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Research Report

Cross-modal and compensatory plasticity in adult deafened cats: A longitudinal PET study

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ABSTRACT

Although much is known about the cerebral neural plasticity that occurs after deafness, it is unclear how much time is required for its development or what other cortical changes may consequently occur. This study provides a longitudinal assessment of cerebral cortical neural plasticity, as manifested in adult deafened cats. A total of 5 male cats were subjected to whole cortex analysis of glucose metabolic activity via 2-deoxy-2[^{18}F] fluoro-D-glucose (FDG) micro-positron emission tomography (PET). The imaging was performed at the baseline state of normal hearing and then at 4, 9, 24, and 33 months after the induction of deafness. We compared glucose metabolism between the normal hearing state and each deafened state by using voxel-based statistical analysis ($P<0.005$). Significant changes were observed in the primary auditory (A1) and primary visual (V1) cortices. A bilateral metabolic decrease was observed in A1 areas and in temporal auditory fields, the extent of which was significantly increased at Month 9. Then it was declined at Month 24. And finally it was disappeared by Month 33. Auditory cortical plasticity subsequent to deafness was thus demonstrated. Furthermore, a significant metabolic upsurge occurred in bilateral occipital areas at Month 33. This increase, involving bilateral occipital and thalamic areas of V1, suggests compensatory hyperactivity of the visual cortex after deafness.

1. Introduction

Sensory deprivation induces cortical glucose metabolic changes, electrophysiologic changes, and subcortical reorganization, known as neural plasticity. Compared to adult humans with normal hearing, those with postlingual deafness show a decrease in auditory metabolic rate, indicating that neural plasticity exists in the adult brain (Lee et al., 2003). Investigations of cerebral glucose metabolism in deaf patients by positron emission tomography (PET) have provided functional evidence of neuroplasticity (Lee et al., 2001, 2007a). However, the natural course of cortical metabolic changes in

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humans, including time duration, amount and extent, has not been reported.

Several methods can be used for functional imaging of the cerebral cortex, such as functional magnetic resonance imaging (fMRI), PET, and electric and magnetic encephalography (EEG and MEG). Each approach has its advantages and disadvantages for evaluating deafness. It is notable that PET studies of human neural plasticity after sensory deprivation have two major drawbacks. First, repeated exposure of test subjects to PET scan radiation poses an ethical problem, thus preventing its use in longitudinal studies. Second, it is nearly impossible to distinguish between normal hearing and deaf states in human participants. These problems have resulted in the development of animal models for PET studies of deafness.

Even though the resolution of high tesla MRI is much better than that of PET in functional brain imaging, PET is more useful than MRI, especially in animal study. With recent technological advances, the PET scanner has proved beneficial for neural plasticity studies in small animal species (Kornblum et al., 2000). The resolution of the microPET scanner is much improved and can even be used for imaging of the rat brain (Goffin et al., 2009; Paul et al., 2009). We have previously evaluated the usefulness of microPET in cats (Kim et al., 2007) and have applied voxel-based analysis to the cat brain (Kim et al., 2008).

The aim of this study was to evaluate the changes in glucose metabolism in the cerebral cortex over time by PET after inducing deafness in adult cats. The cat brain is sufficiently large for imaging studies, can provide good anatomical resolution, and has long been studied using neurophysiologic methods (Rebillard et al., 1976).

2. Results

In this study, we observed significant changes of glucose metabolism in the cerebral cortex of deafened cats. Four months after the induction of deafness, glucose metabolism was significantly reduced bilaterally in the primary auditory cortex (A1) and the temporal auditory fields (Fig. 1a). The extent of metabolic reduction increased at Month 9 (Fig. 1b) and then decreased at Month 24 (Fig. 1c). Eventually, these changes disappeared at Month 33 (Fig. 1d). Conversely, an increase in glucose metabolism was observed at the medial aspect of area 17 in the left hemisphere (Fig. 2c). At Month 33, this metabolic increase was spread to the bilateral thalamic and occipital area (Fig. 2d). The representative coordinates and z values of primary auditory and visual areas over time are presented in Table 1.

