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ORIGINAL PAPER

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Regional cerebral blood flow change in a case of Alzheimer's disease with musical hallucinations

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Abstract We examined alteration of regional cerebral blood flow (rCBF) in a case of Alzheimer's disease (AD) patient with musical hallucination. To detect regions related to musical hallucination, single-photon emission computed tomography (SPECT) imaging of the patient and nine sex, age, and cognitive function-matched AD patients without delusions and hallucinations were compared using statistical parametric mapping 99 (SPM99). In comparison with controls, the patient had increased rCBF in left temporal regions and left angular gyrus. This profile could be relevant to the neuroanatomical basis of musical hallucinations.

Key words single-photon emission computed tomography · regional cerebral blood flow · musical hallucination · Alzheimer's disease · superior temporal gyrus

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Introduction

Musical hallucinations represent a particular type of acoustic hallucination, in which the acoustic perception is formed by music, sounds, or songs. Recent reports (Erkwoh et al. 1993; Griffiths 2000; Kasai et al. 1999) have focused on the neuronal basis of musical hallucinations in patients with deafness and have suggested that musical hallucinations might be associated with hyperactivity in the superior temporal lobes.

However, this type of hallucination has rarely been reported in neurodegenerative diseases (Ueda et al. 2002). In the present case study, we found significant regional cerebral blood flow (rCBF) changes in an Alzheimer's disease (AD) patient with musical hallucination using statistical parametric mapping 99 (SPM99) analysis (Friston et al. 1995).

Case report

The patient was a 73-year-old woman with no history of previous neurological or psychiatric disease. There was no family history of dementia or psychiatric disease. She had had 10 years' formal education and then done office work until the age of 60 years. At the age of 69 years, she began to show slowly progressive memory disturbance. She was diagnosed as having AD and prescribed donepezil (maintenance dose 5 mg/day). After one month, she had sustained musical hallucinations. Although donepezil was stopped immediately, musical hallucinations continued.

Neurological examination was unremarkable. She was confirmed to be right-handed by the Edinburgh inventory. Her hearing was normal on clinical examination. Pure tone audiogram, auditory brain stem response (ABR) revealed no hearing impairment. There was no evidence of psychiatric disease.

Blood work including full blood count, routine bio-

chemistry, thyroid function, serum vitamin B12 and folate were normal.

EEG showed diffuse slow waves without epileptiform abnormalities. Brain T1-weighted MRI showed diffuse cerebral atrophy particularly in hippocampal regions; on T2-weighted MRI, there were signal changes consistent with deep white matter ischemia that were considered normal for age.

The Mini-mental State Examination (MMSE) score (Folstein et al. 1975) was 20/30 with a Clinical Dementia Rating (CDR) score (Hughes et al. 1982) of 1. She scored 25/36 on Raven's coloured progressive matrices (Raven 1965). The total score for the Wechsler Adult Intelligence Scale-Revised (Wechsler 1981) was 85, with a verbal IQ of 80 and a performance IQ of 95. Alzheimer's Disease Assessment Scale, cognitive sub-scale (Mohs et al. 1983) was 23.6/70. Frontal lobe testing was unremarkable. On the Neuropsychiatric Inventory (NPI) (Cummings et al. 1994), she endorsed delusions and auditory hallucinations. Her hallucinations were songs, and localized to both ears from a fixed direction; they consisted of various familiar tunes voiced by her neighbours. She did not have insight into her hallucinations.

She was clinically diagnosed as probable AD according to National Institute of Neurological and Communicative Disease and Stroke-Alzheimer's Disease and Related Disorders Association (McKhann et al. 1984). We carefully excluded the possibility of Dementia with Lewy bodies referring to the consensus guidelines of Dementia with Lewy bodies (McKeith et al. 1996). She did not show fluctuating cognitive impairment, parkinsonism or persistent visual hallucination.

