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

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3 **Changes of metabolism and functional connectivity in late-onset deafness:**  
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6 **Evidence from cerebral <sup>18</sup>F-FDG-PET**  
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62 **Abstract**  
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67 Hearing loss is known to impact brain function. The aim of this study was to characterize  
68 cerebral metabolic Positron Emission Tomography (PET) changes in elderly patients fulfilling  
69 criteria for cochlear implant and investigate the impact of hearing loss on functional  
70 connectivity. Statistical Parametric Mapping-T-scores-maps comparisons of  $^{18}\text{F}$ -FDG-PET of  
71 27 elderly patients fulfilling criteria for cochlear implant for hearing loss (best-aided speech  
72 intelligibility lower or equal to 50%) and 27 matched healthy subjects ( $p < 0.005$ , corrected for  
73 volume extent) were performed. Metabolic connectivity was evaluated through interregional  
74 correlation analysis. Patients were found to have decreased metabolism within the right  
75 associative auditory cortex, while increased metabolism was found in prefrontal areas, pre-  
76 and post-central areas, the cingulum and the left inferior parietal gyrus. The right associative  
77 auditory cortex was integrated into a network of increased metabolic connectivity that  
78 included pre- and post-central areas, the cingulum, the right inferior parietal gyrus, as well as  
79 the striatum on both sides. Metabolic values of the right associative auditory cortex and left  
80 inferior parietal gyrus were positively correlated with performance on neuropsychological test  
81 scores. These findings provide further insight into the reorganization of the connectome  
82 through sensory loss and compensatory mechanisms in elderly patients with severe hearing  
83 loss.  
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105 **Key-words:** cochlear implant; connectivity; deafness; elderly;  $^{18}\text{F}$ -FDG-PET  
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## 1. Introduction

Hearing loss affects 40 to 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 being 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 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