3. Discussion

Sensory deprivation results in changes in the neural system due to the absence of sensory input to the brain. One of the consequences of sensory deprivation is cross-modal plasticity. Another phenomenon is compensatory hypertrophy through either a change in responsivity or an increase in the size of the affected cortex. These changes also occur in the auditory system. Many researchers have reported these effects in animals and humans alike, by using various methods such as electrophysiologic, imaging, and behavioral probes. However, most of these previous studies were developmental and addressed congenital or neonatal deafness. Adult-onset deafness differs from congenital deafness with regard to the maturation of the auditory system at the time of hearing deprivation.

Up to now, there have been no substantial reports of individual changes in glucose metabolism occurring over time after deafness. Generally, cortical glucose metabolism in the sensory system characteristically decreases with sensory deficits, pursuant to the absence of central sensory input. However, this decrease has been shown to return to normal after some time. The same pattern has been observed in the auditory system (Rauschecker, 1999). Ahn et al. described the changes in glucose metabolism after deafness in neonatal deafened rats. Glucose metabolism in the auditory cortex was shown to decline after the onset of deafness, but levels returned to normal after 7 months (Ahn et al., 2004). In prelingual human deafness, cortical metabolism was shown to be decreased initially, but after 20 years of deafness, cortical metabolism did not differ from normal controls (Lee et al., 2001). In postlingual human deafness, metabolism in the auditory cortex was also significantly decreased after 8 years of deafness (Lee et al., 2003).

Our results show the same pattern as that described in previous reports. However, we were able to reveal the duration of the cortical changes and their extent. Many other studies have demonstrated the cortical reorganization associated with deafness, but the time sequence has not been clearly defined. In congenitally deaf cats, a deficit in synaptic current has been shown in the infragranular cortical layer, and this deficit was observed even in 29-month-old animals (Kral et al., 2000), although long-term electrical cochlear stimulation reportedly reversed this effect and expanded the area of response (Klinke et al., 1999; Kral et al., 2002). A previous animal study was unable to reveal cortical reorganization using electrophysiological methods and fMRI. In that study, the adult macaque primary visual (V1) area was evaluated after bilateral retinal lesions. The authors noted that adult macaque V1 responsiveness did not approach a normal response during 7.5 months of follow-up (Smirnakis et al., 2005). The authors therefore concluded that the potential for V1 reorganization in adult macaques after blindness was limited. However, as shown by our results, the follow-up period of the adult macaque V1 study may have been too short to observe any later changes in responsiveness. In the somatosensory cortex of the macaque monkey, the period between loss of sensory input and reorganization of the cortex was found to be 22–23 months in an electrophysiologic study (Jain et al., 2008). Allman and his colleagues observed somatosensory input in deafened adult ferrets, (Allman et al., 2009), and Lee et al. reported a visual response in the auditory cortex in profound acquired human deafness (Lee et al., 2007b). In the latter study, the time interval between deafness and response in the auditory cortex was very short. Another fMRI study showed increased activation of the auditory cortex with visual tasking in prelingually deaf adults

