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# Cross-modal activation of auditory regions during visuo-spatial working memory in early deafness

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Early deafness can reshape deprived auditory regions to enable the processing of signals from the remaining intact sensory modalities. Cross-modal activation has been observed in auditory regions during non-auditory tasks in early deaf subjects. In hearing subjects, visual working memory can evoke activation of the visual cortex, which further contributes to behavioural performance. In early deaf subjects, however, whether and how auditory regions participate in visual working memory remains unclear. We hypothesized that auditory regions may be involved in visual working memory processing and activation of auditory regions may contribute to the superior behavioural performance of early deaf subjects. In this study, 41 early deaf subjects (22 females and 19 males, age range: 20–26 years, age of onset of deafness < 2 years) and 40 age- and gender-matched hearing controls underwent functional magnetic resonance imaging during a visuo-spatial delayed recognition task that consisted of encoding, maintenance and recognition stages. The early deaf subjects exhibited faster reaction times on the spatial working memory task than did the hearing controls. Compared with hearing controls, deaf subjects exhibited increased activation in the superior temporal gyrus bilaterally during the recognition stage. This increased activation amplitude predicted faster and more accurate working memory performance in deaf subjects. Deaf subjects also had increased activation in the superior temporal gyrus bilaterally during the maintenance stage and in the right superior temporal gyrus during the encoding stage. These increased activation amplitude also predicted faster reaction times on the spatial working memory task in deaf subjects. These findings suggest that cross-modal plasticity occurs in auditory association areas in early deaf subjects. These areas are involved in visuo-spatial working memory. Furthermore, amplitudes of cross-modal activation during the maintenance stage were positively correlated with the age of onset of hearing aid use and were negatively correlated with the percentage of lifetime hearing aid use in deaf subjects. These findings suggest that earlier and longer hearing aid use may inhibit cross-modal reorganization in early deaf subjects. Granger causality analysis revealed that, compared to the hearing controls, the deaf subjects had an enhanced net causal flow from the frontal eye field to the superior temporal gyrus. These findings indicate that a top-down mechanism may better account for the cross-modal activation of auditory regions in early deaf subjects.

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**Keywords:** early deafness; working memory; functional magnetic resonance imaging; superior temporal gyrus; visuo-spatial recognition

**Abbreviations:** A1 = primary auditory area; BOLD = blood oxygen level-dependent; FEF = frontal eye field; STG = superior temporal gyrus; V1 = primary visual area

## Introduction

Early sensory deprivation can remodel deprived sensory cortices to enable the processing of signals from the remaining intact sensory modalities. Such cross-modal reorganization has been reported in blind subjects for tactile and auditory perception (Weeks *et al.*, 2000; Gougoux *et al.*, 2005; Pito *et al.*, 2005; Poirier *et al.*, 2006; Voss *et al.*, 2008; Collignon *et al.*, 2011), as well as in deaf subjects for visual and tactile perception (Levanen *et al.*, 1998; Finney *et al.*, 2001; Auer *et al.*, 2007; Allman *et al.*, 2009; Lomber *et al.*, 2010; Meredith *et al.*, 2011; Karns *et al.*, 2012). Cross-modal reorganization of deprived sensory cortices has been associated with superior perceptual performance in the remaining sensory modalities in such subjects (Roder *et al.*, 1999; Van Boven *et al.*, 2000; Levanen and Hamdorf, 2001; Goldreich and Kanics, 2003; Gougoux *et al.*, 2005; Alary *et al.*, 2008, 2009; Dye *et al.*, 2009). Furthermore, the functional specialization of remodelled sensory cortices is relatively preserved. For example, area MT+, a visual area that is primarily specialized for visual motion processing, is also involved in processing motion in the auditory and tactile domains following early visual deprivation (Ricciardi *et al.*, 2007; Bedny *et al.*, 2010; Matteau *et al.*, 2010). Thus, sensory cortices may be specialized for different types of perceptual processes regardless of the mode of sensory input. In addition to perceptual processes, deprived sensory cortices are also involved in cognitive processes. In early blindness, visual cortices are activated by non-visual memory, attention, imagery and language tasks (Amedi *et al.*, 2003; Gougoux *et al.*, 2005; Stevens *et al.*, 2007; Weaver and Stevens, 2007; Renier *et al.*, 2010). Similarly, in early deafness, auditory cortices are activated by sign language (Sadato *et al.*, 2004; Obretenova *et al.*, 2010) and attention tasks (Bavelier *et al.*, 2001). These findings suggest that deprived sensory cortices are involved in both low-level perception and high-level cognitive processes.

As a fundamental physiological component of cognitive operations, working memory underlies our ability to temporarily maintain and manipulate attended information in mind to guide behaviour when the information is no longer accessible in the environment (Baddeley, 2003; Gazzaley

and Nobre, 2012). Working memory tasks have been used to investigate the role of normal and deprived sensory cortices in complex cognitive processing. In subjects with normal vision and audition, visual working memory can evoke sustained activation in visual regions (Harrison and Tong, 2009; Lee *et al.*, 2013; Xing *et al.*, 2013), and auditory working memory can induce frequency-specific activity in auditory regions (Linke *et al.*, 2011). Each of these activation patterns could impact final perceptual performance (Cattaneo *et al.*, 2009; Silvanto and Cattaneo, 2010; Zokaei *et al.*, 2014). In early blindness, deprived visual regions have exhibited activation during both auditory and tactile working memory tasks (Bonino *et al.*, 2008; Park *et al.*, 2011). However, it remains unclear whether deprived auditory regions are also involved in visual working memory in early deaf subjects, although they have exhibited superior working memory performance for spaces, faces and shapes compared to hearing subjects (Arnold and Murray, 1998; Cattani and Clibbens, 2005; Cattani *et al.*, 2007). Based on these findings, we hypothesized that auditory regions would be activated during visuo-spatial working memory task in early deafness. Because activity in normal and deprived sensory regions has been associated with superior behavioural performance (Roder *et al.*, 1999; Van Boven *et al.*, 2000; Levanen and Hamdorf, 2001; Goldreich and Kanics, 2003; Gougoux *et al.*, 2005; Alary *et al.*, 2008, 2009; Dye *et al.*, 2009), we also predicted that the activation of auditory regions during the working memory task would correlate with superior behavioural performance. It is a matter of debate whether the primary auditory area (A1) is involved in cross-modal reorganization in deaf subjects. Although a few studies have reported cross-modal activation of part of A1 in deaf subjects performing non-auditory tasks (Finney *et al.*, 2001; Fine *et al.*, 2005; Lambertz *et al.*, 2005; Auer *et al.*, 2007; Karns *et al.*, 2012; Scott *et al.*, 2014), the majority of studies have reported cross-modal activation in auditory association and multisensory regions but not in A1 (Nishimura *et al.*, 1999; Bavelier *et al.*, 2001; Shibata *et al.*, 2001; MacSweeney *et al.*, 2002, 2004, 2006; Sadato *et al.*, 2004, 2005; Lee *et al.*, 2007b; Capek *et al.*, 2008; Emmorey *et al.*, 2011; Cardin *et al.*, 2013; Vachon *et al.*, 2013; Li *et al.*, 2014). In deaf cats, single unit recordings in A1 failed to reveal visual

responses (Stewart and Starr, 1970; Kral *et al.*, 2003), and transient inactivation of A1 did not affect visual performances (Lomber *et al.*, 2010). Based on these studies, we further predicted that early deaf subjects would exhibit cross-modal activation primarily in auditory association and multisensory regions during the visuo-spatial working memory task.