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180 precisely remains unknown (see (Lesicko and Llano, 2017) for review). Kral et al. recently  
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182 conceptualized congenital auditory-loss like a “connectome disease” because of distal effects  
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184 from the sensory system onto higher order neurocognitive functions (Kral et al., 2016), the  
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186 connectome being defined as a map of neural connections in the brain (Sporns et al., 2005).  
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188 Referring to hearing loss as a connectome disease is an opportunity to examine hypotheses  
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190 concerning the effects of hearing loss on brain regions not directly involved in audition per se  
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192 on the large-scale neural network scale, and also to identify potential targets for  
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194 rehabilitation.”  
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198 Cochlear implant (CI) is the only effective therapeutic method for patients suffering from  
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200 profound sensorineural hearing loss (Ramos-Macías et al., 2016). Hearing loss has a  
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202 significant impact on patients' social life, daily activities, and self-esteem (Ramos-Macías et  
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204 al., 2016). In patients over the age of 65, a comprehensive neurocognitive assessment is  
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206 required before surgery in order to rule out a neurodegenerative condition, which could  
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208 interfere with the ability of patients to adapt to CI (see guidelines provided by the French  
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210 National Authority for Health or Haute Autorité de Santé, HAS, France, HAS santé, 2012).  
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213 <sup>18</sup>F-Fluro-deoxy-glucose is a widely used biomarker of synaptic activity that can indicate the  
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215 topography of neurodegeneration using Positron Emission Tomography (<sup>18</sup>F-FDG PET)  
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217 (Didic et al., 2015; Koric et al., 2016; Titov et al., 2015; Varrone et al., 2012). <sup>18</sup>F-FDG-PET  
218  
219 also provides an opportunity to study functional synaptic changes in severely deaf patients,  
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221 not only before, but also after CI, without magnetic limitations or contraindications  
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223 (Strelnikov et al., 2015). However, only two pilot studies, in small sets of adults with hearing  
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225 loss, have so far assessed cerebral metabolism using PET (Deggouj et al., 1995; Lee et al.,  
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227 2003).  
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230 Beyond the identification of metabolic dysfunction within individual brain regions, the  
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232 analysis of functional connectivity leads to a better understanding of neural plasticity on the  
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239 network scale. Hence, PET can be used to study metabolic connectivity by Inter-Regional  
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241 Correlation Analysis (IRCA) (Lee et al., 2008), these resting-state networks being closely  
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243 related to those derived from fMRI studies (Di et al., 2012; Savio et al., 2017; Yakushev et al.,  
244  
245 2013). Although the spatial resolution of PET is worse than that of fMRI, PET targets glucose  
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247 consumption, which reflects synaptic activity, and is therefore particularly well suited to  
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249 assess neural plasticity. Furthermore, glucose consumption has the advantage of preceding the  
250  
251 BOLD (Blood Oxygen Level Dependent) signal and can therefore detect early changes in  
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253 neuronal function (Magistretti and Pellerin, 1999). The assessment of functional connectivity  
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255 using <sup>18</sup>F-FDG PET could thus characterize changes of the connectome in patients with  
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257 impaired hearing at the large neural network scale. Thus, the metabolic connectome studied  
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259 here refers to the same concept as functional connectome or functional connectivity. To our  
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261 knowledge, there is currently no PET study on metabolic connectivity in adults with late-  
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263 onset hearing loss.  
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267 The aim of this study was to characterize cerebral metabolic PET changes in elderly patients  
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269 fulfilling criteria of CI for hearing loss and investigate neural plasticity through the  
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271 assessment of functional connectivity.  
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298 **2. Materials and Methods**  
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302 *2.1 Subjects*  
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304 Thirty-two adults with post-lingual hearing loss were referred from August 2013 to July 2016  
305 to “La Timone” University Hospital at Marseille to perform a neurocognitive assessment  
306 to “La Timone” University Hospital at Marseille to perform a neurocognitive assessment  
307 before cochlear implantation (CI) in order to rule out a neurodegenerative condition. These  
308 patients fulfilled the criterion for CI as defined in France, i.e. speech perception below 50% at  
309 60 dB without lip-reading (HAS santé, 2012). Neurocognitive assessment involved the Mini-  
310 Mental State Examination (MMSE) (Folstein et al., 1975) and the Frontal Assessment Battery  
311 (FAB) (Dubois et al., 2000). Brain MRI and <sup>18</sup>F-FDG-PET were also performed in these  
312 patients. Sufficient and detailed explanations for the procedure, risk, and purpose or benefit of  
313 the study were given to the patients by clinicians. All patients participated with informed  
314 written consent in accordance with the Declaration of Helsinki (number of international  
315 review board of local ethical committee: 00003888).  
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328 Five patients were excluded from further analysis because of neurological or psychiatric co-  
329 morbidity. One patient was reported to have suffered from epilepsy since his childhood, and  
330 from concussion that caused a focal fronto-temporal lesion with right hemiplegia at the age of  
331 46. The second patient had suffered from three consecutive strokes with residual right  
332 hemiplegia. The third patient was suffering from psychosis since the age of 23 and was under  
333 antipsychotic medication. Two additional patients were excluded because of a left temporal  
334 arachnoid cyst detected on CT-scan, which could interfere with the PET analysis.  
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344 Healthy subjects from a local normal <sup>18</sup>F-FDG PET database, matched to patients for age,  
345 gender, and level of education (Clinical Trials Ref: NCT00987090), were also included.  
346 These controls were free of neurological and psychiatric disease with a normal brain MRI.  
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350 **None of these control subjects had a medical history of hearing loss or complained about their**  
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357 **hearing.** Approval from an ethics committee was obtained and all subjects signed informed  
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359 consent.

