Correlation between brain cortex metabolic and perfusion functions in subjective idiopathic tinnitus

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Abstract

Objectives: Subjective tinnitus has associated with abnormal brain metabolism and perfusion found in functional imaging studies by fluorodeoxyglucose (FDG) and technetium99m (TC99m). But there is no study evaluating the association of brain metabolism and perfusion abnormalities in a group of these subjects. The aim of this study was to investigate if there is any significant correlation between the brain perfusion and metabolism abnormalities in subjects with tinnitus. **Materials and Methods:** In this cross-sectional study, 52 patients were undergone TC99m-ECD single photon emission computerized tomography (SPECT) scan and F18-FDG positron emission tomography (PET). The results of PET and SPECT scanning were fused with MRI to accurate anatomical localization of abnormalities. The analysis was performed using Kendal's correlation, t-test and chi square. **Results:** Assessing these 52 tinnitus subjects (containing 42 males [76.4%]) showed that a significant correlation was found between the brain metabolic function and perfusion (p value 0.001).

Keywords: emission-computed, metabolism, perfusion, positron-emission tomography, single-photon, tinnitus, tomography.

INTRODUCTION

Tinnitus is the consciousness of sound that arises in the head without an obvious voluntary origin[1]. The prevalence of chronic tinnitus in general population is between 5%-15% and causes severe impairment of the quality of life in 1% to 3%[1,2]. Most of tinnitus subjects adapt to this phantom sound. Tinnitus may become a source of significant disability for those who fail to adapt. Therefore, the symptom of tinnitus has forced clinicians to establish protocols for the accuracy of tinnitus diagnosis and treatment[3].

A number of mechanisms and suspected origins of tinnitus in the auditory pathway have been hypothesized. Most hypotheses postulate that the generation of tinnitus is in association with cochlear or acoustic nerve or central auditory dysfunction and their interactions[4-9]. Despite this profusion of assumed locations in the generation of tinnitus, most current hypotheses agree that abnormal neural activity is interpreted and perceived as tinnitus in higher cortical centers (e.g., auditory cortex). Abnormal activity at higher levels of the auditory pathways (auditory nuclei, auditory cortex and associative cortices) may contribute significantly to the generation of tinnitus[6,10,11]. Central mechanisms must play a determinant role in generating this auditory phantom sensation as it resistant in most cases follow secession of auditory nerve. One hypothesis emphasis that tinnitus is caused by a reorganization of tonotopic maps in the auditory cortex, which leads to an over representation of tinnitus frequencies. Moreover, the participation of the limbic system in generating tinnitus has been postulated[12]. In recent years, it has been widely acknowledged that maladaptation of central information processing are critically responsible in tinnitus perception and generation[13]. Many investigations have revealed that tinnitus is linked with increased activity in the central auditory system as confirmed by electrophysiology and neuroimaging studies[5,14,15]. It could be a critical step in the task of defining the factors that create these phantom sensations and developing rational treatments for this chronic and disabling disorder[16].

Subjective idiopathic tinnitus is a symptom that could not be detected by routine clinical and paraclinical examinations. But functional imaging, electrophysiological and psycho-acoustical evaluation are among the tools that could be useful to objectify tinnitus. Advances in brain function imaging techniques have made it possible to identify the brain regions associated with the production of transient, subjective sensations, such as phantom limb pain or hallucinations, as well as perception and processing of sound and tinnitus and associating characteristics such as loudness of tinnitus[16-22].

Finding the involved foci in the brain of these patients is important for defining pathophysiology and selecting effective treatment strategy. The results of various functional imaging modalities such as positron emission tomography (PET), single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (FMRI) have shown similar brain abnormalities but there are some studies that have reported different findings in a group of patients[5,7,16-30].

Considering the importance of finding the responsible site of tinnitus in the brain and different functional imaging methods for finding the involved foci, this investigation was designed to evaluate correlation of two nuclear imaging methods evaluating brain metabolic perfusion and function using SPECT and PET in subjects with chronic subjective idiopathic tinnitus.