If cross-modal activation in deaf subjects truly reflects involvement of deprived auditory regions in working memory, this cross-modal activity should be associated with the activity of prefrontal regions that are generally accepted as the source of top-down modulation during working memory tasks (Voytek and Knight, 2010; Zanto *et al.*, 2011; Gazzaley and Nobre, 2012). Thus, we hypothesized that compared to hearing subjects, early deaf subjects would exhibit increased information flow from prefrontal regions to auditory regions during the working memory task. Several factors may promote or constrain cross-modal reorganization in patients with sensory deprivation, such as the duration and age of onset of the sensory deprivation (Li *et al.*, 2012; Collignon *et al.*, 2013; Qin *et al.*, 2014). A recent study has reported that cross-modal activity in auditory regions is correlated with the percentage of lifetime hearing aid use in early deaf subjects (Shiell *et al.*, 2015). Thus, we predicted that earlier and longer hearing aid use would inhibit the cross-modal reorganization of auditory regions in early deafness. In the present study, we aimed to test these hypotheses by analysing the cross-modal activation and effective connectivity of auditory regions in early deaf subjects performing a visuo-spatial delayed recognition task.

## Materials and methods

### Participants

Forty-one right-handed early deaf adults (22 females and 19 males, age range: 20–26 years, age of onset of deafness < 2 years) were recruited from the Technical College for the Deaf of the Tianjin University of Technology. Forty right-handed hearing controls (20 females and 20 males, age range: 20–26 years) were also enrolled in the study. The demographic information for these subjects is shown in Table 1. The hearing thresholds of all of the deaf subjects were > 90 dB, which satisfies the criterion for profound deafness (Elzouki *et al.*, 2012). All deaf participants reported consistent hearing loss over their lifetime. All of 41 deaf subjects had a history of hearing aid use from 1.5 to 21 years of age. The age of onset of hearing aid use in the deaf subjects depended on their parents' awareness of hearing aids and the financial condition of their families. Lifetime auditory input was quantified as a percentage of lifetime hearing aid use (Shiell *et al.*, 2015). All individuals had normal visual acuity and no history of neurological or psychiatric disorders. This study was approved by the Medical Research Ethics Committee of Tianjin Medical University General Hospital, and all participants provided informed consent prior to the experiment.

### Experimental design

Experimental procedures were controlled using E-Prime version 2.0 software (Psychology Software Tools) in conjunction with a functional MRI Hardware System (NordicNeuroLab, NNL), and included six sessions with 16 trials per session.

The experimental paradigm is depicted in Fig. 1. A visuo-spatial delayed recognition task was used to evoke blood oxygen level-dependent (BOLD) signals. The task comprised encoding, maintenance and recognition stages. Participants were instructed to respond if the location of the target in the recognition stage matched that of the encoded items. During the encoding stage, 12 white circles ( $1.2^\circ$  of visual angle in size) were equally arranged in a concentric ring with an eccentricity of  $7^\circ$  around a central green fixation cross ( $1.2^\circ$ ). Small arrows either yellow or red in colour ( $1^\circ$  in size), were placed within these circles and randomly oriented to face one of four directions (up, down, left or right). Participants were instructed to memorize the locations of the up arrows (encoded items), irrespective of the arrow's colour. The locations of arrows in other orientations were ignored (distracter items). The encoding stage comprised four conditions: two loading levels (with one or three encoded items) that were each paired with two set-size levels (with four or 12 items), which were presented in a pseudo-randomized order with equal probability. After a 6-s encoding stage, participants were instructed to fix their gaze on a central green cross ( $1.2^\circ$ ) presented on a black background for 6 s (maintenance stage). Then, a white asterisk (target) was presented in only one of the circles for 2 s (recognition stage). Participants responded with a left or right button to indicate whether the location of the asterisk matched that of any of the encoded items. There was an equal number of matched and mismatched items and left and right locations presented across all of the experiments. During the intertrial interval, subjects were presented with a white cross ( $1.2^\circ$ ) in the centre of a black background for a pseudo-randomized period of either 4 or 6 s. As demonstrated by previous event-related functional MRI studies (Dale and Buckner, 1997; Burock *et al.*, 1998), a pseudo-randomized intertrial interval can effectively reduce the expectancy effect between trials and increase statistical power. Participants were instructed to maintain fixation during the maintenance stage and throughout the intertrial intervals.

### MRI data acquisition

MRI data were acquired using a 3.0-T MRI system (Discovery MR750, General Electric) with an 8-channel head coil. Tight but comfortable foam padding was used to minimize head motion, and earplugs were used to reduce scanner noise. The task-specific functional MRI data were acquired using a gradient-echo single-shot echo planar imaging sequence with the following parameters: repetition time = 2000 ms; echo time = 45 ms; field of view = 220 mm  $\times$  220 mm; matrix = 64  $\times$  64; flip angle =  $90^\circ$ ; slice thickness = 4 mm; gap = 0.5 mm; and 32 interleaved transverse slices. An array spatial sensitivity encoding technique with an acceleration factor of two was used to reduce image distortion and signal loss. Prior to each run, seven dummy scans were performed to enable the BOLD signals to reach steady-state magnetization. The experiment included six runs, each of which consisted of 152 volumes and lasted 5 min and 18 s.

**Table 1** Demographic and clinical information of subjects

	Hearing controls	Early deafness	Statistics	P-value
Gender(males/females)	20/20	19/22	$\chi^2 = 0.109$	0.742
Age (years)	23 $\pm$ 1.0	23 $\pm$ 2.0	$t = 0.662$	0.510
Age of onset of deafness (years)	–	0.8 $\pm$ 0.8	–	–
Duration of deafness (years)	–	22.1 $\pm$ 1.9	–	–
Age of onset of hearing aid use (years)	–	10.9 $\pm$ 6.6	–	–
Percentage of lifetime hearing aid use (%)	–	50.4 $\pm$ 27.7	–	–
Age of onset of sign language use (years)	–	6.8 $\pm$ 1.9	–	–
Percentage of lifetime sign language use (%)	–	16.1 $\pm$ 2.1	–	–
Degree of hearing loss (dB)	–	–	–	–
Left ear	–	102.6 $\pm$ 9.2	–	–
Right ear	–	102.0 $\pm$ 8.7	–	–

## Data preprocessing

Statistical Parametric Mapping version 8 (SPM8; <http://www.fil.ion.ucl.ac.uk/spm>) was used to preprocess the functional MRI data. Preprocessing included the following steps: slice timing (corrected for differences in acquisition time between slices); realignment (corrected for motion-derived inter-volume displacement using rigid body registration); spatial normalization [non-linearly normalized to a standard template in the Montreal Neurological Institute (MNI) space and re-sliced into  $3 \times 3 \times 3 \text{ mm}^3$  voxel size]; and spatial smoothing (with a Gaussian kernel size of  $8 \times 8 \times 8 \text{ mm}^3$  full-width at half-maximum). In this study, all functional MRI images had head motion below the thresholds of 3 mm in translation and  $3^\circ$  in rotation.

## Voxel-based activation analyses

The BOLD effects of the encoding, maintenance and recognition stages of the working memory task were modelled using a general linear model. For the first-level analysis, the time courses of the BOLD signals were convolved with the canonical haemodynamic response function and its first temporal derivative to correct for haemodynamic response delays and variations in time-to-peak values between subjects and regions. Other nuisance covariates, including session effects and six rigid motion parameters, were regressed out of the model. High-pass temporal filtering was implemented with a cut-off period of 128 s to remove low-frequency noise and signal drift. The working memory effects of each subject were estimated by comparing BOLD responses between each of the three conditions and the intertrial interval.

For the second-level analysis, voxel-wise two-sample *t*-tests were performed to estimate differences in the BOLD effects of each condition (encoding, maintenance or recognition) between the two groups. Clusters were considered statistically significant with a  $P < 0.05$ , corrected for multiple comparisons using the family-wise error (FWE) method, and a cluster size threshold of greater than 30 voxels. To investigate whether A1 was involved in cross-modal activation, we calculated the number of voxels that showed cross-modal activation within A1 of the AAL (Anatomical Automatic Labeling) template.