## 360 361 362 363 364 365 *2.2 <sup>18</sup>F-FDG PET Acquisition and Analysis*

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367 <sup>18</sup>F-FDG PET was performed under the same conditions for all patients and healthy subjects,  
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369 using an integrated PET/CT camera (Discovery ST, GE Healthcare, Waukesha, WI) with an  
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371 axial resolution of 6.2 mm allowing 47 contiguous transverse sections of the brain of 3.27 mm  
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373 thickness. <sup>18</sup>F-FDG (150 MBq) was injected intravenously while the subjects were awake, at  
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375 resting state, with eyes closed in a quiet environment. Image acquisition started 30 min after  
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377 injection and ended 15 min later. Images were reconstructed using the ordered subsets  
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379 expectation maximization algorithm with 5 iterations and 32 subsets, and corrected for  
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381 attenuation using a CT transmission scan.  
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385 Whole-brain statistical analysis was performed at voxel-level using SPM8 software  
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387 (Wellcome Department of Cognitive Neurology, University College, London, UK) to  
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389 compare patients with hearing loss and controls using ANOVA (Analysis of Variance). PET  
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391 images were spatially normalized onto an adaptive template derived from PET images of  
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393 controls. The images were then smoothed with a Gaussian filter (8 mm full-width at half-  
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395 maximum) to blur individual variations in gyral anatomy and to increase the signal-to-noise  
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397 ratio. To build the adaptive template, the PET scans of the 27 control subjects were  
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399 normalized to the standard PET template, using the algorithm provided with SPM. Then, the  
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401 template was built by averaging these normalized images and subsequently applying a  
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403 smoothing Gaussian filter (FWHM = 8 × 8 × 8 mm) (Gispert et al., 2003). The dimensions of  
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405 the resulting voxels were 2 × 2 × 2 mm. Between groups SPM (T) maps were obtained at a  
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407 threshold (voxel-level significance) of p<0.005, uncorrected at voxel-level, but with a  
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416 correction for cluster volume, using expected voxels per cluster provided by SPM, to avoid  
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418 type II errors, as recommended (Lieberman and Cunningham, 2009), with age, gender and  
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420 level of education as nuisance covariates. An additional analysis with small volume correction  
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422 (SVC) was applied within the most significant voxel of the left auditory area. Proportional  
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424 scaling was applied, giving the same global value to each PET acquisition, to correct for  
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426 individual variations in global cerebral metabolism. The anatomical localization of the most  
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428 significant voxels was then identified using the MNI (Montreal National Institute) atlas. Mean  
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430 values of Cerebral Metabolic Rate of Glucose (CMRGlc) were extracted at the individual  
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432 level for each significant cluster. To evaluate metabolic connectivity from the previously  
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434 identified metabolic cluster in the intergroup comparison, IRCA was performed according to  
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436 the procedure validated by Lee et al. (Lee et al., 2008). Briefly, mean values of CMRGlc were  
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438 used as interacted covariates for the comparison between connectivity in patients and controls.  
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440 Nuisance covariates and threshold were the same as previously detailed for groups SPM (T)  
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442 maps comparisons.  
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447 A Region of Interest (ROI) analysis of the left associative auditory cortex was also performed  
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449 by extracting CMRGlc of cluster identified after analysis by small volume correction.  
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451 Moreover, an asymmetry index was calculated ((left auditory CMRGlc-right auditory  
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453 CMRGlc)/(left auditory CMRGlc+right auditory CMRGlc).  
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### 460 *2.3 Statistical analysis*

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463 Quantitative variables (age, level of education, deafness duration, MMSE and FAB scores)  
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465 are expressed as means  $\pm$  standard deviations, and categorical variables (gender) as  
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467 percentages. T-tests were performed for mean comparison between two quantitative variables  
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469 with normal distribution and Chi-square tests for comparison between two categorical  
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475 variables. Spearman coefficients were used to determine correlations between CMRGlc of  
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477 identified areas and test scores. A  $p < 0.05$  was determined as significant. Statistical analysis on  
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479 SPM is mentioned above.  
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### 3. Results

#### 3.1 Patients and controls

Of the twenty-seven patients with post-lingual hearing loss who only used spoken language, as well as lip-reading, included into the present analysis (mean age  $72.9 \pm 5.8$  years, 15 women, AFPA educational score,  $4.2 \pm 1.2$ ; French assessment of educational level, <https://www.afpa.fr>), the duration of a speech perception score at 50% or below with hearing aids at 60 dB and without lip-reading was  $7.0 \pm 3.1$  years. The duration of hearing aid use was  $18 \pm 11$  years. The etiology of hearing loss was most frequently unknown (52%) (Table 1). Twenty-seven healthy subjects were matched to patients for age ( $72.3 \pm 7.6$  years), gender (15 women), and level of education (AFPA educational score:  $3.7 \pm 1.2$ ;  $p > 0.17$ ). Cognitive performance of patients on the MMSE (Folstein et al., 1975) and the FAB (Dubois et al., 2000) was below that of healthy subjects ( $p < 0.05$ ; Table 2).

#### 3.2 Metabolic PET findings

In comparison to healthy controls, patients showed decreased metabolism within the right superior temporal gyrus (BA21 and 22), part of the associative auditory cortex ( $p < 0.005$ , uncorrected,  $k > 213$ ; Figure 1). For the left associative auditory cortex, no supra-threshold cluster was initially found when a p-value of 0.005 corrected for the cluster volume was applied. However, an additional analysis with SVC (sphere of  $4160 \text{ mm}^3$ , which is an equivalent volume of the cluster found in right area with center coordinates at  $-52; -22; 0$ , i.e. the most significant voxel of the left auditory area) secondarily identified a significant cluster after SVC for this same voxel threshold ( $p\text{-cluster} = 0.037$ , FWE-corrected).

