Hearing and cognitive impairment: a functional evaluation of associative brain areas in patients affected by Alzheimer's disease

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Summary

Auditory dysfunction observed in patients with cognitive diseases is probably due to the alteration of some brain areas involved in sound stimulus processing. The present study aimed to investigate differences in such processing and in connectivity of the primary auditory cortex in patients affected by Alzheimer's disease (AD) and in normal subjects. We examined 131 diagnosed AD patients and a control group (CG) of 36 normal subjects. After a complete clinical investigation, focused on hearing function, all subjects underwent a brain FDG PET/CT. AD subjects *vs* CG showed reduced glucose consumption in BA 6,7,8,39, whereas we did not find differences in the primary auditory cortex. In AD, connectivity analyses showed a positive correlation of the primary auditory cortex with BA 6,8,21,31,39,40,42 and a negative correlation with BA 19, cerebellum and basal ganglia. Our findings suggest that neurological evaluation of patients with hearing loss might allow earlier (preclinical) identification of those affected by cognitive impairment.

KEY WORDS: Alzheimer's disease, cognitive decline, hearing loss, hearing networks, neuroimaging, PET.

Introduction

Dementia and hearing impairment are closely related. Untreated hypoacusis can increase the risk of developing dementia by more than three times, and three out of four people with a cognitive deficit also present a reduction in hearing ability (Lin et al., 2013; Golub et al., 2017; Rutherford et al., 2018). Auditory dysfunction observed in patients with cognitive diseases is probably due not only to mechanisms of aging or dysfunction of the peripheral auditory pathway, but also to the alteration of some brain areas that play an important role in sound stimulus processing. This has been demonstrated by recent studies that highlighted brain volume changes and a general "cortical reorganization" in subjects with peripheral hearing impairment (Lin et al., 2014). Central hearing is an elaborate process, which activates not only the auditory cortex, but also several associative areas where words are cognitively connected (Vandenberghe et al., 2013). In fact, associative brain areas seem to play a fundamental role in the comprehension of the auditory message, allowing the subject not only to perceive the sound stimulus, but also to understand its semantic value. Recent studies, by performing functional magnetic resonance imaging (MRI) in healthy subjects exposed to sound stimuli, have mapped the selectivity of various semantic regions located in different cortical areas, however, the functioning of auditory areas in patients with cognitive diseases remains poorly known and difficult to assess (Blaxton et al., 1996; Ottaviani et al., 1997; Binder et al., 2009; Bigler et al., 2007; Jou et al., 2010; Huth et al., 2016; Hardy et al., 2016).
For these reasons, we recruited patients with Alzheimer's disease (AD), one of the most important forms of cognitive impairment, selecting those with a normal (i.e. for age and gender) audiometric evaluation, and compared them with normal subjects. Focusing specifically on individuals with cognitive impairment, the aim of our study was to evaluate, through 2-deoxy-2-[18F]fluoroglucose (18F FDG) positron emission tomography/computed tomography (PET/CT) neuroimaging, the functional hearing networks in the primary auditory cortex and in other associative brain areas involved in the hearing process.

Materials and methods

We recruited 131 patients with a new diagnosis of AD (diagnosed according to the NINCDS-ADRDA criteria). They had a mean (±SD) age of 70 (±7) years; 74 (56.49%) were males and 57 (43.51%) were females. A complete clinical investigation was performed in all the subjects, including medical history, Mini-Mental State Examination (MMSE), complete blood screening, and neurological, otolaryngological, neuropsychological and neuropsychiatric examinations (Table I). All the patients underwent MRI (1.5 T). The otolaryngological evaluation included otological anamnesis, otoscopic examination, acoustic impedance test and pure tone audiometry.

Hearing loss was calculated considering each ear separately, and pure tone frequency stimulation (from 125 to 8000 Hz) was carried out for each. The exclusion criteria were: isolated deficits and/or unmodified MMSE score (25/30) on re-evaluation (at 6, 12 and 18 months of follow-up), clinical manifestation of acute stroke in the last 6 months with a Hachinski score of 4, pyramidal and/or extrapyramidal signs, and evidence of cortical lesions. In order to avoid possible central effects due to drug therapy, all subjects were taken off cholinesterase inhibitors, antidepressants or any other neuroactive drugs (i.e. benzodiazepines, anti-epileptic drugs or neuroleptics) throughout the study. Patients with a previous history of otological/labyrinthine disorders, significant loud noise exposure, ototoxic drug consumption, or diabetes were excluded.