MATERIALS AND METHODS

Subjects

This cross-sectional study was performed on 52 patients referred to ENT and Head & Neck Research Centre of Iran University of Medical Sciences (IUMS) for evaluation and treatment of their tinnitus, and 6 control subjects from February 2008 to February 2009. All subjects gave written informed consent in accord with the declaration of Helsinki, National Committee of Ethics in Medical Research (Technology and Research Deputy of Hygiene Ministration) and the Committee on Ethics at the ENT and Head & Neck Research Centre of Tehran University of Medical Sciences, radiation safety, and radioactive drug research committees to participate in the study.

Inclusion criteria were: good general health, do not have any invasive therapeutic interventions of the brain, should not be pregnant or have made any decision to become pregnant, no psychiatric disorders or its history (according to a psychiatric evaluation), any treatment for tinnitus during last three months, dementia, seizure or alcohol/drug abuse in last six months, head and neck diseases or space occupying lesions, or any organic disease that could cause tinnitus should not be present. Also MRI with and without Gadolinium injection were performed to rule out any organic lesions in suspected patients. All patients were over 18 years old.

Tinnitus assessment

Pitch and Loudness Matching of tinnitus (PMT and LMT) were evaluated in tinnitus subjects in the affected ear to an external tone presented to the contralateral ear. This task was accomplished using a Tinnitus Evaluation Device (TinED®) which includes 6 channels to reconstruct the Most Troublesome Tinnitus (MTT) with a similar frequency and intensity. The accuracy of the calibrating equipment shall

be sufficient to determine that the TinED® is within the tolerances permitted by American Standard Specification for Audiometers, S3.6-2004. The subjects had to have LMT over 6 decibel sensation level (dB SL) to be included in this study.

Using Persian version of Tinnitus Handicap Inventory (THI), severity of tinnitus was evaluated and subjects with THI score of 44 or more were considered to have moderate to severe tinnitus[31].

Imaging

Each patient underwent scanning first with TC99m-ethyl cysteinate dimer (EDC) and two weeks later with F18-FDG. Then the MRI of patients was fused with the PET and SPECT images using Brain Anatomical Functional Images Coregistration Software (BrainAFICS®).

TC99m Perfusion imaging

The patients were placed in a quiet, dimly lit room and instructed to keep the eyes open (or use a mask) and the ears unplugged. They were also instructed not to speak, read, or move during 5 min prior to and 5 min post injection. They were asked to think about their tinnitus during the test. A commercial ethyl cysteinate dimer (ECD) preparation was used. After approximately 30 min, each subject received a 15mCi intravenous injection of tracer while they were still lying down. No sedation was used. One hour after intra venous injection of 15 mCi 99mTc-ECD, SPECT scanning was done (120 projections; 40 projections per head; 25 sec/projection). Scanning was performed using a dual head SMV gamma camera, equipped with a pair of low energy, high resolution collimators.

Planar and processed SPECT images were visually assessed by a nuclear medicine physician twice who was blinded to all other clinical and imaging information. The images were visually graded as normal for no appreciable abnormal activity and abnormal for hyper activity. Semiquantitative evaluation of planar images was also performed by drawing regions of interest (ROI) over the lesion and background areas on the anterior, posterior or contralateral hemisphere images without any lesion. Geometric means of the contralateral, posterior and anterior ROI values were used for calculation of lesion-to-background ratio. Transverse views with the best visualization of the lesions were selected for ROI drawing on the SPECT images. Lesion to background ratio was calculated accordingly for all sets of images. All activity ratios were classified to determine the intensity of activity as: 1 > = normal, 1-1.5 mild, 1.5-2 moderate and > 2 as sever hyperactivity. If the ratio was less than 1, the visually suspected sites were considered normal and if more than one, those were classified as abnormal sites or lesions.