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593 Patients were also found to have increased metabolism in bilateral superior, middle, medial  
594 and precentral frontal gyri (BA4, 6, 8 and 9), the cingulum (BA24, 31 and 32), bilateral  
595 postcentral parietal gyri (BA2, 3 and 7) and the left inferior parietal gyrus (BA40) ( $p < 0.005$ ,  
596 uncorrected,  $k > 213$ ; Figure 2). Detailed coordinates for these findings are available in Table  
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602 3. Individual analysis of the PET-scans showed that none of the patients had a typical profile  
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604 of neurodegenerative disease.

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609 Mean values of CMRGlc of previously identified areas were extracted for each individual  
610 patient. No association was found between duration of deafness and metabolism of any of  
611 these areas, including the right superior temporal gyrus ( $p > 0.20$ ). However, metabolism of  
612 both the right superior temporal and left inferior parietal gyri was positively correlated with  
613 performance on cognitive tests. In detail, decreased metabolism of the right superior temporal  
614 gyrus was correlated with lower MMSE and FAB scores (respective correlation coefficients  
615 of 0.48 and 0.54,  $p < 0.05$ ). Concerning regions with increased metabolism in comparison to  
616 healthy subjects, increased metabolism of the left inferior parietal gyrus was positively  
617 correlated with better performance on the FAB (correlation coefficients of 0.51,  $p < 0.05$ ).

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629 Otherwise, decreased metabolism of the left associative auditory cortex was correlated with  
630 lower performance on FAB (correlation coefficient of 0.70,  $p = 0.01$ ). Moreover, right  
631 prevalent asymmetry was associated with better performance on MMSE score (correlation  
632 coefficient of -0.50,  $p = 0.02$ ).

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638 In a second step, we studied metabolic connectivity of the right temporal gyrus (BA21 and  
639 22), part of the associative auditory cortex, which was found to be the only area with  
640 decreased metabolism. Figure 3 illustrates the direct comparison of right BA21-22  
641 connectivity between patients with hearing loss and controls. Patients showed increased  
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650 connectivity of this region with the right superior and middle temporal gyri (BA21, 22 and  
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652 42), right precentral frontal and postcentral parietal gyri (BA4, 6 and 3), right inferior parietal  
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654 gyrus (BA40), the cingulum (BA23, 24 and 32), as well as with the right and the left striatum  
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656 (P<0.005, uncorrected, k>136). Detailed coordinates of all these findings are available in  
657  
658 Table 3. No reduced connectivity was observed in patients in comparison to controls.  
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## 667 **4. Discussion**