The study was approved by the ethics committee of the "Tor Vergata" University in Rome and complied with the Declaration of Helsinki. All the participants gave their written informed consent to participate after receiving extensive information about the study. Table I provides a general overview of the AD population.

Control group

18F FDG PET/CT imaging was performed in 36 chemotherapy naïve subjects. The mean (±SD) age of the patients was 71 (±7) years (males, 15; females, 21). Every member of the control group (CG) had previously been evaluated for the absence of clinical signs of AD by an experienced neurologist (A.M.), and had been found to be negative for brain injury on MRI evaluation, performed 7 ± 2 days before PET/CT examination (Chiaravalloti et al., 2016).

PET/CT scanning

As in studies previously published by our group (Chiaravalloti et al., 2016; 2018b), we used the Discovery VCT (GE Medical Systems, Tennessee, USA) PET/CT system to assess 18F FDG brain distribution in patients and controls. The acquisition parameters were: 3D-mode; 256x256 matrix; reconstruction with the ordered-subsets expectation maximization (OSEM) algorithm with 20 subsets and 4 iterations. In each patient, a low-amperage CT scan for attenuation correction (40 mA;120Kv) was performed. All subjects fasted for at least 5 h before injection of 18F FDG; their serum glucose levels were in the normal range. All the subjects were injected intravenously with 185-210 MBq of 18F FDG; the scan started 30 minutes after injection.

Brain distribution of 18F FDG was analyzed using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB 2012b (Mathworks, Natick, Mass., USA). 18F FDG PET data were submitted to the same imaging processing proposed elsewhere (Jou et al., 2010; Huth et al. 2016; Hardy et al., 2016). For correlation analysis, extracted mean regional volume-of-interest counts, after the normalization process (described in detail in the papers cited above), were used as a covariate to find regions showing significant (corrected <0.05) voxel-wise correlations across scans (subjects) using SPM8 (Liguori et al., 2016).

For the comparison between the AD subjects and the CG, the voxel-based analysis was performed using a modality-adjusted paired t-test (two conditions, one scan/condition) and the following comparison was assessed: AD vs CG using gender and age as nuisance variables (Liguori et al., 2016). In the SPM maps, we investigated the brain areas showing a significant correlation using a statistical threshold of p = 0.001; familywise error (fwe) corrected for the problem of multiple comparisons, with an extent threshold of 100 voxels. Moreover, a selected inclusive mask that included the primary auditory cortex was generated (WFU Pickatlas®, Radiology Informatics and Imaging Laboratory, Winston-Salem, NC). Then, cortical 18F FDG activity of the superior temporal gyrus (STG) bilaterally was extrapolated and then normalized for the counts of the cerebellum; it was then used for a two-sample t-test comparison between the AD and CG subjects. After this process, the activity of the STG bilaterally was used as a regression factor in SPM8 for the connectivity analysis of the remaining cortical regions, using gender, age and MMSE as covariates in both groups (Lancaster et al., 1997; Schmahmann et al., 1999; Soonawala et al., 2002).

Results

The final sample consisted of all the subjects recruited. The comparison of glucose metabolism between the AD patients and the CG showed significant hypometabolism in the temporo-parietal lobes (with the higher differences being reported in right precuneus, angular gyrus, left inferior parietal lobule) and frontal lobe (right and left middle frontal gyrus, right superior frontal gyrus), corresponding to BA6, BA7, BA8, BA39 (p fdr and fwe corr <0.001; ce 1944-22722). Figure 1 provides a graphical overview. The metabolism of the STG showed a nonsignificant difference between the AD and CG subjects. In the AD group, the connectivity analysis of the STG bilaterally showed a significant positive correlation with the right supramarginal gyrus (BA40), right precuneus (BA31), left STG (BA39,42), left middle temporal gyrus (BA21), right superior and middle frontal

Table I - General overview of the AD population examined.