## Region of interest-based activation analyses

Each region of interest was defined as a sphere (9 mm in diameter) centred at the peak activation of each contrast. Deafness-specific regions of interest were defined as auditory regions that exhibited higher activity in the deaf group than in the hearing group. A one sample *t*-test was used to examine whether each region of interest showed significant activation in each group. To test whether the intergroup differences in activation of the auditory regions resulted from differences in eye movements, we examined whether weak intergroup differences could be detected in the region of interest of the frontal eye field (FEF) during each stage (Bavelier *et al.*, 2001). The FEF is a putative region for the control of eye movements, and its region of interest was extracted based on the peak activation (left FEF:  $-29 -13 46$ ; right FEF:  $29 -3 60$ ) in an eye movement task (Corbetta *et al.*, 1998).

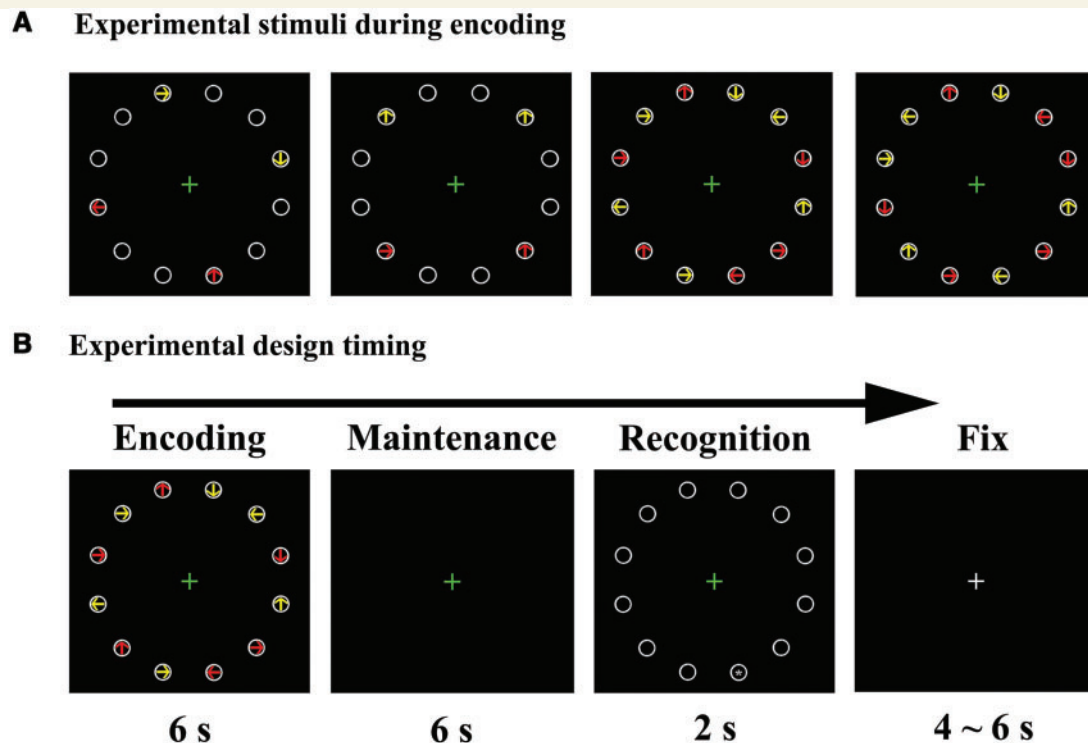
## Voxel-based correlations between activation and behavioural performance

Voxel-based partial correlation analyses over the whole brain were used to investigate associations between activation amplitude and behavioural performance in each group, controlling for age and gender effects. A corrected threshold ( $P < 0.05$ , FWE corrected) was used to identify significant correlations and an uncorrected threshold ( $P < 0.001$ ) was used to identify a trend towards significant correlations.

## Region of interest-based correlations between activation and behavioural performance

To reduce the possibility that the definition of regions of interest would be biased towards the deaf group, we also combined subjects from the two groups and defined auditory regions that exhibited significant activation in the combined population as unbiased regions of interest. These regions of interest were defined according to peak activation at the first-level analysis for each condition in all subjects. After regressing out the





**Figure 1 Experimental stimuli and task design.** (A) Stimuli used in the functional MRI experiment. Participants are instructed to memorize the locations of up arrows (encoded items) irrespective of the arrow's colour. The locations of arrows with other orientations are ignored (distractor items). The encoding stage contains four conditions: two load levels (one or three encoded items) paired with two sets of size levels (four or 12 items in total). (B) Task design timing in the functional MRI experiment.

effects of age and gender, Spearman correlation was used to test correlations between behavioural accuracy and activation amplitude in the two types of regions of interest during each stage in each group. Partial correlation coefficients were used to investigate associations between activation amplitude and reaction times in each group, controlling for age and gender effects. Both significant ( $P < 0.05$ , Bonferroni correction) and a trend towards significant correlations ( $P < 0.05$ , uncorrected) were reported.

## Region of interest-based correlations between activation and clinical parameters

After controlling for the effect of gender, partial correlation coefficients were used to investigate associations between the activation amplitude in the deafness-specific regions of interest during each task stage and the duration of auditory deprivation, percentage of lifetime hearing aid and sign language use in the deaf subjects. After controlling for the effects of gender and age, partial correlation coefficients were used to investigate associations between the activation amplitude in deafness-specific regions of interest during each task stage and the age of onset of hearing aid and sign language use in the deaf subjects. Both significant ( $P < 0.05$ , Bonferroni correction) and a trend towards significant correlations ( $P < 0.05$ , uncorrected) were reported.

## Granger causality analysis

Three pairs of regions of interest [peak MNI coordinates of (−6 −87 0) and (9 −81 3) for the primary visual area (V1); (−21 −3 54) and (27 0 57) for the FEF; and (−51 −33 6) and (63 −21 3) for the superior temporal gyrus (STG)] were included in a coefficient-based conditional Granger causality analysis (Hamilton *et al.*, 2011). The V1 region of interest was selected as the source of information and was defined as the V1 region with significant activation during the encoding stage in both groups of subjects (Supplementary Fig. 1). The STG region of interest represented the auditory region with cross-modal activation during the working memory task and was defined as the STG region with a significant intergroup difference in activation during the maintenance stage. We identified the prefrontal regions with the most significant activation during the maintenance stage in all subjects by analysing the load effect of the working memory task. Because FEF exhibited the greatest load effect (Supplementary Fig. 1), the FEF region of interest was selected as a source of top-down modulation.

The time course of BOLD signals of each voxel of each region of interest in each session was extracted from the normalized and smoothed functional MRI images. The temporal linear trend and the mean value of the time course of each voxel in each session were removed to achieve a status of covariance stationary, which is the primary prerequisite for Granger causality analysis (Seth, 2010). Subsequently, the first eigenvariate of all of the time courses across all voxels of each region of interest in each session was calculated to

represent the average BOLD response curve of each region of interest in each session. Finally, for each region of interest, the average BOLD response curves of the six sessions were concatenated before the Granger causality analysis. The Augmented Dickey-Fuller Test (Seth, 2010) confirmed that the preprocessed time courses of all regions of interest met the requirement for stationary covariance.

According to Granger causality theory (Granger, 1969), a time course  $X$  ‘Granger causes’ a timecourse  $Y$  if the past of  $X$  (defined by model order) predicts the future of  $Y$  more accurately than when considering only the past of  $Y$  itself. When more than two regions of interest are included in the model, the traditional bivariate Granger causality analysis may introduce spurious (indirect) causalities if there are causal dependencies between  $X$  and  $Y$  and a third set of variables  $Z$ . In this situation, a multivariate conditional Granger causality analysis is more reasonable (Gao *et al.*, 2011). This method regresses out the dependencies on the  $Z$  variables when calculating the causalities between  $X$  and  $Y$ . This model can be expressed as following equation:

$$Y_t = \sum_{k=1}^p \beta_{k(X \rightarrow Y|Z)} X_{(t-k)} + \sum_{k=1}^p \beta_{ky} Y_{(t-k)} + \sum_{m=1}^p \beta_{mz} Z_{(t-m)} + \varepsilon_t$$

$Y_t$  represents the current time course of  $Y$ , and  $Y_{(t-k)}$  and  $X_{(t-k)}$  represent the  $k^{\text{th}}$  past timecourses of  $Y$  and  $X$ , respectively.  $Z_{(t-m)}$  represents the  $m^{\text{th}}$  past time course of  $Z$ . The term  $\beta_{k(X \rightarrow Y|Z)}$  represents the coefficient of the autoregressive model. If  $\beta_{k(X \rightarrow Y|Z)}$  is significantly different from zero, we can infer that  $X$  Granger causes  $Y$  when controlled for the contribution(s) of  $Z$ . The term  $p$  represents the order of the model. In this study, the model order was set as one repetition time (2 s) based on previous studies (Hamilton *et al.*, 2011; Liao *et al.*, 2011; Wen *et al.*, 2012). To investigate net information flow between each pair of regions of interest, a net causal flow between  $X$  and  $Y$  was calculated as  $\beta_{k(X \rightarrow Y|Z)}$  minus  $\beta_{k(Y \rightarrow X|Z)}$ . A one-sample  $t$ -test was used to examine the net causal flow between each pair of regions of interest in each group. Then, a two-sample  $t$ -test was used to test for the intergroup differences in the net causal flow after controlling for the effects of age and gender. Both significant ( $P < 0.05$ , Bonferroni correction) and a trend towards significant correlations ( $P < 0.05$ , uncorrected) were reported.