F18-FDG Metabolic Function Imaging

Serum level of glucose had to be under 6 mmol/dl after 4 hours fasting. All subjects had an intravenous line. They were lying down with closed eyes (or covered) and unplugged ears in a dark and silent room. They were asked to concentrate on their tinnitus and not to speak, read, or move for at least 5 min prior to injection. No sedation was applied. Approximately 30 min after 5 miliCurie intravenous injection of F18-FDG (Fluoro Deoxy Glucose), scans were obtained. Imaging procedure was performed with a dual head SMV camera, with a pair of low energy, high-resolution collimators. The projections data were processed with a FBP butherworth 5-0.5 to show a 3D view of the brain. Anatomical tissue images were generated and standard circular regions of interest were created for each subject in the study. Standard uptake values were calculated for each region of interest. After subtracting areas with normal uptake from PET images of subjects, an average normal scanning of control group were used. Regions with abnormal uptake were identified. All these abnormal regions constituted eight regions of interests, which were found to be related to tinnitus. These regions consisted of middle temporal, inferotemporal, medial temporal, superior temporal, temporoparietal, frontal, frontoparietal, and parietal areas. These areas were separated by anatomical sulci in three-dimensional images and were localized by one expert.

The criteria to define the hyperactivity of brain were with both visual and semi quantitatively analysis. First an abnormal area of hyperactivity in cerebral gray cortex was found by the expert and then an ROI (1pixel size) was drowning around that area and background. An ROI on the opposite side (as mirror image) for unilateral lesion and on the cerebellum (as reference) for bilateral lesion was analyzed simultaneously. Counts per voxel of all bilateral lesions (hyperactivity) was calculated in cerebral cortex and compared with cerebellum to calculate the activity ratio. Also the ROI value of any unilateral lesion was compared with the value of the ROI on the other side to give an activity ratio as well. All activity ratios were classified to determine the intensity of activity as: 1 > = normal, 1-1.5 mild, 1.5-2 moderate and > 2 as sever hyperactivity. If the ratio was less than 1, the visually suspected sites were considered normal and if more than one, those were classified as abnormal sites or lesions.

MRI

Magnetic resonance imagings were obtained using tool Q11 marked Siemens, 1.5 Tesla, Avanto 18 channels. The participants were kept approximately 8 min without any movement. The images were stored in Dicom format to be applied in Brain Anatomical Functional Images Coregistration Software (BrainAFICS®).

Image Fusion

PET and SPECT imaging are inherently metabolic and perfusion modalities, so it is sometimes difficult to exactly interpret the anatomical area of disturbed function. Therefore, it is helpful to correlate the relatively coarse functional images to high-resolution anatomical MRI. BrainAFICS®, a software system designed in the ENT and Head and Neck research Center of IUMS, is capable of registering and fusing unsynchronized PET and SPECT with MRIs with different dimensions, in the same subjects (Figures 1 and 2).
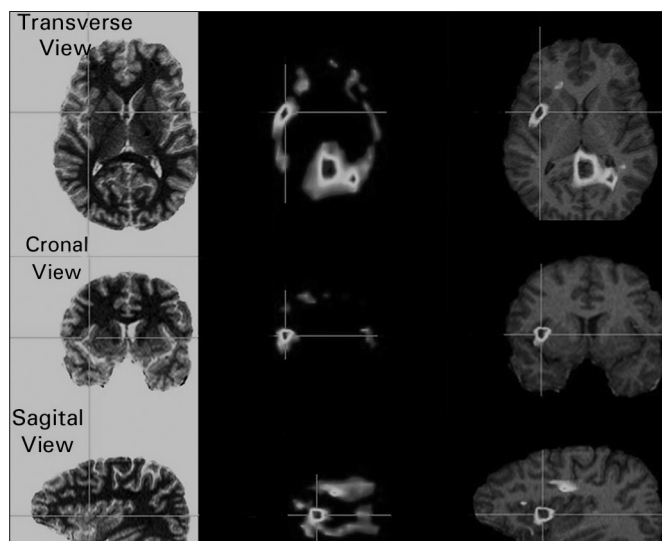
Figure 1. Involvement of left Infrotemporal area in a subject with left ear tinnitus. Note: Fusion of SPECT and magnetic resonance imaging of a patient shows hyperactivity of left Infrotemporal area.
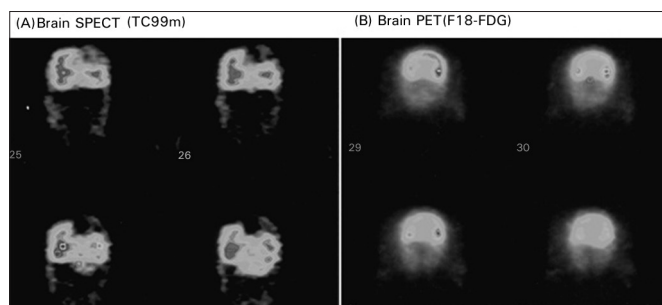
Figure 2. TC99m-ECD single photon emission computerized tomography scan (A) and F18-FDG positron emission tomography (B) in tinnitus subjects.