AD subjects (n=131)	
Mini-Mental State Examination score	19.3 ± 5.9
Rey Auditory Verbal Learning Test, immediate recall score	21.7 ± 8.5
Rey Auditory Verbal Learning Test, delayed recall score	2.4 ± 2.6
Rey Complex Figure Test, copy score	18.6 ± 10
Rey Complex Figure Test, delayed recall score	7.6 ± 5.9
Raven's Colored Progressive Matrices score	20.8 ± 6.8
Phonological Word Fluency Test score	22.3 ± 9.8

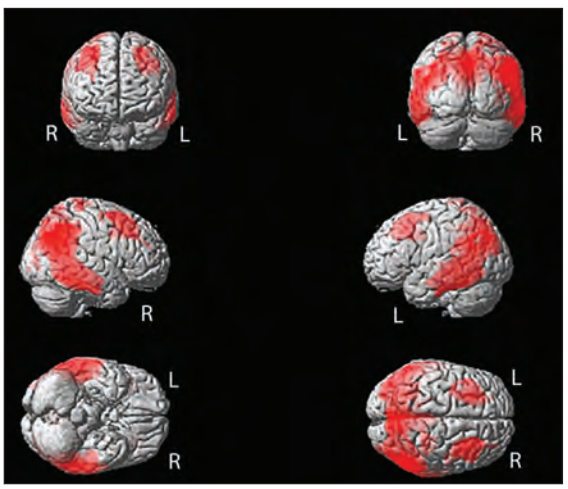

Figure 1 - 3D rendering of SPM data showing significant hypometabolism in AD subjects as compared to CG in a wide cluster involving temporo-parietal lobes (right precuneus and angular gyrus, left inferior parietal lobule) and frontal lobe (right and left middle frontal gyrus, right superior frontal gyrus). AD: Alzheimer disease; CG: control group; R: right; L: left.

gyrus (BA8), and left superior and middle frontal gyrus (BA6,8) (p fdr and fwe corr<0.001; ce 565-6347), as reported in Table II (Fig. 2).

Furthermore, in AD a significant negative correlation of the primary auditory cortex with the right limbic parahippocampal gyrus (BA19), left cerebellum, right occipital lobe on lingual gyrus (BA19), right putamen, right globus pallidus, left thalamus, left pulvinar, and right medial dorsal nucleus (p fwr and fwe corr <0.001; ke 607-2034) was reported. In the CG the connectivity analysis showed a positive correlation of the primary auditory cortex with the STG (BA22,39,42), left medial frontal gyrus (BA10), bilateral anterior cingulate cortex (BA32), left inferior frontal gyrus (BA9) and left STG (BA41) (p fwr and fwe corr<0,001; ke 1550- 3948), as reported in Table III (Fig. 3).

Discussion

The exact mechanism underlying hearing loss in patients with cognitive impairment is still unknown, a possible explanation being that this loss may be due to the alteration, in cognitive impairment, of functional brain networks involved in cognitive and semantic functions. The present comparison between glucose metabolism in AD patients *versus* a CG reported significant hypometabolism in the parietal lobe (right precuneus and angular gyrus, left inferior parietal lobule) and frontal lobe (right and left middle frontal gyrus, right superior frontal gyrus) in AD.

These findings are consistent with previous research papers and neurological guidelines (Shimizu et al., 2018). A previous meta-analysis suggested that hearing and semantic processes are linked to 7 brain regions, namely i) the angular gyrus and adjacent supramarginal gyrus, ii) the lateral temporal lobe, including the entire length of the middle temporal gyrus and posterior portions of the inferior temporal gyrus, iii) the ventromedial region of the temporal lobe centered on the mid-fusiform gyrus and adjacent parahippocampus, iv) the dorsomedial prefrontal cortex in the superior frontal gyrus and adjacent middle frontal gyrus, v) the inferior frontal gyrus, especially the pars orbitalis, ventromedial and orbital prefrontal cortex, vi) the posterior cingulate gyrus, and vii) the adjacent ventral precuneus (Blaxton et al., 1996). Two main theories have been proposed to explain how concepts are formed and recognitions are activated in the brain in healthy subjects. The first hypothesis suggests that knowledge is tied to certain experiences and, therefore, that related sensory attributes determine which areas of the brain are more important for certain concepts (for example, the most frontal areas seem to be important for verbs of motion). On the other hand, a second theory assumes that there are intrinsic anatomical-functional foundations that lead to an organization of hearing and knowledge. Hence, even a simple word may have the capacity to activate not only the auditory cortex but also several other areas where words are semantically and cognitively connected (Gainotti, 2012).