## Behavioural statistical analyses

A Mann-Whitney U-test was used to compare differences in behavioural accuracy between the two groups. A two-sample  $t$ -test was used to assess the intergroup differences in reaction time and age. A Chi-square test was used to assess the intergroup differences in gender ( $P < 0.05$ ).

## Results

### Demographic and behavioural data

As shown in Table 1, there was no significant difference in age ( $t = 0.662$ ,  $P = 0.510$ ) or gender ( $\chi^2 = 0.109$ ,  $P = 0.742$ ) between the two groups. The mean hearing thresholds for

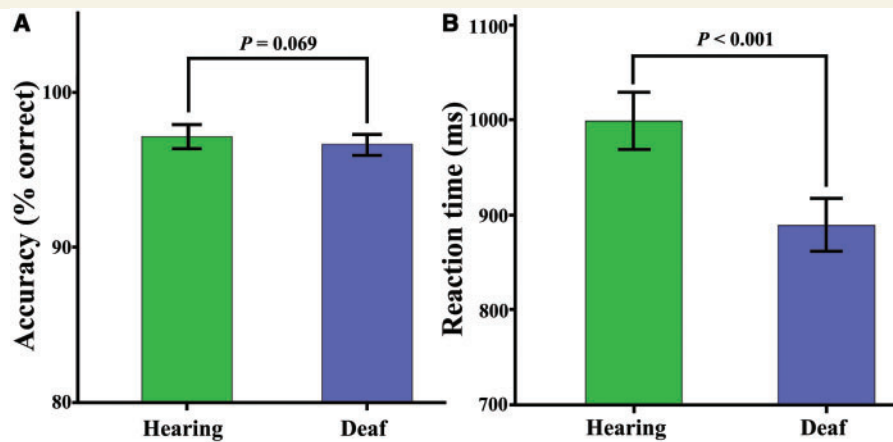
the deaf group were 102.6 dB in the left ear and 102.0 dB in the right ear, without the use of hearing aids. The mean duration of auditory deprivation (including time when hearing aids were used) was  $22.1 \pm 1.9$  years, the mean age of onset of hearing aid use was  $10.9 \pm 6.6$  years, the mean percentage of lifetime hearing aid use was  $50.4 \pm 27.7\%$ , the mean age of onset of sign language use was  $6.8 \pm 1.9$  years, and the mean percentage of lifetime sign language use was  $16.1 \pm 2.1\%$ . There was no significant difference in behavioural accuracy ( $z = -1.816$ ,  $P = 0.069$ ) between the deaf (range: 83–100%) and hearing (range: 75–100%) groups (Fig. 2A). The deaf group had a significantly shorter reaction time ( $888 \pm 180$  ms) than the hearing group ( $998 \pm 191$  ms) ( $t = 5.312$ ,  $P < 0.001$ ) (Fig. 2B).

## Activation analyses

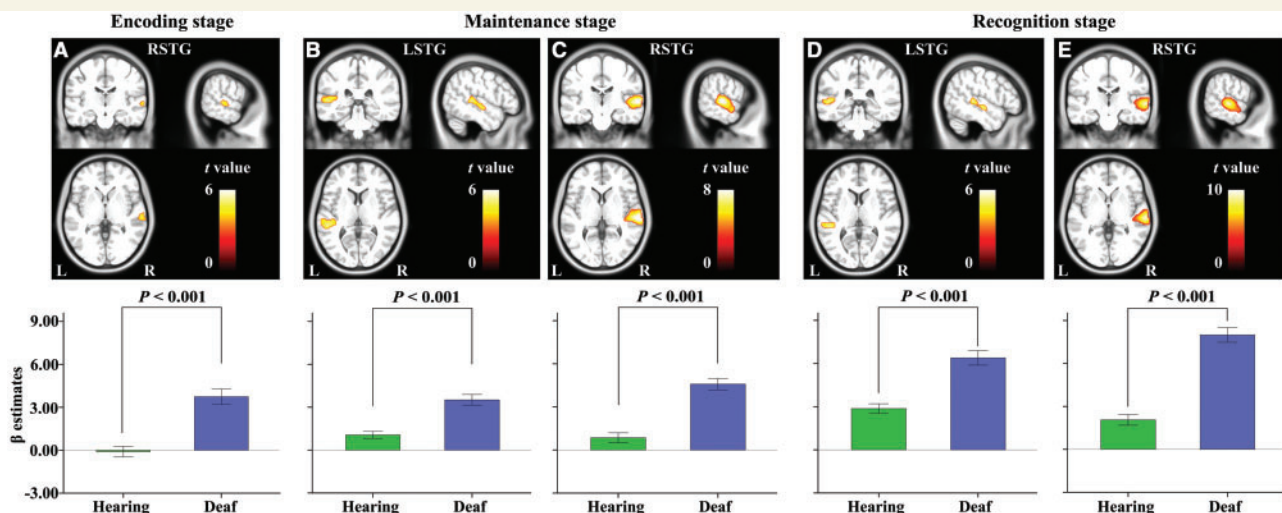
During the encoding stage, voxel-wise activation analyses showed that the deaf subjects exhibited greater activation in the right STG [peak MNI coordinates (66 –24 3), cluster size = 52 voxels, peak  $t$ -value = 5.52] than did the hearing controls ( $P < 0.05$ , FWE corrected) (Fig. 3A). Region of interest-based analyses of the activation amplitude ( $\beta$  estimates) demonstrated that only the deaf group displayed significant positive activation during the encoding stage ( $t = 13.740$ ,  $P < 0.001$ ) (Fig. 3A).

During the maintenance stage, the deaf subjects exhibited greater activation in the STG bilaterally [left STG, peak MNI coordinates (–51 –33 6), cluster size = 231 voxels, peak  $t$ -value = 5.80; right STG, peak MNI coordinates (63 –21 3), cluster size = 510 voxels, peak  $t$  value = 8.56] than did the hearing controls ( $P < 0.05$ , FWE corrected) (Fig. 3B and C). The activation pattern exhibited a trend towards right-side dominance when assessed using both peak  $t$ -values and cluster sizes. region of interest-based analyses of the activation amplitude demonstrated that both the deaf ( $t = 18.80$ ,  $P < 0.001$  for the left STG and  $t = 22.90$ ,  $P < 0.001$  for the right STG) and hearing ( $t = 8.52$ ,  $P < 0.001$  for the left STG and  $t = 4.97$ ,  $P < 0.001$  for the right STG) groups displayed positive activation during the maintenance stage (Fig. 3B and C).