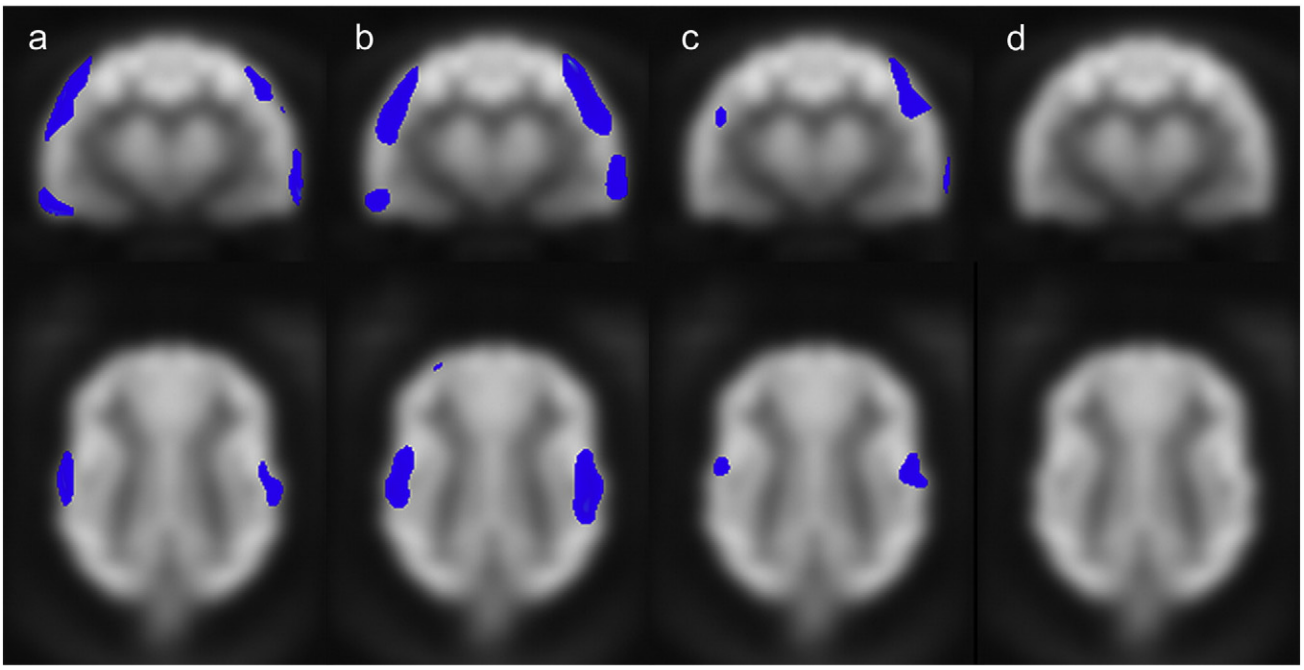

Fig. 1 – Serial metabolic changes at Months 4 (a), 9 (b), 24 (c), and 33 (d) after deafness. The upper images are coronal, and the lower ones are axial views. The colored area represents a significant decline in glucose metabolism, compared with a normal hearing state ($P<0.005$, uncorrected). In the coronal image, the colored areas are bilateral primary and temporal auditory fields. Area dimensions were maximal at Month 9 (b), disappearing by Month 33 (d).

(Finney et al., 2001; Shibata et al., 2001). On the other hand, Kral and colleagues also reported that visual stimulation could not evoke field potentials in A1 areas of congenitally deaf cats (Kral et al., 2003). Cross-modal reorganization has also been encountered in blindness. The anterior ectosylvian visual area of binocularly deprived cats has been shown to be completely