Validation

After final fusion of images, each image was evaluated and reported by one expert in nuclear medicine twice at separate times. Almost all images were reported similar in both times ($r = 0.8$, $p > 0.001$).

If the assessment was not similar, images were assessed by an expert for a third time and repeated reports (in the previous evaluations) were considered to be the result.

Statistical Analysis

For the association between localization by FDG and TC99m scans the analysis was performed using Kendall's tau-b correlation coefficient test. The amount of increase was assessed using Pearson correlation test. The association and difference of qualitative data was tested by chi square and the quantitative data by independent *t*-test. A probability value less than 0.05 was considered significant. The data are presented as mean ± SD. All analyses were performed using the statistical package for social science version 16 (SPSS v.16).

RESULTS

Description

There were 52 tinnitus subjects and six healthy subjects in this study with a mean age 48 ± 13.5 and 35.8 ± 12.4 years old and male to female ratio of 40:12 and 3:3, respectively. Of the tinnitus subjects, 16 (31%) had left ear tinnitus, 12 (23%) had right ear tinnitus and 24 (46%) had bilateral tinnitus. The mean duration of tinnitus was 70 ± 57.2 months for left and 82.6 ± 69.3 months for right ears. Within tinnitus subjects 45 (86.5%) had abnormality by FDG and 40 (76.9%) by TC99m in the left hemisphere, and 40 (76.9%) had abnormality by FDG and 39 (75%) by TC99m in the right hemisphere ($p < 0.001$, Figure 3). Number of abnormal area in PET scan was also significantly associated with SPECT scan (Table 1). Middle temporal, temporoparietal and inferotemporal were the most common abnormal areas detected by F18-FDG PET coincidence imaging and TC99m-EDC SPECT imaging in these patients (Tables 2 and 3).
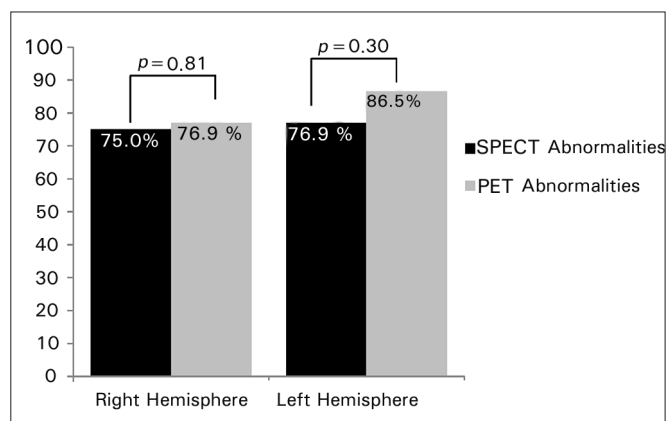
Figure 3. Comparison between metabolic (PET) and perfusion (SPECT) function abnormalities.