During the recognition stage, the deaf subjects exhibited increased activation in the STG bilaterally [left STG, peak MNI coordinates (–51 –33 6), cluster size = 151 voxels, peak  $t$  value = 5.86; right STG, peak MNI coordinates (63 –21 0), cluster size = 382 voxels, peak  $t$  value = 9.65] relative to hearing subjects ( $P < 0.05$ , FWE corrected) (Fig. 3D and E). The activation pattern during the recognition stage also exhibited a trend towards right-side dominance. Region of interest-based analyses showed that both the deaf ( $t = 24.89$ ,  $P < 0.001$  for the left STG and  $t = 30.90$ ,  $P < 0.001$  for the right STG) and the hearing ( $t = 16.53$ ,  $P < 0.001$  for the left STG and  $t = 10.73$ ,  $P < 0.001$  for the right STG) groups displayed positive activation (Fig. 3D and E).



**Figure 2 Differences in working memory performance between the early deaf and hearing groups.** Compared to the hearing controls, the deaf subjects exhibited no significant differences in task accuracy (A), but displayed faster reaction time (B).



**Figure 3 Differences in cross-modal activation between the early deaf and hearing groups during the visuo-spatial working memory task.** Compared to the hearing controls, the early deaf subjects exhibit increased activation in the right STG during the encoding stage (A) and increased activation in the STG bilaterally during the maintenance (B and C) and recognition (D and E) stages ( $P < 0.05$ , FWE corrected). Top: Brain regions with significant intergroup differences in activation during each task stage. Bottom: Activation amplitudes ( $\beta$  estimates) of the STG in each group during each stage relative to the baseline.

Supplementary Table 1 shows the number of A1 voxels that exhibited a difference in activation between the two groups. We found that no A1 voxels exhibited an intergroup difference in activation during the encoding stage. Only one voxel of the left A1 and six voxels of the right A1 had intergroup differences in activation during the maintenance stage and only three voxels of the right A1 had intergroup differences in activation during the recognition stage.

We did not find any significant intergroup differences in FEF activation bilaterally during the encoding (left FEF:  $P = 0.802$ ; right FEF:  $P = 0.409$ ) and recognition (left FEF:  $P = 0.572$ ; right FEF:  $P = 0.119$ ) stages. However, we observed significantly enhanced activation in FEF bilaterally

during the maintenance stage (left FEF:  $P < 0.001$ ; right FEF:  $P = 0.002$ ). We compared intergroup differences in activation between FEF and STG via observing interaction effects between region of interest and group in a three-way repeated measures analysis of covariance model with group (deaf versus hearing) as between-subject factor, and side (left versus right hemisphere) and region of interest (STG versus FEF) as within-subject factors, controlling for the effects of age and gender. We found a significant interaction effect ( $F = 72.696$ ,  $P < 0.001$ ) between region of interest (FEF versus STG) and group (deaf versus hearing), suggesting that the intergroup difference in the STG activation was significantly greater than the intergroup difference in the FEF activation (Supplementary Fig. 2).



**Table 2** Correlations between STG activity and working memory performance

	Hearing controls				Deaf subjects			
	Deafness-specific ROI		Unbiased ROI		Deafness-specific ROI		Unbiased ROI	
	Accuracy	Reaction time	Accuracy	Reaction time	Accuracy	Reaction time	Accuracy	Reaction time
Encoding stage	<b>−0.214*</b>	0.133	<b>−0.215*</b>	0.065	0.119	<b>−0.319**</b>	0.116	<b>−0.286**</b>
Right STG	<b>(0.007)</b>	(0.097)	<b>(0.006)</b>	(0.418)	(0.130)	<b>(&lt; 0.001)</b>	(0.139)	<b>(&lt; 0.001)</b>
Maintenance stage	0.036	<b>−0.165*</b>	0.025	−0.123	0.075	<b>−0.429**</b>	<b>0.169*</b>	<b>−0.464**</b>
Left STG	(0.650)	<b>(0.038)</b>	(0.752)	(0.125)	(0.341)	<b>(&lt; 0.001)</b>	<b>(0.031)</b>	<b>(&lt; 0.001)</b>
Maintenance stage	−0.026	−0.121	0.085	<b>−0.215*</b>	0.129	<b>−0.449**</b>	0.036	<b>−0.336**</b>
Right STG	(0.740)	(0.131)	(0.286)	<b>(0.007)</b>	(0.100)	<b>(&lt; 0.001)</b>	(0.647)	<b>(&lt; 0.001)</b>
Recognition stage	−0.035	−0.028	−0.025	−0.053	<b>0.251**</b>	<b>−0.493**</b>	<b>0.210*</b>	<b>−0.465**</b>
Left STG	(0.663)	(0.723)	(0.750)	(0.511)	<b>(0.001)</b>	<b>(&lt; 0.001)</b>	<b>(0.007)</b>	<b>(&lt; 0.001)</b>
Recognition stage	−0.030	−0.062	−0.027	−0.101	<b>0.216*</b>	<b>−0.498**</b>	<b>0.184*</b>	<b>−0.378**</b>
Right STG	(0.703)	(0.440)	(0.732)	(0.205)	<b>(0.005)</b>	<b>(&lt; 0.001)</b>	<b>(0.018)</b>	<b>(&lt; 0.001)</b>

ROI = region of interest.

Data are presented as correlation coefficient (*P*-value). \* *P* < 0.05, uncorrected; \*\* *P* < 0.05, Bonferroni correction.

## Voxel-based correlations between activation and behavioural performance

Voxel-based correlations between brain activation and behavioural performance are shown in Supplementary Figs 3 and 4. In deaf subjects, behavioural accuracy showed a trend towards positive correlations ( $P < 0.001$ , uncorrected) with activations mainly in the lateral temporal region, but these correlations could not pass FWE correction ( $P < 0.05$ ). The reaction time was negatively correlated with activations mainly in the lateral temporal region and occasionally in some non-temporal regions ( $P < 0.05$ , FWE corrected); this trend was also confirmed in the analyses using an uncorrected threshold ( $P < 0.001$ ). In hearing subjects, behavioural accuracy was negatively correlated with activations mainly in the frontal and parietal regions; and only a small portion of the lateral temporal region showed a trend towards negative correlations with accuracy ( $P < 0.001$ , uncorrected). The relationship between reaction time and activations was rather complex: there was a positive correlation in the lateral frontal and parietal regions but a negative correlation in some other regions including a portion of the lateral temporal cortex.

## Region of interest-based correlations between activation and behavioural performance

The spatial locations of deafness-specific and unbiased regions of interest are shown in Supplementary Fig. 5. These two types of regions of interest were completely spatially distinct from each other. The deafness-specific regions of interest were located approximately in auditory association areas. In contrast, the unbiased regions of interest were located in multisensory auditory areas. Region of interest-based correlations between STG activation and behavioural

performance are shown in Table 2. In deaf subjects, the STG activation of both types of regions of interest during all three stages was significantly correlated with reaction time ( $P < 0.05$ , Bonferroni correction). Although the activation of the left (deafness-specific region of interest) and right STG (unbiased region of interest) showed a trend towards significant correlation ( $P < 0.05$ , uncorrected) with reaction time in hearing controls, none of the correlations were present following Bonferroni correction. The activation of the left STG, a deafness-specific region of interest, during the recognition stage was significantly correlated with behavioural accuracy in deaf subjects ( $P < 0.05$ , Bonferroni correction). In deaf subjects, a trend towards correlation ( $P < 0.05$ , uncorrected) was also found in other regions of interest during the recognition stage and in the left STG (unbiased region of interest) during the maintenance stage. In hearing subjects, only the activation of the right STG during the encoding stage showed a trend towards being negatively correlated with behavioural accuracy ( $P < 0.05$ , uncorrected).

To determine the possible role of the FEF activation during maintenance stage, we also investigated correlations between FEF activity and behavioural performance during this stage. We found a significant negative correlation ( $P < 0.05$ , Bonferroni correction) between the right FEF activity and accuracy in both deaf and hearing groups. We also found a trend towards significant correlation ( $P < 0.05$ , uncorrected) between the left FEF activity and accuracy in both groups and between the right FEF activity and reaction time in hearing group (Supplementary Table 2).

## Region of interest-based correlations between activation and clinical parameters

The correlations between STG activation and clinical parameters in deaf subjects are shown in Table 3.