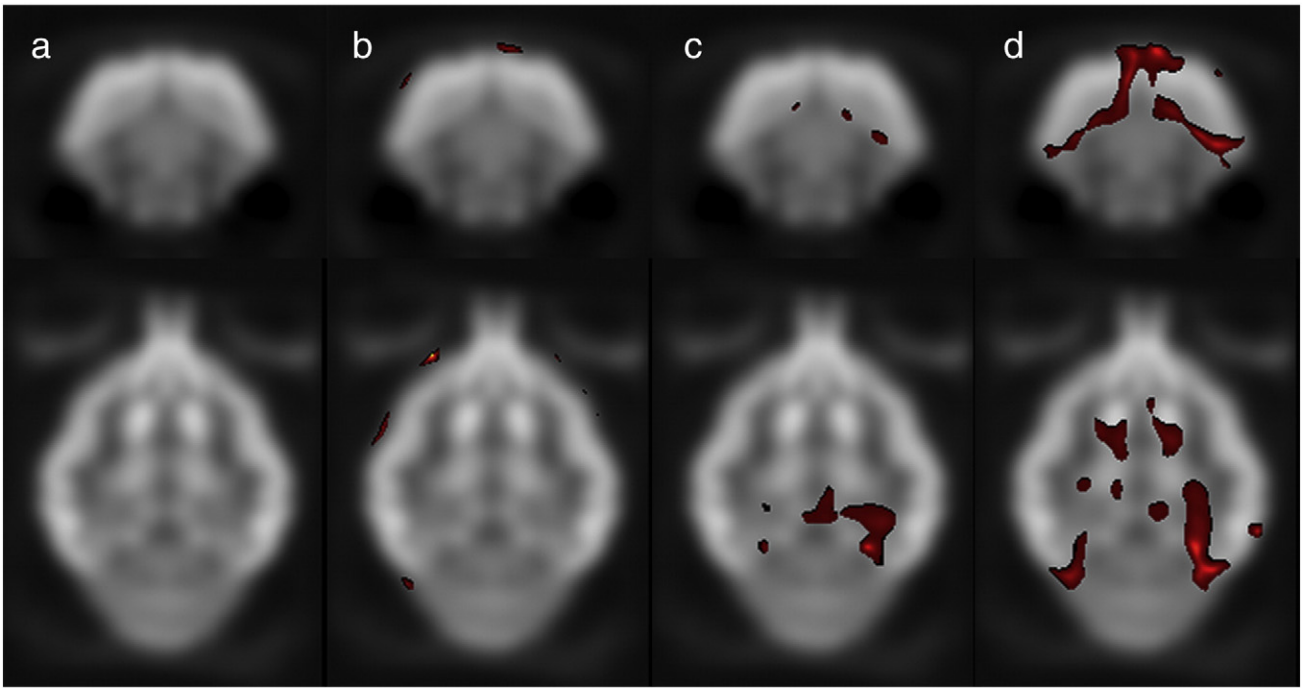

Fig. 2 – Serial metabolic changes at Months 4 (a), 9 (b), 24 (c), and 33 (d) after deafness. The colored area represents a significant increase in glucose metabolism, compared with a normal hearing state ($P<0.005$, uncorrected). The upper images are coronal, and the lower ones are axial views. The area of increase appeared at Month 24 (c) and increased further by Month 33 (d). These areas overlap with primary visual cortex.

Table 1 – The changes of z values over time in primary auditory and visual area of both hemispheres. (Threshold: $P<0.005$, Uncorrected).

Brain area	Coordinates (x, y, z)	4 months		9 months		24 months		33 months	
		Cluster size	z value	Cluster size	z value	Cluster size	z value	Cluster size	z value
Right hemisphere									
primary auditory	(14, –4, 7)	7123	2.98	10816	4.22	1297	3.6	N/A	N/A
primary visual	(11,–14, 0)	N/A	N/A	N/A	N/A	40699	4.26	63136	4.63
Left hemisphere									
primary auditory	(–15, 0, 6)	5769	3.99	19079	5.05	4187	5.13	N/A	N/A
primary visual	(–10, 4, –3)	N/A	N/A	N/A	N/A	759	3.75	655	3.55

overtaken by auditory and somatosensory inputs, according to one older study (Rauschecker, 1995).

Our results can be distinguished from the aging phenomenon. Some studies have suggested that primary auditory and visual cortices of adults do not show significant metabolic changes over time until they reach old age. Chugani and his colleagues performed 2-deoxyglucose autoradiography in kittens. After the age of 2 months, the glucose metabolism of visual and auditory cortices had reached adult levels and did not change significantly thereafter (Chugani et al., 1991). In humans, Ibanez and his colleagues reported that resting state brain glucose metabolism was not reduced in healthy men during aging, as assessed by 2-deoxy-2[^{18}F] fluoro-D-glucose (FDG)-PET after correction for brain atrophy, (Ibanez et al., 2004). Some studies have described the glucose metabolic changes associated with aging, with the main affected areas being the frontal gyri, amygdale, parahippocampus, cingulate, cerebellum, and thalamus (Fujimoto et al., 2008; Kim et al., 2009). In our study, the oldest cat was 51 months old, which is equal to approximately 35 years in humans, too early for shrinkage of the gray matter to occur. Furthermore, no previous studies have shown a V-shaped pattern with aging.

In the auditory system, hearing deprivation can evoke enhanced activation of the cortical area of other sensory systems such as visual and somatosensory systems. Some authors have suggested that this phenomenon is compensatory (Bavelier and Neville, 2002). We found an increase in glucose metabolism in the primary visual cortex in our study. Although this particular phenomenon is new to the scientific literature, there have been prior reports of visual compensation with deafness (Neville and Lawson, 1987; Neville, 1990; Rettenbach et al., 1999).

