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Research Paper

Changes of metabolism and functional connectivity in late-onset deafness: Evidence from cerebral ^{18}F-FDG-PET

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ABSTRACT

Hearing loss is known to impact brain function. The aim of this study was to characterize cerebral metabolic Positron Emission Tomography (PET) changes in elderly patients fulfilling criteria for cochlear implant and investigate the impact of hearing loss on functional connectivity. Statistical Parametric Mapping-T-scores-maps comparisons of ^{18}F-FDG-PET of 27 elderly patients fulfilling criteria for cochlear implant for hearing loss (best-aided speech intelligibility lower or equal to 50%) and 27 matched healthy subjects ($p < 0.005$, corrected for volume extent) were performed. Metabolic connectivity was evaluated through interregional correlation analysis. Patients were found to have decreased metabolism within the right associative auditory cortex, while increased metabolism was found in prefrontal areas, pre- and post-central areas, the cingulum and the left inferior parietal gyrus. The right associative auditory cortex was integrated into a network of increased metabolic connectivity that included pre- and post-central areas, the cingulum, the right inferior parietal gyrus, as well as the striatum on both sides. Metabolic values of the right associative auditory cortex and left inferior parietal gyrus were positively correlated with performance on neuropsychological test scores. These findings provide further insight into the reorganization of the connectome through sensory loss and compensatory mechanisms in elderly patients with severe hearing loss.

1. Introduction

Hearing loss affects 40–50% of adults over the age of 65, and 83% of adults over the age of 70 (Cruickshanks et al., 1998). It is the third most prevalent chronic medical condition amongst elderly patients after arthritis and hypertension (Lethbridge-Cejku et al., 2004). Downstream consequences of reduced hearing include negative effects on perceptual effort for encoding of what has been heard (McCoy et al., 2005; Cousins et al., 2014), and increased resource demand for comprehension of sentences with complex syntax (Wingfield et al., 2006). This can lead to decreased performance on standardized cognitive tests (Lin et al., 2011a), and might explain an association with dementia (Gates et al., 2011; Lin et al., 2011b). Hearing loss, cognitive impairment and dementia can be thus intertwined, especially in elderly patients, with aging as a major risk factor for neurodegenerative disorders. However, the functional mechanisms that lead to cognitive dysfunction in these patients are poorly understood. Over the past decades, there has been extensive evidence for cortical reorganization following hearing loss in studies involving both experimental animals and humans (Irvine and Rajan, 1996; Rajan et al., 1993; Kang et al., 2003; Lee et al., 2003). Mechanisms of reorganization involve cross-modal

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plasticity, where deprivation in one sensory modality (e.g. the auditory modality in hearing loss) results in the recruitment of cortical resources of the deprived modality by intact sensory modalities (e.g. visual or somatosensory systems), as described in congenital but also post-lingual deafness (see (Glick and Sharma, 2017) for review). Moreover, in the auditory system, in addition to ascending auditory pathways that carry information on sound from the cochlea to auditory cortices, descending pathways from higher auditory centers project back towards the periphery. These "top-down mechanisms" are thought to play a compensatory role after peripheral deafferentation through descending projection systems, but how these networks are modulated precisely remains unknown (see (Lesicko and Llano, 2017) for review). Kral et al. recently conceptualized congenital auditory-loss like a "connectome disease" because of distal effects from the sensory system onto higher order neurocognitive functions (Kral et al., 2016), the connectome being defined as a map of neural connections in the brain (Sporns et al., 2005). Referring to hearing loss as a connectome disease is an opportunity to examine hypotheses concerning the effects of hearing loss on brain regions not directly involved in audition per se on the large-scale neural network scale, and also to identify potential targets for rehabilitation.

Cochlear implant (CI) is the only effective therapeutic method for patients suffering from profound sensorineural hearing loss (Ramos-Macías et al., 2016). Hearing loss has a significant impact on patients' social life, daily activities, and self-esteem (Ramos-Macías et al., 2016). In patients over the age of 65, a comprehensive neurocognitive assessment is required before surgery in order to rule out a neurodegenerative condition, which could interfere with the ability of patients to adapt to CI (see guidelines provided by the French National Authority for Health or Haute Autorité de Santé, HAS, France, HAS santé, 2012).

^{18}F-Fluro-deoxy-glucose is a widely used biomarker of synaptic activity that can indicate the topography of neurodegeneration using Positron Emission Tomography (^{18}F-FDG PET) (Didic et al., 2015; Koric et al., 2016; Titov et al., 2015; Varrone et al., 2012). ^{18}F-FDG-PET also provides an opportunity to study functional synaptic changes in severely deaf patients, not only before, but also after CI, without magnetic limitations or contraindications (Strelnikov et al., 2015). However, only two pilot studies, in small sets of adults with hearing loss, have so far assessed cerebral metabolism using PET (Deggouj et al., 1995; Lee et al., 2003).