**Table 3** Correlations between STG activity and clinical parameters in early deaf subjects

Deafness-specific ROIs	Encoding	Maintenance		Recognition	
	Right ROI	Left ROI	Right ROI	Left ROI	Right ROI
Duration of auditory deprivation	−0.022 (0.892)	−0.116 (0.476)	−0.025 (0.880)	−0.122 (0.453)	0.084 (0.607)
Age of onset of hearing aid use	0.251 (0.123)	<b>0.340</b> <b>(0.034)</b>	<b>0.335</b> <b>(0.037)</b>	0.076 (0.644)	0.117 (0.281)
Percentage of lifetime hearing aid use	−0.247 (0.124)	<b>−0.328</b> <b>(0.039)</b>	<b>−0.345</b> <b>(0.029)</b>	−0.072 (0.659)	−0.207 (0.200)
Age of onset of sign language use	−0.153 (0.347)	0.004 (0.979)	0.031 (0.849)	−0.102 (0.531)	0.057 (0.727)
Percentage of lifetime sign language use	0.118 (0.467)	−0.056 (0.729)	−0.049 (0.766)	−0.046 (0.776)	−0.053 (0.747)

ROI = region of interest.

Data are presented as correlation coefficient (*P*-value, uncorrected).

After controlling for the effect of gender, activation amplitudes during the maintenance stage showed a trend towards negative correlation with the percentage of lifetime hearing aid use in both the left ( $pr = -0.328$ ,  $P = 0.039$ , uncorrected) and right ( $pr = -0.345$ ,  $P = 0.029$ , uncorrected) STG in deaf subjects (Fig. 4A and B). However, in deaf subjects, correlations between the activation observed during any of the stages and the duration of auditory deprivation were not significant ( $P > 0.05$ , uncorrected). Similarly, correlations between the activation observed during the encoding and recognition stages and the percentage of lifetime hearing aid use were also not significant in deaf subjects ( $P > 0.05$ , uncorrected). After controlling for the effects of age and gender, activation amplitudes during the maintenance stage showed a trend towards positive correlation with the age of onset of hearing aid use in both the left ( $pr = 0.340$ ,  $P = 0.034$ , uncorrected) and right ( $pr = 0.335$ ,  $P = 0.037$ , uncorrected) STG in deaf subjects (Fig. 4C and D). However, we did not find any significant correlations between STG activation and sign language experience (age of onset of sign language use or percentage of lifetime sign language use) in deaf subjects ( $P > 0.05$ , uncorrected). We also investigated correlations between FEF activity during maintenance stage and clinical parameters in deaf subjects, but did not find any significant correlations ( $P > 0.05$ , uncorrected).

### Granger causality analyses

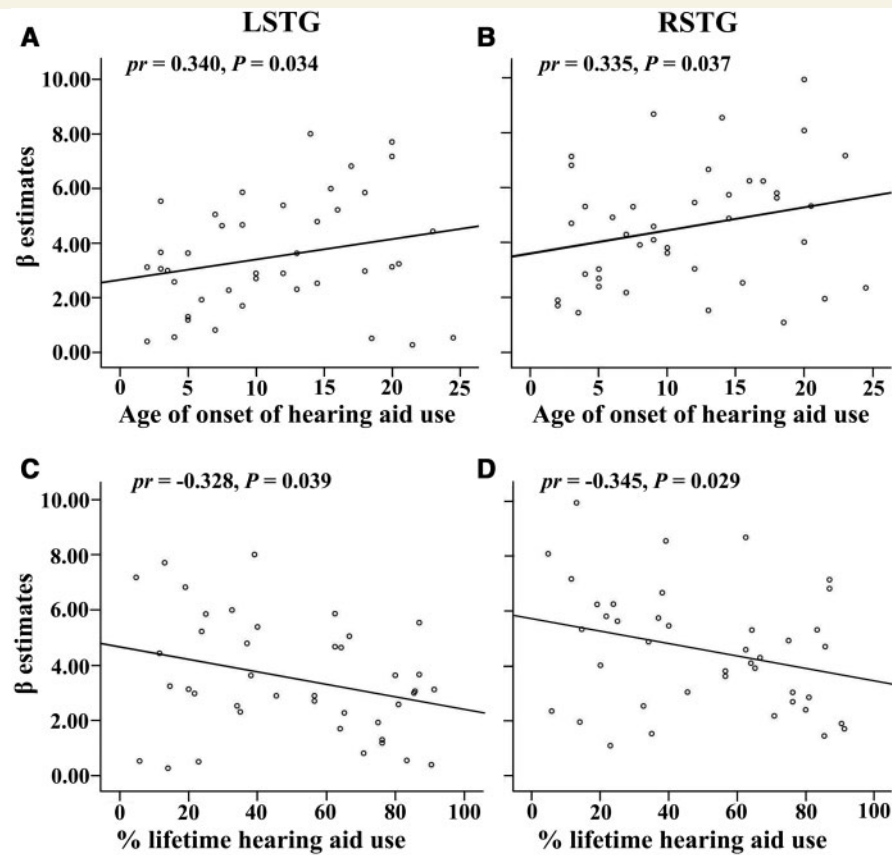
The results of the conditional Granger causality analysis are shown in Fig. 5 and Supplementary Table 3. Both the deaf and hearing groups showed significant net causal flow from FEF to V1, from FEF to STG and from V1 to STG in both hemispheres ( $P < 0.05$ , Bonferroni correction). Compared with hearing controls, deaf subjects had significantly increased net causal flow from right FEF to right STG during the task ( $P < 0.05$ , Bonferroni correction) and a trend towards significant increase from left FEF to left STG ( $P = 0.023$ , uncorrected).

## Discussion

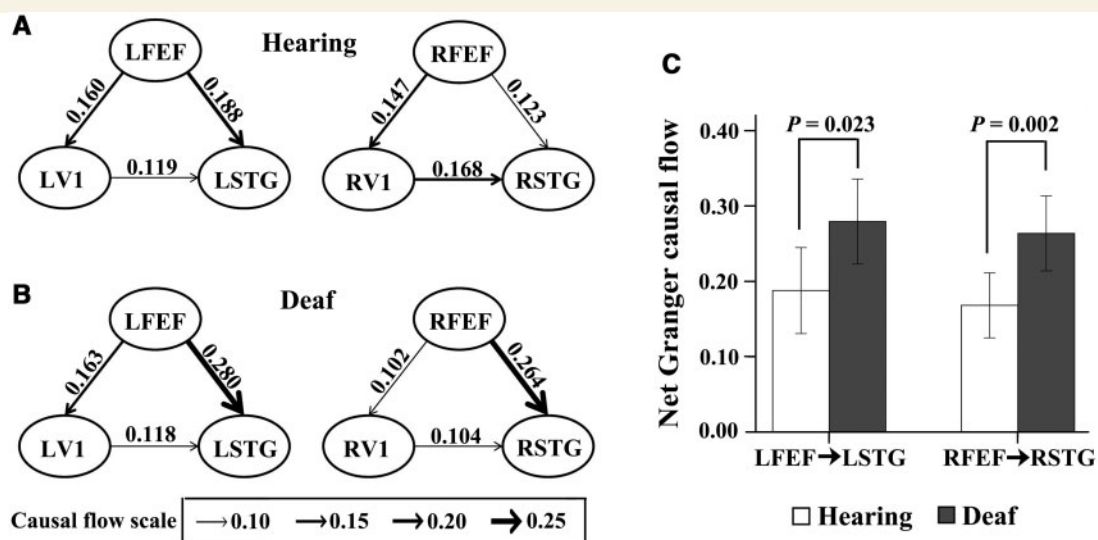
In this study, we used a visuo-spatial delayed recognition task to investigate cross-modal reorganization in auditory regions in early deaf subjects. We found superior working memory performance in the deaf group. Throughout the working memory task, deaf subjects consistently showed greater activation in the STG than did hearing controls. The amplitude of cross-modal activation was correlated with spatial perceptual performance in deaf subjects. These findings suggest that cross-modal plasticity in early deafness occurs in auditory association areas, which are involved in visuo-spatial working memory. Moreover, the amplitude of activation during the maintenance stage was correlated with the age of onset of hearing aid use and the percentage of lifetime hearing aid use in deaf subjects, indicating that earlier and longer hearing aid use may inhibit cross-modal reorganization in deaf subjects. Finally, deaf subjects showed an enhanced net causal flow from FEF to STG compared to hearing controls, suggesting that a top-down mechanism may underlie the cross-modal activation of auditory regions in deaf subjects.