SPECT imaging

SPECT scans were carried out using 740 MBq 99mTc-HMPAO with eyes closed in a quiet dimly lit room. The musical hallucinations were active at the time of injection. The SPECT system used a four-head rotating gamma camera (SPECT 2000H, HITACHI, Tokyo, Japan) equipped with high resolution low-energy collimators that permit a spatial resolution of 7.5 mm full width at half maximum (FWHM). Data were obtained from the 140keV photo peak (10 % window) over a 360 degree rotation and 128*128 matrix. The step and shoot format was utilized with an acquisition time of 20 s/step and zoom factor of 1.33. Transaxial images of 99mTc-HMPAO SPECT were reconstructed by filtered backprojection using Butterworth and Ramp filters (cut-off frequency 0.12 cycle/cm) with attenuation correction (Chang, 0.08/cm). Slice thickness of SPECT images was 2.0 mm (one pixel).

Control subjects

For comparison with the patient's SPECT imaging, we selected a control group from 747 consecutive Japanese patients who were examined in the Higher Brain Function Clinic for outpatients of the Ehime University Hospital, between January 1996 and August 2003. The inclusion criteria were: (1) 65 years of age or older, (2) female, (3) right handedness, (4) the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD (McKhann et al. 1984), (5) CDR score = 1, (6) MMSE score between 18 and 23, (7) absence of apraxia, (8) absence of hallucinations and delusions on the NPI, (9) absence of neuroleptic medication at the time of SPECT scanning. Nine controls fulfilling these criteria were extracted. The mean age was 78.5 (SD = 5.7) years, the mean years of education was 9.5 (SD = 1.9), the mean MMSE score was 20.1 (SD = 1.9). The SPECT scanning protocol for controls was identical to that described above for the case.

SPECT image analysis

We analysed the data using MATLAB 6.5 and SPM99 (Friston et al. 1995). The SPECT images from each subject were spatially transformed to the SPM99 SPECT template, which approximates the standard space of Talairach and Tournoux (1988). The spatial normalization included both affine transformations and a liner combination of smooth spatial basis functions (7*8*7 mm) that model global nonlinear differences in shape. The spatially normalized structural images were resliced to a 2*2*2 mm voxel size. Finally, the images were smoothed with isotropic 16 mm FWHM Gaussian filter. The SPM analysis was performed with design model of one scan per subject, two-sample t test, between the case and control subjects. Global CBF was controlled for proportional scanning and grey matter threshold of 0.8 was used. Each individual image was scaled to a mean global CBF of 50 mL/100 mL/min. The threshold images show voxels, which are significantly different using $p < 0.001$(uncorrected).

Results

Compared to controls, rCBF of the case was significantly increased in the left superior temporal gyrus (Z-score = 5.41), left angular gyrus (Z-score = 4.26) (Figs. 1, 2). There was no significant decrease in rCBF.

Discussion

In this case report, an altered profile of rCBF was found in an AD patient with musical hallucinations in comparison to a control AD group. The patient's rCBF was significantly increased in the left superior temporal gyrus, and left angular gyrus. To our knowledge, this is the first study of musical hallucination analysed by a statistical imaging technique in neurodegenerative disease.

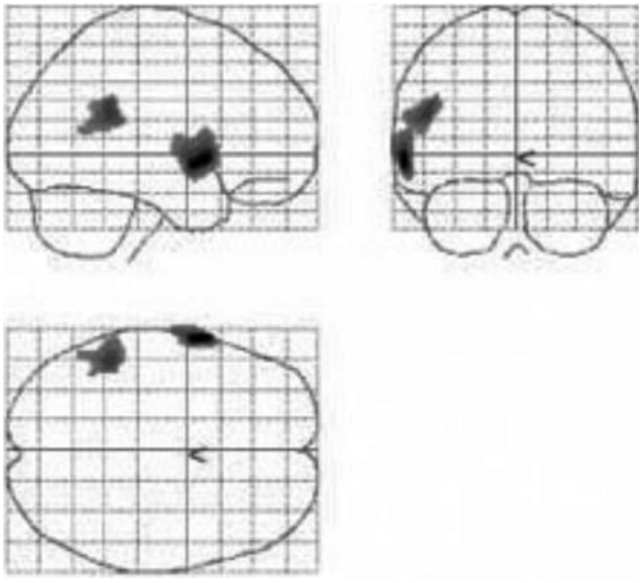

Fig. 1 Increased rCBF of the case compared with control subjects (n = 9) by SPM99 on a "glass brain". Compared with controls, rCBF of the case was significantly increased in the left superior temporal gyrus (Z-score = 5.41), left angular gyrus (Z-score = 4.26)

