auditory, visual and somatosensory responses in the profoundly-deaf group ($n = 30$) and normally-hearing controls ($n = 30$). Red lines represent HbO and blue lines represent HbR responses. Mean time courses are shown in solid lines (\pm standard error in dotted lines). Shaded grey box indicates duration of presented stimulus.

($p = 0.17$). Therefore this result is consistent with previous findings using alternative imaging techniques (Finney et al., 2001, 2003; Vachon et al., 2013) to suggest that the right auditory cortex is activated by visual stimulation following profound hearing loss.

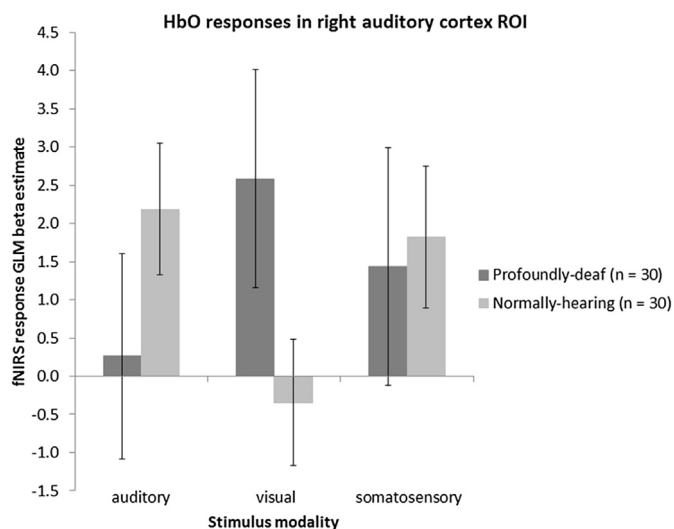


Fig. 3. Group mean (\pm standard error) general linear model beta estimates of fNIRS response in auditory, visual and somatosensory modalities in the right side ROI. Group difference in the visual modality is significant to $p = 0.041$.

In the somatosensory domain, neither ROI showed any significant difference in cortical activation between the two groups of individuals (left ROI: $p = 0.17$; right ROI: $p = 0.42$).

To investigate whether the group difference in cross-modal visual responsiveness was dominated by pre-lingually deaf individuals, a subgroup analysis was performed. When including only those profoundly-deaf individuals who lost their hearing before the onset of language (assumed to be 2–3 years of age) a subgroup analysis on the responses of $n = 22$ profoundly-deaf individuals did not reveal a significant difference in cross-modal visual response in the ROI ($p = 0.24$) in comparison to normally-hearing controls ($n = 30$).

4. Discussion

This is the first study to report cross-modal cortical responses in profoundly-deaf individuals using fNIRS, a neuroimaging modality that is non-invasive, silent and compatible with a CI. As expected, we found in normally-hearing participants that a significant fNIRS response was elicited by broadband noise, compared with rest. Interestingly, we only found a non-significant trend for auditory responses to be larger in the normally-hearing group when compared with profoundly-deaf individuals. Our inclusion criteria for the profoundly-deaf group were audiometric thresholds of ≥ 90 dB at 2 and 4 kHz, based on UK CI candidacy (NICE, 2009). Three of our profoundly-deaf participants had thresholds below 90 dB SPL at 0.5, 1 kHz, and further participants may have residual

hearing at frequencies other than those measured. This may explain why we did not find a statistically-significant difference in auditory responses between the two groups.

Consistent with our hypothesis, we found that moving visual stimuli evoked responses in the right ROI that were significantly larger in profoundly-deaf individuals, compared with normally-hearing controls. Our sample size of $n = 30$ profoundly-deaf participants was substantially larger than most previous imaging studies in this field, for example Finney and colleagues (2003; $n = 5$) and Neville and Lawson (1987; $n = 12$). Hearing loss can arise at any age, from diverse aetiologies that may account for some of the variance in cortical cross-modal responsiveness observed between individuals (Fig. 3). As shown in Table 1, residual hearing at low thresholds, duration of deafness, age at onset of deafness, hearing aid use and reliance on sign language all varied between participants. Although we found no significant correlation between any of these factors and responsiveness of auditory cortex to visual stimulation, there was a weak negative ($R = -0.24$) correlation between duration of deafness and responses to coherent visual stimuli, which was only observable in the right ROI. Interestingly in response to all stimulus conditions, cortical activation varied more between individuals in the profoundly-deaf group, compared with controls (Fig. 3). Future studies may choose to investigate the correlation between cross-modal responses and the degree of visual communication used, as this information was not sought from participants in the present study. Importantly, no correlation was found between cross-modal responsiveness of auditory cortex and participant age, thus confirming that the difference in participant age between the two groups was not responsible for the cross-modal plasticity reported.