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672 The main finding of the present study in elderly patients with severe to profound hearing loss  
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674 is that decreased metabolism within the right associative auditory cortex (BA21-22) is  
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676 combined with increased metabolism in prefrontal, pre- and post-central areas, the cingulum  
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678 as well as the left inferior parietal gyrus and integrated within a network of increased  
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680 metabolic connectivity that includes pre- and post-central areas, the cingulum, the right  
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682 inferior parietal gyrus, as well as the striatum on both sides. Moreover, metabolism of the  
683  
684 right superior temporal and left inferior parietal gyri was positively correlated with  
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686 performance on cognitive tests. Decreased metabolism was also found for the left associative  
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688 auditory cortex after SVC. These findings contribute to the identification of neural plasticity  
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690 and changes of functional connectivity in elderly patients with severe hearing loss.  
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697 *4.1 Decreased cerebral metabolism in elderly patients with hearing loss: a specific metabolic*  
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699 *pattern?*  
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701 **Decreased metabolism within the right associative auditory cortex is in line with previous <sup>18</sup>F-**  
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703 **FDG PET pilot studies in two adults with late-onset hearing loss (one man aged 61 and one**  
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711 woman aged 47) (Deggouj et al., 1995) and in 9 late-onset deaf younger adults with severe  
712 hearing loss, without cognitive impairment (mean age : 44.5±9.5 years) (Lee et al., 2003).  
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715 However, unlike the findings of the present study, Lee et al. reported an additional decrease of  
716 cerebral glucose metabolism in superior temporal cortices of both hemispheres, as well as the  
717 anterior cingulate gyri and in the right parahippocampal gyrus, with a similar or more  
718 restricted level of significance than that used in the present study, but with a slightly different  
719 target population (Lee et al., 2003). A decrease of glucose metabolism in the right superior  
720 temporal gyrus might be expected due to the role of this region in the evaluation of sentence  
721 and context processing (Vigneau et al., 2011). Indeed, right hemispheric activity allows one to  
722 move beyond the literal meaning of a word, a task necessary to appropriately interpret an  
723 utterance in its context (Lindell, 2006).  
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735 The relationship between cognitive dysfunction and hearing loss remains incompletely  
736 understood. An association of hearing loss with lower MMSE scores was reported in a study  
737 that included more than 300 participants (>55 years old) (Lin et al., 2011a). Here, we found  
738 that right prevalent asymmetry was associated with better performance on the MMSE, with a  
739 positive correlation of metabolism in the right associative auditory cortex with performance  
740 on neuropsychological tasks (MMSE and FAB). Indeed, a PET study involving healthy  
741 controls showed higher metabolism in the right associative auditory cortex in comparison to  
742 the left (Geven et al., 2014). A right prevalent asymmetry within the associative auditory  
743 cortex might therefore be associated with the auditory status of healthy subjects and thus a  
744 better MMSE. This association with neuropsychological tests was also found after SVC for  
745 the left associative auditory cortex with FAB. Although poor verbal communication  
746 associated with hearing loss may confound cognitive testing (Gordon-Salant, 2005), the  
747 patients in the present study clearly gave the impression of having understood the instructions  
748 that they were given (including the repetition of the sentence of the MMSE where they failed  
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770 because of difficulty hearing given the complexity of the sentence). While a relationship  
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772 between metabolism within the left associative auditory cortex with performance on language  
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774 based cognitive scores could have been expected, as auditory comprehension is likely to  
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776 impact speech processing of the left hemisphere, the present finding of an association with  
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778 metabolism in the right auditory cortex could be related to a compensatory involvement of the  
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780 right hemisphere (Lazard et al., 2014).

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783 Finally, the pattern of hypometabolism in elderly patients with hearing loss is also distinct  
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785 from that usually found in common cortical neurodegenerative diseases (Mosconi et al.,  
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787 2008). Although the possibility that sensory deprivation directly triggers a neurodegenerative  
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789 cascade cannot be formally ruled out, a more likely explanation is that hearing loss may  
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791 cause cognitive decline through social isolation or cognitive load, or a combination of these  
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793 mechanisms (Strawbridge et al., 2000; Lin et al., 2011a; Amieva et al., 2015). Hence,  
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795 cognitive load induced by hearing loss is thought to reduce resources being available for other  
796  
797 cognitive tasks as suggested by the “resource capacity model” (Kahneman, 1973) and thereby  
798  
799 affect cognitive function as previously reported in patients with impaired hearing (Lin et al.,  
800  
801 2011a). In this context, compensatory resource-allocation for sensory deprivation through  
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803 reorganization of cerebral networks may be critical but not sufficient to maintain cognitive  
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805 function.  
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#### 812 *4.2 Increased cerebral metabolism and changes of connectivity in elderly patients with* 813 814 *hearing loss: towards functional reorganization?* 815

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817 A network of areas with increased metabolism and changes of connectivity was found in  
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819 patients in comparison to controls. This is likely to result from a compensatory effect, as  
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821 increased metabolism in the left inferior parietal gyrus was correlated with better performance  
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829 on the FAB. Plastic changes in the cerebral cortex have been largely demonstrated in animal  
830 studies (Irvine and Rajan, 1996; Rajan et al., 1993; Çakır et al., 2015; Suh et al., 2016). In the  
831 auditory system, experience-dependent alterations in receptive field properties were  
832 investigated by partial destruction of the cochlea, leading to reorganization within the primary  
833 auditory cortex (Irvine and Rajan, 1996; Rajan et al., 1993). There is also evidence for  
834 somatosensory cross-modal plasticity in post-lingually deaf adults (Doucet et al., 2006;  
835 Sandmann et al., 2012). In this line, Kang et al. reported changes in functional PET  
836 connectivity with the auditory cortex in 91 deaf children and 20 young adults (Kang et al.,  
837 2003). Functional connectivity was mostly loco-regional, involving the temporal cortex and  
838 was more increased in deaf children than in deaf or normal hearing adults (Kang et al., 2003).  
839 In addition, distant activations from the primary auditory cortex were observed in adults with  
840 hearing loss, involving the left inferior frontal gyrus, in a rhyme-task activation fMRI study  
841 (MacSweeney et al., 2009). In this study, the authors showed a greater activation in the deaf  
842 and dyslexic groups than in the hearing non-dyslexic group across a large portion of the left  
843 inferior frontal gyrus, suggestive of compensatory effects.