An investigation of congenitally deaf mice indicated that visual and somatosensory stimulation was detectable in the auditory cortex and that the visual area of the neocortex was expanded (Hunt et al., 2006). In contrast, Fine et al. used fMRI to examine early auditory stimulus-deprived adults and found that for a given visual stimulus, there was cross-modal plasticity of the auditory cortex. The authors did not, however, demonstrate a significant functional difference in the visual cortex during visual tasking, nor was there any evidence of visual compensatory hypertrophy (Fine et al., 2005).

Nonetheless, some authors were able to show sensory compensation in human subjects. Specifically, adults deprived of auditory input since birth have been found to display increases in visual areas and increased activity of the posterior visual cortex using the event-related potential method (Neville, 1990). Another study also claimed that congenitally deaf adults possess a partially compensated capacity for visual processing in attention-dependent trials (Rettenbach et al., 1999). This visual enhancement has also been reported in visual attention to peripheral motion in deaf people. (Bavelier et al., 2000; Neville and Lawson, 1987). Relative to the enhancement of other modalities by deafness, increased tactile sensitivity has also been reported (Levanen and Hamdorf, 2001). Hence, the activated visual cortex delineated in our study may be similarly explained on a compensatory basis.

Sensory compensation may also accompany visual deprivation. In congenitally blind human adults, the capacity for auditory spatial tuning surpasses that of sighted controls, as measured by scalp electrophysiologic recordings (Roder et al., 1999). This unique ability of blind people suggests that compensatory reorganization of the brain results in and contributes to this improved hearing function. Blind humans have additionally shown an enhanced capability to focus on peripheral auditory stimuli (Fieger et al., 2006) and early blindness, in particular, can heighten auditory perception skills (Wan et al., 2010).

These characteristics associated with deafness and blindness are largely reliant on the perceptions of the test subject; therefore, the hypermetabolism of the visual cortex that we have demonstrated is an interesting finding. It does not readily equate with enhanced visual function, but it certainly is in keeping with the basic tenet—that of compensatory plasticity following sensory deprivation.

In summary, our analysis of glucose metabolism in the auditory and visual cortices of deafened cats is the first longitudinal investigation of such group dynamics. The results are confirmatory of auditory cortical plasticity and offer evidence of compensatory visual activation in a deafened state.

4. Experimental procedures

Five domestic adult male cats, aged 6–18 months (mean age: 11.6 months, standard deviation: 4.39 months), were selected for the study. The study protocol was approved by the

Institutional Animal Care and Use Committee. The hearing level of each cat was first verified under anesthesia, using the auditory-evoked brainstem response (ABR) to click sound (System 3, Tucker-Davis Technologies, USA). All animals had a normal hearing state, showing a wave V at 30 dB sound pressure level (SPL). Deafness was then induced using a single co-administration of kanamycin and ethacrynic acid (MSD, USA; Xu et al., 1993). Kanamycin was injected subcutaneously (300 mg/kg), and ethacrynic acid was continuously infused (1 mg/min) until no response in ABR was observed. Two weeks later, deafness in each cat was confirmed through repeat ABR testing (Nourski et al., 2004). FDG-PET images were acquired on 5 separate occasions using a microPET Focus scanner (Siemens Medical Solutions, Inc., Knoxville, TN, USA). The first session documented a baseline of normal hearing in each cat. Successive scans were performed at 4, 9, 24, and 33 months after the deafening procedure. The cats were fasted for at least 8 h before imaging. They were also anesthetized through intramuscular injection of xylazine (10 mg/kg; Rumpun, Bayer, Germany) and ketamine (100 mg/kg; Veterinary Ketalar, Sankyo, Japan). Thirty minutes after the injection of 1 mCi/kg FDG, half-hour emission data recordings were performed. The image acquiring room had an environmental noise of 60 dB SPL. Facility lighting was purposefully dim, thus limiting visual stimulation and metabolic demand.

Attenuation and scatter correction were performed for all the acquired data sets. The brain region in each PET image was extracted, spatially normalized, and smoothed. Global normalization was performed to diminish the possible age effect or time effect on FDG metabolism. Detailed description of the image pre-processing procedures can be found in our previous report (Kim et al., 2008). A voxel-wised paired *t*-test between the normal and deafened states was performed using the Statistical Parametric Mapping 5 program ($P<0.005$, $K>50$).

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