Table 1. Correlation between numbers of abnormalities in each patient.

Abnormalities	Left hemisphere N (%)		Right hemisphere N (%)	
	PET	SPECT	PET	SPECT
Unifocal	41(78.8%)	28(53.8%)	34(65.4%)	28(53.8%)
Multifocal	4(7.7%)	12(23%)	6(11.5%)	11(21.1%)
No abnormality	7(13.5%)	12(23%)	12(23%)	13(25%)
p value	< 0.001*		< 0.001*	

* The asterisk indicates a significant level between localization by FDG and TC99m scans using Kendall's tau-b correlation coefficient test

Correlation and difference between metabolism function and perfusion imaging

Based on the Kendal's Tau-b test, significant relation was found between abnormal foci by metabolic perfusion (SPECT) and function (PET) scanning ($p < 0.001$, r = 0.56 for the left and $p < 0.001$, r = 0.54 for the right hemisphere, Figures 4 A-B). But the amount of increased absorption of TC99m-EDC and F18-FDG was not found to be significantly correlated by Pearson correlation ($p > 0.05$).

Within patients 30/52 (58%) had a completely similar pattern of metabolism and perfusion findings in the left and 31/52 (60%) in the right hemisphere. The other patients had different pattern (the abnormal sites were not matched). Age, tinnitus severity and duration of tinnitus were not significantly different between patients with similar and different abnormal areas ($p > 0.05$). Also no association was seen between sex and side of tinnitus with metabolism-perfusion similarity ($p > 0.05$).

DISCUSSION

Non-pulsatile tinnitus is a conscious experience of a sound without an external or environmental source and can be considered as an auditory phantom perception. Lack of crucial knowledge about the locus of tinnitus-related changes in the brain has held up an investigation of the mechanisms leading to tinnitus and, hence, approaches to successful treatment. Several investigations have been reported the relationship between tinnitus and brain cortex hyperactivity. In humans, functional imaging studies on tinnitus are hindered by the lack of an adequate control condition and have pointed to different structures within the auditory pathways. Changes at the level of the auditory cortex have been suggested by work using PET[32,33], magneto-encephalography[34], and functional magnetic resonance imaging (MRI)[20,27], whereas the inferior colliculus has been implicated by others[35]. Early neuroimaging studies have established altered activity of the auditory cortex in tinnitus subjects. The auditory cortex is but one of the areas involved in the generation of the phantom sound. Functional imaging studies have demonstrated that both the tinnitus sound perception and the tinnitus related distress have altered neural networks that are possibly overlapped to each other. TC99m-EDC and F18-FDG have been used in many researches to localize the abnormal brain foci in the tinnitus subjects[5,7,16-21,23-27]. Imaging using TC99m and FDG reflects the changes of cerebral perfusion and glucose-metabolism.

The auditory cortex can be subdivided into a primary (A1), secondary (A2) and associative cortex (A3). Farhadi et al.[19] obtained more pronounced values of regional cerebral blood flow (rCBF) in fusion of PET and MRI in the middle temporal, inferotemporal, and temporoparietal areas. They concluded that in functional attributions of tinnitus associative auditory cortices are more affected than primary auditory cortex. Also, in another study by Osaki et al.[36], in 2005, significantly increased rCBF was seen in the anterior area of the right middle and superior temporal gyri using PET scan during residual inhibition (RI) in the tinnitus subjects. They stated that the rCBF alterations in the right anterior temporal cortex would reflect auditory higher-order processing and memory function in relation to RI.