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861 In the present study, increased metabolic changes and increased connectivity with the auditory  
862 cortex were mainly found in prefrontal areas, the cingulum and striatum bilaterally, regions  
863 involved in executive and limbic functions (Hanlon et al., 2013; Roxo et al., 2011),  
864 reinforcing the hypothesis of plasticity. This is in line with an fMRI task activation study that  
865 showed increased activation of frontal cortices during degraded listening situations in adults  
866 with or without hearing loss (Pelle et al., 2011), suggesting that frontal cortices improve  
867 sensory perception via top-down modulatory control. Indeed, in the case of hearing-loss,  
868 frontal areas are probably recruited because of their implication in selective attention (Pelle  
869 et al., 2011), as observed in visual deprivation (Frezzotti et al., 2014). The findings are also  
870 coherent with increased activation in frontal cortical areas observed using auditory evoked  
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888 potentials in early stages of adult hearing loss (combined with decreased activation in  
889 temporal cortex) thought to be related to changes in cortical resource allocation (Campbell  
890 and Sharma, 2013). **Taken together, the present findings therefore provide additional support  
891 that hearing loss does result in a change of the connectome, the connectome being defined as  
892 a network map of effective synaptic connections and neural projections and higher order  
893 neurocognitive functions that can access the auditory cortex via top-down interactions (Kral et  
894 al., 2016).**

#### 895 896 897 898 899 900 901 902 903 904 905 906 907 *4.3 Compensation: both cross-modal plasticity and top-down modulatory control?*

908  
909 It is noteworthy that the finding of increased metabolism within inferior parietal gyri could be  
910 related to compensation through proprioceptive processing, suggesting cross-modal  
911 recruitment (Gick and Derrick, 2009). Moreover, pre- and post-central areas, regions of the  
912 sensitive-motor cortex, were also found to have increased metabolism or increased  
913 connectivity with associative auditory cortex, such as pre- and post-central gyri (BA2, 3, 4, 6  
914 and 7). In this case, cross-modal recruitment by the somatosensory system may be related to:  
915 i) the close proximity of auditory and somatosensory cortices (Allman et al., 2009), ii) the  
916 overlap of the auditory and somatosensory pathways sub-cortically (Dehmel et al., 2008), iii)  
917 increased reliance on vibrotactile inputs known to play a role in auditory speech perception  
918 and production (Gick and Derrick, 2009), or iv) increased reliance on lip-reading, and on a  
919 parieto-premotor “mirror system” involved in both the production and observation of mouth-  
920 related actions (Buccino et al., 2004, 2001). In this line, a cross-modal model with visual  
921 function has also been described previously in deaf patients (Strelnikov et al., 2011; Barone et  
922 al., 2016). Such cross-modal influence is observed in speech and in non-speech situations,  
923 such as face-voice interactions, which are crucial to social interaction. The clear visual impact

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947 is supported by a strengthening of the connectivity that occurs specifically during deafness  
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949 between the face and voice cortical areas (Barone et al., 2016).  
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952 Moreover, the recruitment of a cortico-subcortical network involving the striatum, as found in  
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954 the present study, could contribute to improve auditory processing through top-down  
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956 mechanisms. This could be related to mechanisms of temporal expectancies and predictive  
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958 coding, implicating that higher-order representations influence lower-order representations by  
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960 generating predictions about sensory input through the recruitment of subcortico-cortical  
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962 networks (Kotz and Schwartze, 2010). This is thought to explain the fact that when something  
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964 is expected to happen, the reaction is more effective to the event, thought to be mediated  
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966 through the beneficial effects of temporal expectancies on phonetic verbal processing (Cason  
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968 and Schön, 2012).  
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#### 974 *4.4 Limitations of the present study*

