Initial Study on Functional Connectivity of Children with Profound Bilateral Prelingual Hearing Loss

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Introduction:

One of the fundamental unsolved questions in auditory neuroscience is the development and elaboration of auditory cortical areas and its interactive connections with other brain areas. This topic is of primary importance to development of speech, language, cognition (memory and attention), literacy, etc. Establishing normal developmental connectivity patterns will help to understand how these neural networks are reshaped as a result of profound hearing loss (HL), and how disorders of communication such as attention deficit hyperactivity disorder (ADHD) and autistic spectrum disorders [1] are correlated to HL. However, few studies, if any, have compared the functional connectivity between young children (2-5 y/o) with profound bilateral HL and normal hearing (NH). It is commonly accepted that cochlear implant operation is best for normal psychological and cognitive development if it's done before a critical age, which is about 1.5 to 3 years old [2]. In this study, we will explore the variations in resting state (RS) functional connectivity related to hearing capability after such critical age, and to obtain an insight to what can be at stake if HL is not properly treated in a timely manner.

Methods:

Nineteen children (age 26-55 m/o, mean ± std = 36 ± 7 m/o, 12 boys) with profound bilateral HL (ABR > 95dB), and 16 age matched NH children (age 25-68 m/o, mean ± std = 40 ± 13 m/o, 12 boys) were enrolled in the study, excluding those with cognitive or neurodevelopmental delay or syndrome and with contradiction to MRI scans. Written consent forms were obtained from parents or guardians. The subjects were anesthetized using 10% chloral hydrate with dosage of 0.7 ml/kg. RF-fMRI data were collected at Siemens 3T Verio system using EPI sequence with following parameters: 64×64 matrix, 4×4×3.5 voxel size, TR/TE=3000/30ms, flip angle = 90°, and 210 volume of data were collected. High resolution 3D T1W MPRAGE data were also collected. All data were preprocessed with motion correction, detrending, low pass filtering (0.01~0.08Hz), smoothing (6mm FWHM) and normalized to MNI space, and routine seed based correlation coefficient (cc) maps were calculated to reveal the important functional networks of Auditory (Heschl's area, [±48,-28,12]), DMN ([4,-53,26]), Attention ([40,-4,48]) and Language (Broca's area,[±42,32,12]). The cc value where then converted to Fisher z cores for one- and two-sample t-test for both HL and NH groups.

Results:

The one-sample t-test connectivity maps of HL and NH groups, as well as the two-sample t-test comparison of these two groups for the four functional networks are shown in Fig.1. It can be seen that the HL group would have reduced connectivity than the NH group in all networks shown. The regions with significant difference for each network are listed in Table.1.

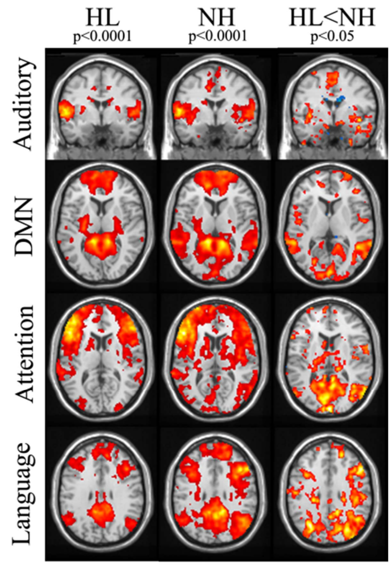

Fig.1 One sample t-test connectivity maps of HL (left column) and NH (middle column) groups, and the two-sample t-test comparison between these two groups (right column).

Table.1 Regions where NH has significantly stronger connectivity than HL group.

	Regions
Auditory	Precentral gyrus
	Medial frontal gyrus
	Insula
	Left lingual lobe
DMN	Middle temporal gyrus
	Precuneus
	Middle cingulate gyrus
	Fusiform gyrus
Attention	Anterior cingulate
	Cuneus
	Superior/middle temporal gyrus
Language	Middle temporal gyrus
	Precuneus
	Cuneus
	Inferior frontal gyrus

Discussion:

Apart from the classical auditory network which includes auditory cortex and various nuclei in the brain stem/mid brain/thalamus, the hearing process involves other important cognitive functions such as attention and language/speech. Deprivation of hearing will lead to delay and deficiency in developing these important cognitive functions. We have preliminarily chosen 4 resting state functional networks that are closely related to these brain functions, and compared between children of 2-5 years old with bilateral hearing loss and normal hearing.

For the classical auditory network (Fig.1, 1st row), the auditory cortices including the Heschl's gyrus and Wernicke's area, insula and postcentral syrus are seen to be highly correlated with each other for both HL and NH children, suggesting that sensory cortices may still develop at a normal pace even with HL. However, strongest differences in connectivity are found in medial frontal gyrus, insula and left lingual lobe (Table. 1). Such areas are responsible for facilitating access to attentions and working memory resources [3] as well as visual process, suggesting a delay or deficiency in coordinating these cognitive resources has begun emerging at this age. On the other hand, it has been suggested that auditory cortex may take over functionalities of other cortices such as visual or motor via the so-called cross-modal reorganization process [4]. If such reorganization process is complete, the auditory cortex will no longer be able to response to auditory stimulation even when cochlear implant is installed afterwards. Although the complete loss of auditory functionality may take place at a later age, such reorganization process in children born with profound bilateral HL is unknown. From our preliminary results, no significant connectivity difference between HL and NH children, either stronger or weaker, were observed in auditory cortex in those networks calculated using seed points from visual cortex or motor cortex (data not shown). This may or may not be sufficient to determine whether the reorganization is in process, because the brain is in developmental stage and the plasticity of the brain may also modify the connectivity. Further analysis to these data is needed to determine whether the cross modal reorganization is taking place at such early age.

Similarly in DMN, Attention and Language networks, significant differences in connectivity can be found in various brain regions that are responsible for important cognitive functions, especially for middle temporal gyrus and precuneus in DMN, anterior cingulate and cuneus in Attention network, and middle temporal gyrus, precuneus/cuneus and inferior frontal gyrus in Language network. All these regions are highly correlated to the characteristic connectivity pattern of the respective networks, suggesting a modified functional architecture of the brain in HL in comparison to NH. This is in accordance to the suggested time frame for best outcomes with cochlear implant installation, that it's best done before 1.5-3 y/o. The subjects enrolled in this study either have passed or are approaching the end of this time frame, and for the first time the possible brain regions (and their related functionality) that are most affected by the void of auditory input as a result of HL are revealed here. Our results indicate that prelingual HL will indeed significantly modify the brain's functional architecture, at least in terms of resting state functional connectivity, if not treated in a timely manner.

For further studies, RS-fMRI data will be collected on children less than 2 years old with bilateral HL. Comparing between the <2 y/o group and 2-5 y/o groups with HL, and between age matched HL and NH groups, we will be able to determine the specific brain regions that can be used as a biomarker for HL effects on brain functional developments. Once such brain regions are determined, it can be used as a reference to analyze, on an individual level rather than group level as currently done in this study, the developmental status of brain functions and whether the critical timing is passed for the recovery of the delay in those important brain functions.

Reference:

[1]Anderson, *et al*. Cereb Cortex. 2011; [2] Cole and Flexer. Plural Publishing. 2007; [3] Seeley, *et al*. J Neurosci. 2007; [4] Doucet, *et al.* Brain. 2006