### Cross-modal activation of auditory regions in early deafness

The deprived auditory regions exhibited greater cross-modal activation during a visuo-spatial working memory task in deaf subjects than in hearing controls. Moreover, cross-modal activation in auditory regions correlated with working memory performance in deaf subjects, but not in hearing controls. These findings provide the first evidence of the involvement of deprived auditory regions in working memory in early deaf subjects. Similarly, cross-modal activation in deprived visual regions is observed in early blind subjects when they are performing non-visual working memory tasks (Bonino *et al.*, 2008; Park *et al.*, 2011). In addition to working memory tasks, other cognitive tasks



**Figure 4** Correlations between the amplitude of cross-modal activation and clinical parameters in early deaf subjects. After controlling for the effect of gender, activation amplitudes observed during the maintenance stage are negatively correlated with the percentage of lifetime hearing aid use in both the left (A) and right (B) superior temporal gyri. After controlling for the effects of gender and age, activation amplitudes observed during the maintenance stage are positively correlated with the age of onset of hearing aid use in both the left (C) and right (D) superior temporal gyri ( $P < 0.05$ , uncorrected).



**Figure 5** Coefficient-based conditional Granger causality analysis. Both the early deaf (A) and hearing (B) groups show significant net causal flow from the frontal eye field (FEF) to the primary visual area (V1), from FEF to the superior temporal gyrus (STG), and from V1 to STG in both hemispheres. Compared with hearing controls, deaf subjects had increased net causal flow from FEF to STG in both hemispheres (C) ( $P < 0.05$ , uncorrected).

also recruit deprived sensory cortices after early sensory deprivation. For example, deprived auditory cortices of early deaf subjects are activated by sign language (Sadato *et al.*, 2004; Obretenova *et al.*, 2010) and attention tasks (Bavelier *et al.*, 2001), and deprived visual cortices of early blind subjects are recruited by memory, attention, imagery and language tasks (Amedi *et al.*, 2003; Gougoux *et al.*, 2005; Stevens *et al.*, 2007; Weaver and Stevens, 2007; Renier *et al.*, 2010). These findings suggest that involvement in cognitive processing is an important property of deprived sensory cortices. Is this ability specific to deprived sensory cortices or a general property of sensory cortices? Indeed, the recruitment of early sensory cortices in cognitive processing has been observed in healthy subjects with normal vision and audition. Taking working memory as an example, working memory tasks can evoke sustained activity in normal visual (Harrison and Tong, 2009; Lee *et al.*, 2013; Xing *et al.*, 2013) and auditory (Linke *et al.*, 2011; Bonte *et al.*, 2014) cortices, which then affects working memory performance (Cattaneo *et al.*, 2009; Silvanto and Cattaneo, 2010; Zokaei *et al.*, 2014). It seems that involvement in cognitive processing is a general property of sensory cortices. Deprived sensory cortices preserve this ability for cognitive processing following early sensory deprivation, even though the sensory modality of the information input has changed.

The voxel-based correlation analyses between activation and performance suggest that neural correlates of behavioural performance are largely different between deaf and hearing subjects. In hearing subjects, working memory performance is mainly associated with activations in the lateral frontal and parietal regions and negative correlations between performance and activation are in line with the neural efficiency hypothesis (Neubauer and Fink, 2009). However, in deaf subjects, working memory performance is mainly associated with activations in the lateral temporal cortex and positive correlations between performance and activation suggest that a higher performance is related to the investment of more cortical resources in this region. These correlations are not restricted to the STG in deaf subjects, suggesting that they are not specific to cross-modally reorganized areas, but are more general. Thus, correlation analyses between activation and performance may provide extra information about brain functional reorganization in deaf subjects that intergroup activation comparison alone would not reveal.

Although some of the activated voxels appeared to encroach onto portions of A1 in AAL template, we cannot draw any specific conclusion on the involvement of this area because previous studies have argued that A1 should only be anatomically defined in individual brains (Karns *et al.*, 2012; Scott *et al.*, 2014) but not solely on the basis of anatomical landmarks at a group-level (Rademacher *et al.*, 2001). However, we found strong evidence for involvement of auditory association areas in cross-modal reorganization in early deaf subjects, which is consistent with previous findings of cross-modal activation

in non-primary auditory regions (Nishimura *et al.*, 1999; Bavelier *et al.*, 2001; Shibata *et al.*, 2001; MacSweeney *et al.*, 2002, 2004, 2006; Sadato *et al.*, 2004, 2005; Lee *et al.*, 2007b; Capek *et al.*, 2008; Emmorey *et al.*, 2011; Cardin *et al.*, 2013; Vachon *et al.*, 2013; Li *et al.*, 2014). Although a few studies have reported cross-modal activation in A1 (Finney *et al.*, 2001; Fine *et al.*, 2005; Lambertz *et al.*, 2005; Auer *et al.*, 2007; Karns *et al.*, 2012; Scott *et al.*, 2014), cross-modal plasticity in A1 is not supported by single unit recording in deaf cats. In deaf cats, A1 does not respond to visual stimuli (Stewart and Starr, 1970; Kral *et al.*, 2003), and transient inactivation of A1 does not affect visual performance (Lomber *et al.*, 2010). A dissociation of A1 and auditory association areas in cross-modal plasticity is also supported by the differing responses of auditory regions to acoustic input following cochlear implantation. A1, rather than auditory association areas, could respond to auditory stimulation after cochlear implantation (Hartmann *et al.*, 1997; Tillein *et al.*, 2012). Thus, our results may support the hypothesis that cross-modal reorganization occurs in auditory association regions in early deaf subjects. This idea is further supported by the finding that only auditory association regions receive abnormal, non-auditory cortical projections in deaf cats (Barone *et al.*, 2013). Although multisensory auditory areas did not exhibit significantly enhanced activation in deaf subjects ( $P < 0.05$ , FWE corrected), the activation of these regions (unbiased regions of interest) was correlated with behavioural performance during the working memory task primarily in deaf subjects. These findings suggest that these multisensory auditory areas may also reorganize themselves to process working memory.

Functional specialization for domain-specific processing is an important property of sensory cortices. Taking the auditory cortex in hearing subjects as an example, transient perturbation of the posterior STG can damage sound localization abilities, whereas inhibition of the anterior STG can impair identity discrimination (Ahveninen *et al.*, 2013). These findings indicate that sound identity features are processed in anterior areas of the auditory cortex and sound location information is encoded in posterior areas. During the spatial working memory task, we found that the deaf group exhibited cross-modal activation primarily in the posterior STG, which is specialized for the spatial perception of sound in hearing subjects. These findings suggest that the functional specialization of the posterior STG for spatial processing is maintained following early auditory deprivation.

Functional lateralization is another property of sensory cortices. In hearing subjects, left auditory regions are preferred for processing language tasks (Lazard *et al.*, 2012; Price, 2012); however, the right hemisphere is dominant in spatial processing (Zatorre and Penhune, 2001; Krumbholz *et al.*, 2005; Weisz *et al.*, 2014). This functional lateralization is also preserved in auditory regions in early deaf subjects. For example, sign language can evoke greater activation in the left STG in deaf subjects (MacSweeney



*et al.*, 2004, 2006; Sadato *et al.*, 2005), whereas visual motion and spatial processing can evoke greater activation in the right STG (Finney *et al.*, 2001; Fine *et al.*, 2005; Sadato *et al.*, 2005). In this study, we found that the right STG exhibited more extensive and stronger activation than the left STG during the visuo-spatial working memory task. Moreover, this rightward lateralization of activation cannot be explained by the experimental protocol because the number of stimuli presented on the left and right were equal during the encoding and recognition stages. These findings suggest that functional lateralization for spatial processing is preserved in early deaf subjects.