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977 The present study has several limitations. Although the pattern of decreased metabolism  
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979 differed from that of patients with neurodegenerative diseases, we cannot rule out that  
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981 metabolic changes on PET related to neurodegenerative disorders in some patients might have  
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983 influenced these findings. A more precise assessment of neurocognitive function should be  
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985 performed in these patients and correlated with PET findings. Secondly, in order to increase  
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987 sensitivity, a threshold of  $p < 0.005$  corrected for cluster volume was chosen for statistical  
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989 significance in SPM, leading to exposing to type I error. However, this threshold has been  
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991 widely used in quantitative analysis studies, including the previously described PET  
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993 examination of glucose metabolism in deaf adults (Lee et al., 2003). Finally, a post-CI-  
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995 evaluation is needed to assess functional reorganization after cochlear implantation, in order  
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997 to address the potential reversibility of compensatory mechanisms. In this line, the selection  
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1006 of PET imaging to study the changes of the connectome makes sense given the absence of  
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1008 magnetic interference caused by cochlear implantation.  
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## 1010 1011 1012 1013 **5. Conclusions** 1014

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1018 This study shows that hearing loss in elderly patients, as assessed by cerebral  $^{18}\text{F}$ -FDG-PET,  
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1020 leads to a specific metabolic pattern of decreased of metabolism in the associative auditory  
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1022 cortex, and is associated with functional reorganization of the connectome. In addition,  
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1024 associated multimodal increased metabolism and connectivity, correlated with better  
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1026 performance on cognitive tasks, indicates functional reorganization likely to be related to  
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1028 compensatory mechanisms. The topography of increased metabolism and the changes of  
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1030 connectivity suggest that compensation may not only involve cross-modal plasticity but also  
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1032 top-down modulatory control. These findings add to the evidence that neuroplasticity  
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1034 continues through age. Future studies with extensive neuropsychological assessment need to  
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1036 address how changes of cognition are related to functional reorganization, and how CI can  
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1038 contribute to reestablish the connectome and therefore contribute to successful aging.  
1039

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1064  
1065 **Conflict of Interest:**  
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1067 The authors declare that they have no conflict of interest.  
1068

1069 **Authors role:**  
1070

1071 All authors have participated either to: 1) conception and design or analysis and interpretation  
1072 of data, or both (AV, SR, RMC, MD, EG); 2) drafting of the manuscript or revising it critically  
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**Table 1: Patient data with gender, age at time of assessment, educational level, duration of speech perception scores  $\leq 50\%$  at 60 dB with hearing aids in years, experience with hearing aids in years and etiology of hearing loss.**

Patients	Gender	Age	Educational level (in years)	Speech perception score $\leq 50\%$ at 60 dB with hearing aids (in years)	Use of Hearing aids (in years)	Etiology of Hearing Loss (HL)
1	F	75	11	10	27	unknown
2	M	75	18	7	10	unknown
3	F	76	0	7	12	unknown
4	M	79	5	7	17	unknown
5	F	60	11	6	19	genetic
6	M	73	14	10	19	unknown
7	F	72	5	4	7	unknown
8	M	66	9	8	26	unknown
9	M	75	5	6	10	right cholesteatoma and left sudden HL
10	F	67	9	9	27	unknown
11	F	76	5	1	1	labyrinthitis
12	F	73	12	7	12	unknown
13	F	69	9	0.6	0	bacterial meningitis
14	F	67	5	10	27	otosclerosis
15	F	82	9	6	12	unknown
16	M	76	17	7	26	progressive HL complicated by sudden HL
17	F	64	11	9	40	genetic HL
18	M	83	12	11	43	unknown
19	M	66	2	9	15	unknown
20	F	71	5	12	41	otosclerosis
21	M	77	11	12	27	unknown
22	F	70	8	4	8	unknown right HL and left otosclerosis
23	M	73	12	7	12	unknown
24	F	76	9	4	8	otosclerosis
25	M	69	5	7	19	Meniere's disease
26	F	84	5	1	1	sudden HL
27	M	73	12	7	20	sudden HL

**Table 2. Characteristics of patients and healthy subjects**

	<b>Patients</b>	<b>Healthy Subjects</b>	<b>p-value</b>
	<b>n=27</b>	<b>n=27</b>	
<b>Age, years</b>	72.9 (SD=5.8)	72.3 (SD=7.6)	0.75
<b>Gender: female</b>	15 (56%)*	15 (56%)*	1
<b>Level of Education (AFPA score)</b>	4.2 (SD=1.2)	3.7 (SD=1.2)	0.17
<b>Duration of deafness, years</b>	7.0 (SD=4.1)	-	-
<b>Psychometric assessment</b>			
MMSE (/30)	26.3 (SD=3.1)	28.9 (SD=1.1)	0.01*
FAB (/18)	16.3 (SD=1.6)	17.3 (SD=1.1)	0.04*

\*: Percentage of categorical variables; MMSE: Mini Mental State Examination; FAB: Frontal Assessment Battery.