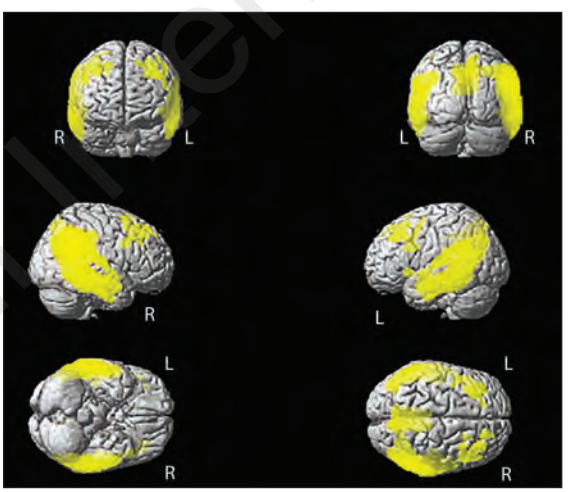

Figure 2 - 3D rendering of SPM data reported in Table II showing the connectivity of the STG in AD in a wide area involving temporal and parietal lobe bilaterally. AD: Alzheimer disease; R: right; L: left.

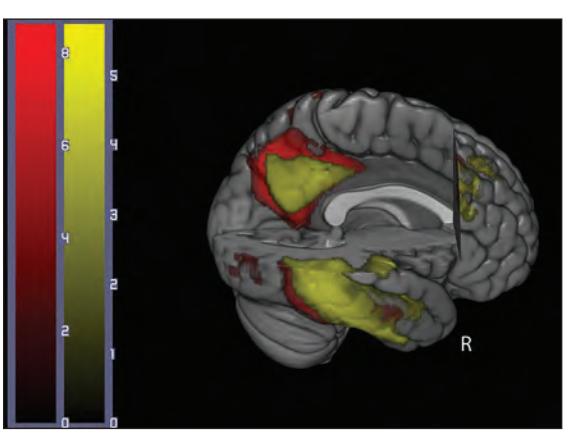

Figure 3 - 3D rendering of SPM data reported in Tables II and III showing the partial superimposition of clusters. In red, hypometabolism in AD subjects as compared to CG; in yellow, the connectivity of STG in AD.

Table II - Multiple regression analysis showing the connectivity of superior temporal gyrus bilaterally in AD.

Analysis	Cluster level					Voxel level	
Positive correlation	cluster p(FWE-corr)	cluster p(FDR-corr)	cluster extent	Cortical region Gray Matter nearest	Z score of maximum	Talairach coordinates	Cortical region
	0.000	0.000	1361	R Cerebrum, Parietal Lobe, Supramarginal Gyrus	7.53	60 -44 28	BA40
				R Cerebrum, Temporal Lobe, Supramarginal Gyrus	7.26	56 -52 18	BA 40
				R Cerebrum, Parietal Lobe, Precuneus	6.75	8 -48 38	BA31
	0.000	0.000	6347	L Cerebrum, Temporal Lobe, Superior Temporal Gyrus	6.63	-52 -54 20	BA39
				L Cerebrum, Temporal Lobe, Superior Temporal Gyrus	5.75	-58 -34 16	BA42
				L Cerebrum, Temporal Lobe, Superior Temporal Gyru	5.57	-56 -32 -10	BA42

The 'Cluster level' section on left reports, for each significant cluster, the number of voxels, the corrected p value of significance, and the cortical region where the voxel is found. The 'Voxel level' section on the right reports, for each significant cluster, all the coordinates of the correlation sites (with the Z-score of the maximum correlation point), and the corresponding cortical regions.
Abbreviations: L, left; R, right; FWE, familywise error; FDR, false discovery rate.

The connectivity analysis in our GG revealed an obviously positive correlation of the primary auditory cortex with the STG bilaterally. A further positive correlation shows a functional connectivity network between the primary auditory cortex and the left medial and inferior frontal gyrus. A positive correlation has previously also been described between the primary auditory cortex bilaterally and the anterior cingulate cortex bilaterally (Blaxton et al., 1996), while in previous reviews, a specific network involved in the semantic process has been described in the posterior cingulate cortex and precuneus. Hence, our results mainly confirm the role of these cortical areas in the semantic process in healthy subjects.

However, very few papers describe functional networks involved in the hearing process in AD or dementia subjects. On the subject of connectivity in people affected by cognitive diseases, a previous review describes several theories that involve different brain areas: previous research suggests that in lateralized forms of "semantic dementia" (SD), the cognitive impairment is modality-specific; there is a prevalent involvement of the left temporal lobe in verbal and of the right temporal lobe in pictorial and sensorial aspects of conceptual knowledge; there is also the model of a bilateral amodal semantic hub and that of two lateralized, modality-specific semantic networks. It has been suggested that the semantic disorder observed in SD is due to the co-occurrence of verbal and non-verbal defects resulting from temporal atrophy, and that the multimodal semantic impairment observed in advanced stages of SD is due to disrupted connections (Gainotti, 2012).