Because deaf subjects can more quickly process peripheral stimuli than can hearing controls (Neville and Lawson, 1987; Bosworth and Dobkins, 2002), it is possible that the correlation between STG activation and reaction time could reflect enhanced peripheral reactivity in deaf subjects rather than anything to do with spatial working memory. To clarify this possibility, we also looked for correlations between STG activity and task accuracy. In deaf subjects, we found significant correlations between behavioural accuracy and the activity of the left STG during the maintenance stage and the activity of the STG bilaterally during the recognition stage. This result indicates that the enhanced STG activation observed in deaf subjects relates, at least in part, to the enhanced spatial working memory found in these subjects.

Background sounds are inherent to the technique of MRI and cannot be exactly matched between deaf and hearing subjects. The baseline activation of the auditory cortex produced by the acoustic noise of the scanner is expected to be greater in hearing controls than in deaf subjects. As a result, the lack of the small effects on cross-modal activity in the STG of hearing subjects could be attributable to elevated baseline activity in auditory regions. However, the effect of scanner noise in hearing subjects may also have been largely eliminated by our contrast analysis between the experimental and baseline conditions because scanner noise occurred equally in the two conditions.

There is evidence of a difference in working memory between signers and non-signers (Boutla *et al.*, 2004; Rudner *et al.*, 2009). One may argue that cross-modal activation in auditory regions occurs in response to sign language experience rather than as a result of sensory deprivation. Without a control group of hearing signers, we cannot directly dissociate the effects of sign language experience from the effects of sensory deprivation on cross-modal activation. However, we did not find any significant correlations between STG activation and sign language experience (age of onset and percentage of lifetime use) in early deaf subjects, providing evidence against the possibility that cross-modal activation occurs primarily in response to sign language experience. Moreover, STG activation exhibited a rightward lateralization, which also argues against this possibility because sign language is highly associated with left STG activation (MacSweeney *et al.*, 2004, 2006; Sadato *et al.*, 2005).

Although subjects were instructed to maintain fixation during the maintenance stage and throughout the intertrial intervals, eye movements were not recorded during the functional MRI runs or offline. However, the group difference in STG activation cannot be easily explained by eye movements because the STG is not one of the regions thought to be involved in eye movements. Furthermore, we did not find any significant intergroup differences in any brain regions associated with eye movements during any stages of the task using the same statistical threshold for identifying STG activation. To further verify that STG activation differences were unlikely to result from eye movements, we extracted a FEF region of interest according to a previous investigation of eye movements (Corbetta *et al.*, 1998). If eye movements were responsible for the increase in STG activation in deaf subjects, greater activation should have been observed in FEF in the deaf group, especially during the encoding and recognition stages, because we did not ask subjects to fixate during these two stages. We did not find any intergroup differences in FEF activation bilaterally during the encoding and recognition stages of the task. We observed a significant group difference in FEF activation bilaterally during the maintenance stage; however, intergroup differences in activation were much weaker in FEF than in STG. Moreover, we observed that FEF activation during maintenance stage was correlated with working memory performance, which is consistent with the concept that FEF is a putative region of working memory (Curtis, 2006; Wallentin, 2012). Thus, the enhanced FEF activation observed in deaf subjects during the maintenance stage may reflect functional reorganization in cognitive-related regions rather than eye movement.

## Neural pathways conveying information to the reorganized STG

Two candidate hypotheses have been proposed to explain how visual signals are transferred to deprived auditory regions in deaf subjects. The ‘rewiring’ mechanism hypothesizes that visual signals reach auditory regions via rewired subcortical connections. This hypothesis is supported by the following evidence: (i) normal auditory relays (such as the inferior colliculus) can receive visual signals (Groh *et al.*, 2001) that originate from the retina (Itaya and Van Hoesen, 1982) or the superior colliculus (Doubell *et al.*, 2000); (ii) the ‘rewiring’ of visual inputs into the auditory thalamus can subsequently allow the auditory cortex to process visual information (Horng and Sur, 2006); and (iii) A1 in deaf cats receives a weak projection from the visual thalamus, which is not observed in hearing cats (Barone *et al.*, 2013). The ‘unmasking’ theory proposes that the loss of auditory input induces unmasking and/or the strengthening of existing neural pathways. In hearing animals, there are direct (Budinger *et al.*, 2006) and indirect (Driver and Noesselt, 2008; Smiley and Falchier, 2009;

Romanski, 2012) connections between auditory and visual cortices. These existing connections between auditory and visual cortices may explain why both deaf and hearing subjects exhibited a net causal flow from V1 to STG and displayed STG activation during the visual task. Although auditory association areas receive a greater number of projections from visual areas in deaf cats than in hearing cats (Barone *et al.*, 2013), the lack of significant intergroup differences in the net causal flow from V1 to STG indicates that the enhanced STG activation in deaf subjects cannot be easily explained by a bottom-up mechanism. Although deprived auditory cortices have a small fraction of abnormal connections, most connections, including those linking the prefrontal cortex to auditory areas, are preserved in deaf cats (Barone *et al.*, 2013). This observation is consistent with our finding of a significant net causal flow from FEF to STG in both groups. Thus, the strengthening of existing connections between FEF and STG may explain why deaf subjects exhibited enhanced cross-modal activation in the STG. Furthermore, Granger causality analysis revealed that deaf subjects had an enhanced net causal flow from FEF to STG compared to hearing controls. These findings indicate that a top-down mechanism may better account for the cross-modal activation of auditory regions in deaf subjects. These findings also support the idea that top-down interactions are more affected by auditory deprivation (Kral and Eggermont, 2007; Kral, 2013).

## Residual auditory input and cross-modal activation in early deafness

Consistent with a recent finding of correlations between STG activity during visual motion and the percentage of lifetime hearing aid use in deaf subjects (Shiell *et al.*, 2015), we also found a correlation between STG activation during the maintenance stage of the working memory task and this clinical measure in deaf subjects. Moreover, we also found a correlation between STG activation during the maintenance stage and the age of onset of hearing aid use. Because hearing aid use may be the main source of auditory input for profoundly deaf subjects, a later age of onset and shorter duration of hearing aid use may result in less auditory input. Thus, our finding suggests that greater cross-modal activation is associated with reduced auditory input, further supporting the idea that auditory deprivation leads to cross-modal reorganization. These correlations also suggest that early and long-term auditory input may inhibit cross-modal reorganization via the preservation of auditory neuronal function (Shiell *et al.*, 2015). Because auditory regions with cross-modal reorganization cannot easily recover their function in the processing of auditory inputs following cochlear implantation, cross-modal reorganization is considered one of several factors responsible for closing the sensitive period for therapy with cochlear implants (Lee *et al.*, 2007a; Kral, 2013). Thus, these correlations indicate that early and long-term hearing aid use

may benefit the improvement of auditory function in late-implanted subjects by inhibiting cross-modal reorganization. This inference is consistent with the suggestion that hearing aid use is associated with improved outcomes following cochlear implantation (Santarelli *et al.*, 2008). However, it is important to note that cochlear implantation is the best available approach for recovering auditory input; accordingly, early cochlear implantation remains the best way to inhibit cross-modal reorganization and to recover the normal functional organization of the auditory cortex (Fryauf-Bertschy *et al.*, 1997; Hammes *et al.*, 2002).

We also noted that STG activity during the encoding and recognition stages and FEF activity were not correlated with residual auditory input, suggesting that certain functional reorganization is mainly caused by early deafness itself and has nothing to do with residual auditory input. However, the present study cannot provide a definite explanation why the enhanced FEF activation and clinical correlations of the STG activation only occurred during the maintenance stage in deaf subjects. These findings may be related to the fact that the maintenance stage is devoid of any extra input and output and is a pure stage reflecting working memory processing.

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## Supplementary material

Supplementary material is available at *Brain* online.

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