**Table 3. 18F-FDG-PET findings in patients with hearing loss in comparison with controls (Anatomical locations, spatial extents of significant Clusters, MNI coordinates, maximal z-Scores and height threshold of peak-voxel)**

		Peak Coordinates				
	Cluster Dimension	x	y	z	z-score of Peak	p-Value
<b>Decreased metabolism in patients with hearing loss in comparison to controls</b>						
Right superior temporal gyrus (BA 21 and 22)	322	58	-12	-2	3.36	<0.001
<b>Increased metabolism in patients with hearing loss in comparison to controls</b>						
Left superior, middle, medial and precentral frontal gyri and cingulum (BA 4, 6, 9, 24, 31 and 32)	1934	-14	-10	74	3.89	<0.001
Right superior, middle, medial and precentral frontal gyri, postcentral parietal gyrus and cingulum (BA 3, 4, 6, 8, 31 and 32)	2306	12	-12	60	3.77	<0.001
Left postcentral and inferior parietal gyri (BA 2, 7 and 40)	370	-36	-38	42	3.23	<0.001
<b>Increased connectivity with BA 21-22R in patients with hearing loss in comparison to controls</b>						
Anterior cingulate (BA 24 and 32)	330	-14	20	28	3.84	<0.001
Right superior and middle temporal gyri (BA 21, 22 and 42)	343	48	-38	6	3.67	<0.001

1771							
1772							
1773	Right inferior parietal gyrus (BA 40)	235	42	-40	44	3.42	<0.001
1774							
1775	Posterior cingulate (BA 23)	145	-6	-22	34	3.36	<0.001
1776							
1777	Right striatum	180	24	16	12	3.35	<0.001
1778							
1779	Left striatum	210	-20	18	8	3.28	<0.001
1780							
1781	Right precentral frontal and postcentral parietal gyri (BA 3, 4 and 6)	313	60	-4	12	3.17	<0.001
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*BA: Brodmann's Area.*

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1832 **Figure legends**  
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1836 **Figure 1. Anatomical localization of areas of decreased of metabolism in patients with**  
1837 **hearing loss in comparison to controls**  
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1841 Anatomical localization of areas of decreased of metabolism in patients with hearing loss  
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1843 ( $p < 0.005$ , uncorrected,  $k > 213$ ), in comparison to controls, projected onto sections of a  
1844  
1845 standard SPM8 MRI template. In comparison to controls, patients with hearing loss showed  
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1847 decreased metabolism in the right superior temporal gyrus (BA21 and 22). *MRI: Magnetic*  
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1849 *Resonance Imaging; BA: Brodmann's Area.*  
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1855 **Figure 2. Anatomical localization of areas of increased of metabolism in patients with**  
1856 **hearing loss in comparison to controls**  
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1860 Anatomical localization of areas of increased of metabolism in patients with hearing loss  
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1862 ( $p < 0.005$ , uncorrected,  $k > 213$ ), in comparison to controls, projected onto sections of a  
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1864 standard SPM8 MRI template. In comparison to controls, patients with hearing loss showed  
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1866 increased metabolism in bilateral superior, middle, medial and pre-central frontal gyri, the  
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1868 cingulum, bilateral post-central parietal gyri, and the left inferior parietal gyrus. *BA:*  
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1870 *Brodmann's Area.*  
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1876 **Figure 3. Anatomical localization of areas of increased right BA 21-22 connectivity in**  
1877 **patients with hearing loss in comparison to controls**  
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1881 Anatomical localization of areas of increased right BA21-22 connectivity in patients with  
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1883 hearing loss ( $p < 0.005$ , uncorrected,  $k > 136$ ) in comparison to controls projected onto 3D  
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1885 volume rendering (A) and standard SPM8 MRI template centered on the left caudate (B).  
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Patients with hearing loss showed increased connectivity of BA21-22 on the right with the right superior and middle temporal gyri, the right precentral frontal and postcentral parietal gyri, the right inferior parietal gyrus, the cingulum, and the right and the left striatum. *MRI: Magnetic Resonance Imaging; BA: Brodmann's Area.*