Beyond the identification of metabolic dysfunction within individual brain regions, the analysis of functional connectivity leads to a better understanding of neural plasticity on the network scale. Hence, PET can be used to study metabolic connectivity by Inter-Regional Correlation Analysis (IRCA) (Lee et al., 2008), these resting-state networks being closely related to those derived from fMRI studies (Di et al., 2012; Savio et al., 2017; Yakushev et al., 2013). Although the spatial resolution of PET is worse than that of fMRI, PET targets glucose consumption, which reflects synaptic activity, and is therefore particularly well suited to assess neural plasticity. Furthermore, glucose consumption has the advantage of preceding the BOLD (Blood Oxygen Level Dependent) signal, and can therefore detect early changes in neuronal function (Magistretti and Pellerin, 1999). The assessment of functional connectivity using ^{18}F-FDG PET could thus characterize changes of the connectome in patients with impaired hearing at the large neural network scale. Thus, the metabolic connectome studied here refers to the same concept as functional connectome or functional connectivity. To our knowledge, there is currently no PET study on metabolic connectivity in adults with late-onset hearing loss.

The aim of this study was to characterize cerebral metabolic PET changes in elderly patients fulfilling criteria of CI for hearing loss and investigate neural plasticity through the assessment of functional connectivity.

2. Materials and methods

2.1. Subjects

Thirty-two adults with post-lingual hearing loss were referred from August 2013 to July 2016 to "La Timone" University Hospital at Marseille to perform a neurocognitive assessment before cochlear implantation (CI) in order to rule out a neurodegenerative condition. These patients fulfilled the criterion for CI as defined in France, i.e. speech perception below 50% at 60 dB without lip-reading (HAS santé, 2012). Neurocognitive assessment involved the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Frontal Assessment Battery (FAB) (Dubois et al., 2000). Brain MRI and ^{18}F-FDG-PET were also performed in these patients. Sufficient and detailed explanations for the procedure, risk, and purpose or benefit of the study were given to the patients by clinicians. All patients participated with informed written consent in accordance with the Declaration of Helsinki (number of international review board of local ethical committee: 00003888).

Five patients were excluded from further analysis because of neurological or psychiatric co-morbidity. One patient was reported to have suffered from epilepsy since his childhood, and from concussion that caused a focal fronto-temporal lesion with right hemiplegia at the age of 46. The second patient had suffered from three consecutive strokes with residual right hemiplegia. The third patient was suffering from psychosis since the age of 23 and was under antipsychotic medication. Two additional patients were excluded because of a left temporal arachnoid cyst detected on CT-scan, which could interfere with the PET analysis.

Healthy subjects from a local normal ^{18}F-FDG PET database, matched to patients for age, gender, and level of education (Clinical Trials Ref: NCT00987090), were also included. These controls were free of neurological and psychiatric disease with a normal brain MRI. None of these control subjects had a medical history of hearing loss or complained about their hearing. Approval from an ethics committee was obtained and all subjects signed informed consent.

2.2. ^{18}F-FDG PET acquisition and analysis

^{18}F-FDG PET was performed under the same conditions for all patients and healthy subjects, using an integrated PET/CT camera (Discovery ST, GE Healthcare, Waukesha, WI) with an axial resolution of 6.2 mm allowing 47 contiguous transverse sections of the brain of 3.27 mm thickness. ^{18}F-FDG (150 MBq) was injected intravenously while the subjects were awake, at resting state, with eyes closed in a quiet environment. Image acquisition started 30 min after injection and ended 15 min later. Images were reconstructed using the ordered subsets expectation maximization algorithm with 5 iterations and 32 subsets, and corrected for attenuation using a CT transmission scan.

Whole-brain statistical analysis was performed at voxel-level using SPM8 software (Wellcome Department of Cognitive Neurology, University College, London, UK) to compare patients with hearing loss and controls using ANOVA (Analysis of Variance). PET images were spatially normalized onto an adaptive template derived from PET images of controls. The images were then smoothed with a Gaussian filter (8 mm full-width at half-maximum) to blur individual variations in gyral anatomy and to increase the signal-to-noise ratio. To build the adaptive template, the PET scans of the 27 control subjects were normalized to the standard PET template, using the algorithm provided with SPM. Then, the template was built by averaging these normalized images