The results in our AD group showed that STG activity, bilaterally, was significantly and positively correlated with the activity in the right supramarginal gyrus, right precuneus, left superior and middle temporal gyrus, right superior and middle frontal gyrus, and left superior and middle frontal gyrus. The correlation bilaterally with the primary and secondary auditory cortex was clearly positive and is consistent with findings in the scientific literature concerning the hearing process. In particular, the positive correlation between primary auditory cortex uptake and left temporal lobe activity may support the hypothesis that SD presents prevalent involvement of the left temporal lobe when the cognitive impairment is mainly verbal, as suggested by previous work (Gainotti, 2012).

Moreover, the positive correlation between the primary auditory cortex and the supramarginal gyrus, precuneus, superior and middle frontal gyrus seems consistent with previous studies in healthy subjects concerning the semantic brain and may be related to functional connectivity networks in these areas (Lin et al., 2014). Therefore, primary auditory cortex metabolism and activity do not seem to be affected by AD, but the connectivity with cortical areas, whose hypometabolism is significant in AD, may affect the processing of acoustic stimuli in further stages of the disease, supporting the hypothesis that the hearing loss in AD patients is probably mainly related to SD.

Consequently, acoustic prostheses effective on sensorineural hypoacusis may lead to limited benefits in these subjects. Our hypothesis, if confirmed by further multicenter trials, may lead to personalized manage-

Table III - Multiple regression analysis showing the connectivity of superior temporal gyrus bilaterally in CG.

Analysis	**Cluster level**					**Voxel level**	
Positive correlation	cluster p(FWE-corr)	cluster p(FDR-corr)	cluster extent	Cortical region Gray Matter nearest	Z score of maximum	Talairach coordinates	Cortical region
	0.000	0.000	3948	R Cerebrum, Temporal Lobe, Superior Temporal Gyrus	4.45	66 -20 8	BA42
				R Cerebrum, Temporal Lobe, Superior Temporal Gyrus	4.23	52 -58 22	BA39
				R Cerebrum, Temporal Lobe, Superior Temporal Gyrus	4.08	56 -54 16	BA22

The 'Cluster level' section on the left reports, for each significant cluster, the number of voxels, the corrected p value of significance and the cortical region where the voxel is found. The 'Voxel level' section on the right reports, for each significant cluster, all the coordinates of the correlation sites (with the Z-score of the maximum correlation point), and the corresponding cortical region.
Abbreviations: L, left; R, right; FWE, familywise error; FDR, false discovery rate.

ment of hypoacusis in patients with cognitive impairment. On the other hand, new investigations may highlight the need for early neurological examination in patients affected by sensorineural hearing loss not linked to otological causes or in subjects without benefits after prosthetic treatment.

Our results in the AD group showed a significant negative correlation between the primary auditory cortex and the right limbic parahippocampal gyrus, left cerebellum, right occipital lobe on lingual gyrus, right putamen, right globus pallidus, left thalamus, left pulvinar, right medial dorsal nucleus. These heterogeneous results may be due to different methods but also to a different brain pathology or severity. Our results suggest that patients with cognitive impairment might be able to correctly receive the vocal message, but not to understand it cognitively. A limitation of the present study that prompts further investigation is the unexplored correlation of SPM with audiometric data. Moreover, future studies should include a complete audiological examination and PET/CT evaluation of cerebral 18F FDG uptake during acoustic stimuli.

In conclusion, our findings seem to indicate a disruption of functional networks between the primary auditory cortex and other brain areas that play a fundamental role in the hearing process. These findings may influence ordinary clinical practice by leading to early enrollment of patients who might benefit from hearing habilitation or rehabilitation, and to earlier neurological evaluation of patients with hearing loss in order to allow detection of AD in the preclinical stage. In fact, exploring physiological hearing dysfunction in patients with cognitive impairment may be mandatory for early diagnosis of diseases of mental deterioration, while on the other hand, correction of auditory function through the appropriate hearing rehabilitation seems to be crucial to reduce the risk of cognitive decline.

Therefore our results may represent an initial insight into this still unexplored field, and further studies may be planned to expand knowledge of the connectivity of auditory cortex in cognitive diseases.

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