Whilst the majority of profoundly-deaf participants had larger responses to visual stimulation than did normally-hearing controls, the sizes of individual responses to visual stimulation overlapped between the profoundly-deaf and normally-hearing groups, and some profoundly-deaf individuals exhibited larger ROI responses to auditory than to visual stimulation. Due to the heterogeneity of the profoundly-deaf group, it was not possible to perform extensive subgroup analyses, and we did not have any hypotheses regarding outcome differences across subgroup. More homogeneous groups of exclusively congenitally-deaf participants generally lead to larger group differences with smaller variance, similar to the ones previously reported in the literature (Finney et al., 2001, 2003; Karns et al., 2012; Vachon et al., 2013). The present study did not selectively recruit congenitally-deaf individuals. However, subgroup analyses involving only pre-lingually deaf individuals did not show a significant effect of deafness on cross-modal plasticity. This implies that cross-modal responses in auditory cortex of post-lingually deafened subjects contributed to the group effect. Rather than being ‘all-or-nothing’, our results suggest that deafness may be associated with varying degrees of cross-modal plasticity that may partly depend on an individual’s sensory experience, including their auditory experience and hearing aid use. This further demonstrates the importance and novelty of the heterogeneous sample of profoundly-deaf individuals recruited in this study.

It has been argued that some deaf individuals perceive acoustic vibrations from hearing aids *via* skin receptors or bone conduction. This has been used to explain fMRI responses to somatosensory stimulation in auditory brain regions of deaf individuals (Auer et al., 2007). An electrophysiological study has also reported larger cortical responses to vibrotactile stimulation in deaf, compared with normally-hearing ferrets (Allman et al., 2009). Despite the majority of the profoundly-deaf participants in our study (26 out of 30) reporting occasional or regular hearing aid use, contrary to our hypothesis, fNIRS responses in the ROI to somatosensory

stimulation were similar between profoundly-deaf and normally-hearing groups. Studies reporting multi-modal responses to bimodal somatosensory-auditory stimulation in hearing individuals (Fuxe et al., 2002; Caetano and Jousmaki, 2006) and also unimodal vibrotactile responses in deaf individuals (Auer et al., 2007) have attributed activated areas to be within auditory cortex. Analogous non-human primate studies have shown that the caudomedial (CM) region of auditory cortex responds to unimodal somatosensory and bimodal auditory-somatosensory stimulation (Fu et al., 2003; de la Mothe et al., 2006; Hackett et al., 2007). We believe activity in these areas may be too medial, and too deep in the sulcus (i.e. too far from the scalp surface) to be recorded using fNIRS. Additionally, the somatosensory cortex is located in the post-central gyrus of the parietal lobe, and has been imaged using fNIRS with similar optode placements to our own (Habermehl et al., 2012). Therefore fNIRS responses in the ROI may incorporate activation of this neighbouring region. Further, as responses to the 20 Hz stimulus were expected to be greater than to the 10 Hz stimulus (Golaszewski et al., 2002; Valaparla et al., 2012), these will have been picked up to a greater extent. We plan to investigate this possibility in a future study using synchronous fNIRS and fMRI recordings, since fMRI provides greater spatial resolution than fNIRS.

Many of the cortical activations measured were associated with large post-stimulus deactivations; decreases in HbO and corresponding increases in HbR that are often associated with a post-stimulus undershoot of the haemodynamic response (Schroeter et al., 2006). This was particularly noticeable following visual stimulation and somatosensory stimulation, and was seen in both participant groups. This may represent the localised cerebral blood flow returning to baseline faster than the cerebral blood volume, leading to a higher HbO concentration, which subsequently, slowly returns to baseline (Kong et al., 2004). This could be further investigated by recording the refractory period between consecutive stimuli and subsequent return of signal to baseline (by increasing the inter-stimulus interval).

Using fNIRS we did not find a significant difference between responses to parametric variations of unisensory stimuli. Alternative recording modalities, including fMRI, are able to detect differences in cortical responses to AM noise, compared with unmodulated noise (Giraud et al., 2000). Recording artefacts associated with fNIRS may partially account for our null finding. Due to the curvature of the skull, interference from the scalp and hair and difficulty in securing the optode array to the head due to the location of the ears, measurement of temporal lobe activity using fNIRS is associated with challenges that are not experienced with fMRI. Indeed, pre-processing of fNIRS recordings is essential to remove artefacts arising from motion and physiological noise, while remaining mindful that such methods may introduce systematic errors into the data, or conversely discard useful signals unnecessarily. Other measures to improve fNIRS recordings by increasing optode contact with the scalp, such as applying bandages around the optodes and limiting participant motion using a chin rest have been described (Strait and Scheutz, 2014).