Different findings of functional and perfusion imaging emphasize the importance of evaluation of the association of different imaging methods[5,7,16-26].Some studies described changes in the brain cortex function and perfusion after treatment of tinnitus. Identification of increased activity of the auditory cortex by PET and SPECT has prompted the use of focal brain stimulation techniques such as electrical or transcranial magnetic stimulation in treatment of tinnitus[2,13,21,36-45]. There is no study about the coherency and correlation of different types of functional imaging and radiotracers in tinnitus subjects. Herein evaluating by metabolism (FDG-F18) and perfusion imaging (TD99m-EDC) we found that the involved areas detected by these two methods have significant correlation. Relationships between cerebral blood flow and metabolism have been investigated in humans and animals and these values were tightly coupled reportedly[46]. Also significant correlation was seen between blood flow and glucose metabolism in the same group of rats[47]. In humans, PET studies have shown considerable relation among measures of brain blood flow and metabolism[48-52]. This significant association was seen in spite of a highly heterogenic capillary density in the brain[53]. Significant association between regional cortical perfusion and metabolisms could indicate that the increased metabolism index (FDG- F18 absorption) may be a consequence of increased tracer delivery.

Despite the correlation between the cortical abnormal sites in tinnitus subjects, many represented

Table 2. Brain metabolic function and perfusion abnormalities in left hemisphere. N (%)

Region of Interest (ROI)		Middle Temporal	Infero-temporal	Medial Temporal	Superior Temporal	Temporo-parietal	Frontal	Fronto-parietal	Parietal	No abnormality
Tinnitus subjects N = 52	SPECT	22 (42.3%)	7 (13.5%)	2 (3.8%)	3 (5%)	10 (19.2%)	1 (1.9%)	5 (9.6%)	4 (7.7%)	12 (23%)
	PET	32 (61.5%)	6 (11.5%)	0	1 (1.9%)	7 (13.4%)	1 (1.9%)	0	2 (3.8%)	6 (11.5%)
	p value*	0.07*	0.76	0.49	0.61	0.59	1	0.056	0.67	0.19
Controls N = 6	SPECT	1 (16.6%)	0	0	1(16.6%)	1 (16.6%)	0	0	0	4 (66.7%)
	PET	2 (33.3%)	0	0	0	0	0	0	0	4 (66.7%)

* Chi square and Fisher's exact tests were performed to evaluate differences between metabolic function and perfusion in each site.

Table 3. Brain metabolic function and perfusion abnormalities in right hemisphere.

Evaluated Site		Middle Temporal	Infero-temporal	Medial Temporal	Superior Temporal	Temporo-parietal	Frontal	Fronto-parietal	Parietal	No abnormality
Tinnitus subjects	SPECT	19 (36.5%)	7 (13.5%)	3 (5.7%)	3 (5.7%)	11 (21.2%)	1 (1.9%)	5 (9.6%)	3 (5.7%)	13 (25%)
	PET	28 (53.8%)	5 (9.6%)	2 (3.8%)	1 (1.9%)	7 (13.4%)	2 (3.8%)	0	1 (1.9%)	12 (23%)
	p value*	0.11	0.75	0.95	0.61	0.43	0.95	0.057	0.61	0.81
controls	SPECT	1 (16.6%)	0	0	1 (16.6%)	1 (16.6%)	0	0	0	3 (50%)
	PET	3 (50%)	0	0	0	0	0	0	0	3 (50%)