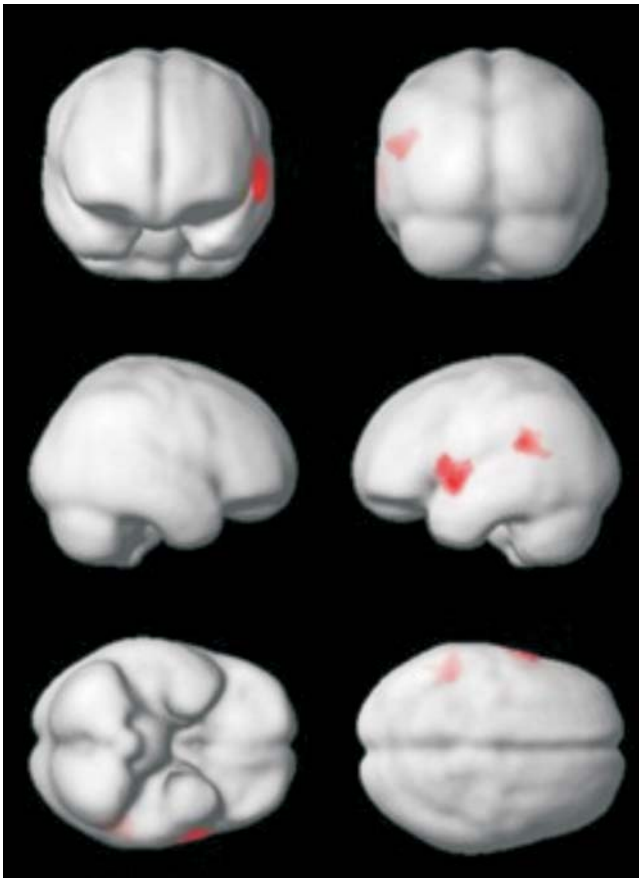

Fig. 2 Brain regions show relative activity of the case compared with severity-matched Alzheimer's disease patients (n = 9). The rCBF of the case was significantly increased in the left superior temporal gyrus (Z-score = 5.41), left angular gyrus (Z-score = 4.26)

The abnormal conditions of primary auditory cortex in the superior temporal plane caused various auditory disorders, such as tinnitus, deafness, auditory agnosias (Griffiths 1999; Griffiths et al. 2002). Particularly, musical hallucinations have been found in deaf cases to be associated with overactivity of the superior temporal gyrus (Erkwoh et al. 1993; Griffiths 2000; Kasai et al. 1999). Electrical stimulation of the same region provokes musical hallucinations (Penfield and Perot 1963). Our case showed relatively increased perfusion in these regions compared to dementia severity-matched AD cases. In our case, rCBF in the left angular gyrus was also increased. It is suggested that this region may have some relation to verbal hallucinations in schizophrenic patients (Matsuda et al. 1988). Hallucinations in this case were music with verbal, which is related to increasing rCBF of this patient in left angular gyrus. Activation of the left angular gyrus might be associated with verbal factor in musical hallucinations.

It is proposed that the distribution of pathology in our case includes relative sparing of the superior temporal gyrus and angular gyrus relative to other brain regions when compared to typical AD. The rCBF ratio of auditory association cortex to other cortical regions is shifted in our case analogous to that described in deaf hallucinations. In other words, in deaf subjects with hallucinations, this ratio is increased because of overactivity of auditory association cortex, while in our case this ratio is also increased to a similar degree, but this is because of relative sparing of auditory association cortex compared to other brain regions. In both situations, it is this change in balance that causes hallucinations to arise.

Previous studies showed increased rCBF of basal ganglia during musical hallucinations (Erkwoh et al. 1993; Griffiths 2000; Izumi et al. 2002). Our case did not present increasing rCBF of basal ganglia. Kasai et al. (1999) reported activation of the superior temporal gyrus without activating of basal ganglia. To clarify the role of basal ganglia for musical hallucinations, advance studies about musical hallucinations are needed in the future.

A major limitation of our study is the possibility that donepezil triggered musical hallucinations in this case on the ground of activating cortex. However, musical hallucinations continued after donepezil was stopped.

In order to disclose precise neuroanatomical basis of musical hallucination and to assess the validity of the present findings, further studies are necessary. In particular, it would be of considerable interest to contrast functional imaging findings from the same cases when actively hallucinating and when in remission.

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