Whilst one animal study found no evidence for cross-modal plasticity following deafness (Kral et al., 2003), other studies have reported visual and somatosensory responses in primary auditory cortex or closely related regions of deaf animals (Allman et al., 2009; Lomber et al., 2010; Meredith and Lomber, 2011; Meredith and Allman, 2012). Furthermore, Lomber et al. (2010) used cooling techniques to reversibly inactivate auditory cortex of cats to show that cross-modal plasticity following deafness enhances visual motion perception and spatial sensitivity in the peripheral visual fields. Conversely, functional neuroimaging studies in humans (Buckley and Tobey, 2011; Rouger et al., 2012; Sandmann

et al., 2012; Strelnikov et al., 2013) suggest that cross-modal plasticity of the deaf auditory cortex may also result in poor perceptual outcomes following the activation of a CI.

Our findings in profoundly-deaf individuals using fNIRS are comparable to previous reports of cross-modal activation of right auditory cortex with fMRI using coherently moving dots (Finney et al., 2001) and MEG using visual gratings (Finney et al., 2003). Conversely, Karns et al. (2012) found that visual and tactile stimulation activated auditory cortex bilaterally following deafness. Unlike previous studies (Sadato et al., 1996; Finney et al., 2001; Auer et al., 2007; Vachon et al., 2013) and our own that all used bilateral stimulus presentation, Karns et al. (2012) presented all stimuli to the right eye only, which may account for the inconsistent findings across studies.

The right auditory cortex has been implicated in the processing of visual sign language in deaf individuals (Nishimura et al., 1999; Petitto et al., 2000) and the processing of silent lip reading stimuli in hearing individuals (Calvert et al., 1997). Furthermore, evidence also suggests that auditory motion is predominantly processed in right auditory cortex (Baumgart et al., 1999). The use of sign language is suggested to affect cortical organisation of those regions involved in the processing of visual motion (Vachon et al., 2013). Together this indicates that even without cross-modal plasticity, the right auditory cortex has a higher propensity toward the processing of sensory motion, which may be enhanced further following sensory deprivation in the form of profound hearing loss. Interestingly, blind subjects exhibit equivalent cross-modal responses to moving auditory stimuli, predominantly in the right visual cortex (Weeks et al., 2000), again showing a hemispheric preference towards processing of sensory motion. It has been suggested that multimodal sensory units may be unmasked through sensory deprivation. Specifically, multisensory regions within primary sensory cortices may respond more strongly to a different sensory input due to the absence or removal of input in the deprived sensory modality (Auer et al., 2007).

It is now possible to partially restore hearing to deaf individuals using a CI, and hence it is important to consider the effects of brain plasticity on CI outcome. Recent evidence obtained using EEG supports the suggestion that cross-modal activation of auditory brain regions prior to implantation correlates with poor speech outcomes with a CI (Lee et al., 2007; Rouger et al., 2012; Sandmann et al., 2012). Further, increased temporal lobe responses to visually cued phonological and environmental sound representations were also associated with poor CI performance (Lazard et al., 2013). The reverse has also been reported, whereby auditory speech recovery was found to correlate positively with visual activity measured using PET (Strelnikov et al., 2013). However the causal relationship between cross-modal brain plasticity and CI outcome remains uncertain. It is possible that individuals who rely on visual modes of communication, and who therefore exhibit stronger cortical activation to visual stimulation, are less likely to switch to aural communication methods with their implant because of their continued reliance on sign language and/or speech reading. This may subsequently lead to poor clinical outcome. Also, this may have contributed to the strong visual activation of temporal regions observed in our profoundly-deaf population, since more than two-thirds of them relied on BSL for communication (Table 1). Alternatively it is possible that the visual takeover of auditory brain regions prevents recovery of aural modes of communication after activation of a CI. The causal relationship between these factors is most likely to be revealed through making a series of longitudinal observations before and after implantation. Unlike most other recording techniques, fNIRS is highly suited to longitudinal recordings in CI populations since it is safe for repeated use and is unaffected by the presence of a CI.

5. Conclusions

In conclusion, we found increased activation to visual stimulation in right auditory cortex of profoundly-deaf individuals compared to normally-hearing controls using fNIRS. This supports the notion that auditory deprivation induces cross-modal plasticity within auditory brain regions. Our findings demonstrate the potential of fNIRS for studying cross-modal cortical plasticity prior to and following cochlear implantation, in all age groups. With further development, fNIRS may prove a useful prognostic indicator of CI outcome, and/or objective measure of CI performance.

Conflict of interest

The authors declare no competing financial interests.

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