* Chi square and Fisher's exact tests were performed to evaluate differences between metabolic function and perfusion in each site.
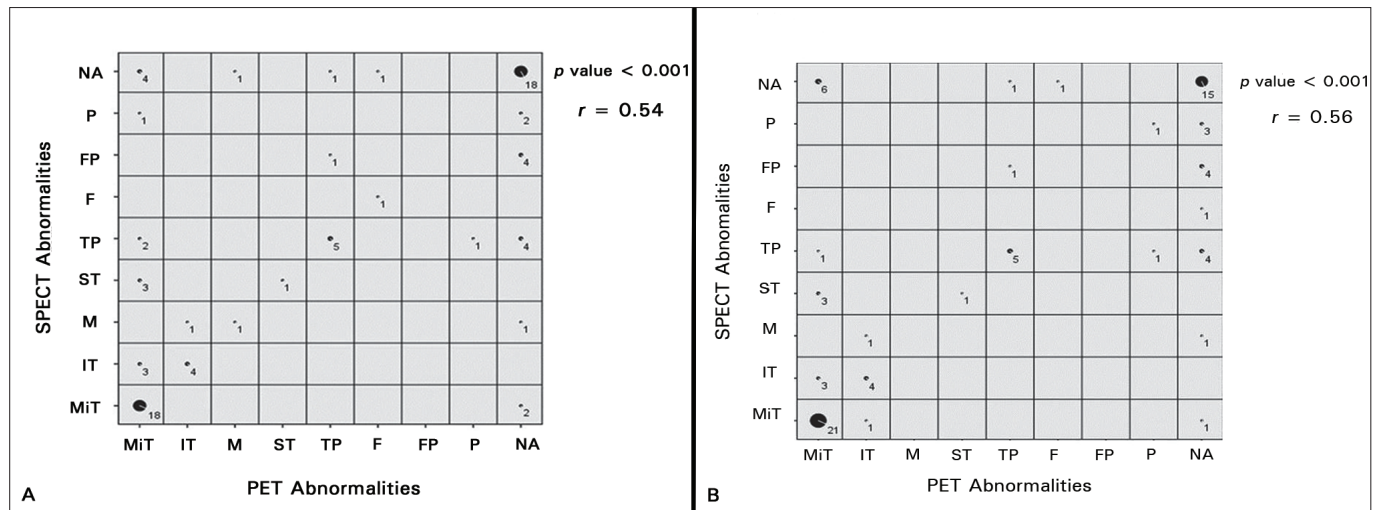
Figure 4. Correlation between brain cortex metabolic and perfusion function in the right (A) and left (B) hemispheres. Note: the circles size indicate the number of subjects with similar involvement in each area. MiT: Middle Temporal; IT: Inferotemporal; MT: Medial Temporal; ST: Superior Temporal; TP: Temporoparietal; F: Frontal; FP: Frontoparietal; P: Parietal; NA: No abnormal area.

foci were not similar in these two methods of imaging. This difference seems to be a major concern in different diseases with confirmed brain function and perfusion abnormalities for diagnosis or direct stimulation therapy (epilepsy, depression, glioma)[28-30,54-57]. Possible factors for incongruent results are: a) differences in molecular structure of ligands caused by adherence of different elements; b) differences in activity level; onset of scanning after injection of the ligand was later in TC99m SPECT compared with F18-FDG PET coincidence imaging; c) Neurovascular coupling should be considered for unmatched findings. Each of these mechanisms may cause unmatched hyperemia[28,58-64]. In some investigations uncoupled neuronal activity and haemodynamic responses has been reported in brain cortex of normal rats and human[65-67]. Additionally regulator factors may be disturbed by tinnitus and tinnitus may be related to abnormalities associated with cerebral

microcirculation. Dissociation between function and perfusion has been reported with a number of disorders, including Parkinson's disease, stroke, migraine, Alzheimer's disease and early onset dementia[59,68].

This was the first study in which the findings of TC99m SPECT and FDG SPECT coincidence imaging in tinnitus subjects has been compared in the same group of tinnitus subjects. In this study we haven't evaluated the size of the abnormality that may vary by different methods or tracers[29].

Evaluating the efficacy of neuronavigated stimulation using different methods of imaging could be useful for finding the accuracy of each type of imaging. Also continuous brain monitoring after tracer injection might give more information about the neurovascular coupling and the time effect of imaging with different tracers.

Acknowledgment

Conflict of interest

The authors declare that they have no conflict of interest.

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