Semi-quantitative analysis of perfusion of Brodmann areas in the differential diagnosis of cognitive impairment in Alzheimer's disease, fronto-temporal dementia and mild cognitive impairment

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Abstract

Different perfusion defects reflect neurological damage characteristics of different kinds of dementia. Our aim was to investigate the role of brain single photon emission tomography (SPET) with semiquantitative analysis of Brodmann areas in dementia, by technetium-99m - hexamethyl-propylenamine-oxime (^{99m}Tc-HMPAO) brain SPET with semiquantitative analysis of Brodmann areas in patients with Alzheimer's disease (AD), frontotemporal dementia (FTD) and mild cognitive impairment (MCI). We studied 75 patients, 25 with AD (NINCDS ADRDA criteria), 25 with FTD (Lund and Manchester criteria), 25 with MCI (EADC criteria). After i.v. injection of 740MBq of ^{99m}Tc-HMPAO, each patient underwent brain SPET. A software application was used able to map the SPET brain image to a stereotaxic atlas (Talairach), providing an affine co-registration by blocks of data defined in the Talairach space. A normal database calculating voxel by voxel the mean and the standard deviation of the measured values was built. Functional SPET data of 3D regions of interest (ROI) of predefined Brodmann's area templates were compared with those of a database of healthy subjects of the same age and gender. Mean values obtained in the Brodmann area ROI in the different groups of patients studied were evaluated. *Our results* showed that different Brodmann areas were significantly impaired in the different categories of dementia subjects. Both areas 37 (temporal gyrus) and 39 (angular gyrus) of AD patients (mean±SD: 37L= -1.6±1.0; 37R= -1.5±1.1; 39L= -2.3±1.3; 39R= -1.9±1.2) showed significant hypoperfusion (P<0.05) versus MCI (37L= -0.9 ±0.7; 37R= -1.1±0.9; 39L= -1.4±1.1; 39R= -1.6±1.6.) and FTD (37L= -1.1±0.8; 37R= -1.0±0.9; 39L= -1.4±1.0; 39R= -1.2±1.2) subjects. AD patients showed significantly (P<0.01) decreased perfusion in areas 40 (supramarginal gyrus) (40L= -2.6±1.0; 40R= -2.3±1.1) with respect to MCI patients (40L= -1.8±0.9; 40R= -1.7±1.2). Finally, FTD patients showed significant hypoperfusion (P<0.05) in both areas 47 (frontal association cortex) (47L= -1.8±0.8; 47R= -1.1±0.8) in comparison with MCI subjects (47L= -1.2±0.9; 47R= -0.9±0.9). *In conclusion,* our results suggest that semiquantitative analysis of single Brodmann areas identify frontal area hypoperfusion in FTD patients and also parietal and temporal impairment in AD patients. In MCI patients, no hypoperfusion pattern is identified.

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Introduction

An early and accurate diagnosis of dementia could allow an early administration of an appropriate treatment. Clinical criteria for the diagnosis of dementia demonstrated an approximate accuracy of 70%, even though accuracy is lower at the earliest stages [1]. Functional imaging may have an useful role as an adjunct to the clinical diagnosis for the proper management of these patients. Brain perfusion single photon emission tomography (SPET) is able to detect changes in regional cerebral blood flow (rCBF), thus providing early markers of functional impairment [2].

In the last few years the introduction of different software of three-dimensional spatial standardization for semiquantitative analysis of SPET data, significantly contributed to a better discrimination of "significant" defects and a correct anatomo-pathological localization. The comparison with normal perfusion data improves the diagnostic performance even in the first and mild stages of disease [3]. Reorientation and spatial normalization permit to define specific hypoperfusion patterns of different pathological categories, thus potentiating the role of SPET in differential diagnosis [3, 4]. The evaluation of perfusion of specific anatomical brain areas using semiquantitative analysis methods and comparing patients' data with those of normal subjects of the same age and gender is also important.

We have investigated the role of brain SPET with semiquantitative analysis of Brodmann areas in dementia patients with different kinds of cognitive decline.

Materials and methods

We have studied 75 patients divided into 3 groups: 25 patients with Alzheimer disease (AD) according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS ADRDA) criteria [5, 6], 25 with frontotemporal dementia (FTD) according to Lund and Manchester criteria [7] and 25 with mild cognitive impairment (MCI) according to European Alzheimer's Disease Consortium (EADC) criteria [8].

AD patients had a range of age of 68-82 years and a duration of disease of 1-3 years. The mini mental state examination (MMSE) scores ranged from 10 to 24, while they had clinical dementia rating (CDR) scores of 1-2, Hachinski ischaemia scale scores <4 and Hamilton depression rating scale (HDRS) scores <18. Patients affected by FTD were from 69 to 84 years old, with MMSE scores of 9-24 and a CDR score of 1-2. For MCI patients, age ranged from 62 to 84 years, MMSE scores ranged between 25-28 and CDR score was 0.5. All subjects had a CT scan or a MRI negative for focal lesions.

Each patient underwent a brain SPET with ^{99m}Tc- hexamethyl-propylenamine-oxime (HMPAO) (GE Healthcare, Milwakee, WI, USA). To each subject 740MBq of the radiopharmaceutical were injected intravenously with the patient in dorsal decubitus position in a room with ambient noise and light under control into an antecubital vein cannulated 10min before the scan.

About 60min after injection, image acquisition was performed using a dual head gamma–camera (Millennium VG, General Electric Medical System, Milwaukee, WI, USA) with high resolution collimators. A 15% window centered on the 140keV photopeak for ^{99m}Tc was used. One hundred and twenty projections were performed using a 128x128 matrix for 25sec per view in a step-and-shoot mode over a 360° orbit with zoom factor 1.5; the total acquisition time was 27min. The acquisition was three-dimensionally reconstructed by filtered back projection by a Butterworth filter (cut-off frequency 0.5, order 10) and Chang's attenuation correction was carried out. We performed oblique reorientation for transaxial, coronal, and sagittal planes. Images were elaborated by NeuroGam program (Segami Corp., Columbia, MD, USA), a software application able to map the SPET brain images to a stereotaxic atlas (Talairach) [4, 9].

We reoriented the three-dimensional volume of the brain defining a line that fits the inferior pole of the occipital lobe and the inferior edge of the frontal lobe; this line was automatically rendered horizontal. We corrected raw data for lateral deviations defining a line above the interhemisphere fissure and automatically orienting this line in the vertical plane. In this reoriented image we defined the intermediate level of the pons and anterior plane of the temporal lobes, thus defining the vertical anterior commissure line (AC) and the posterior commissure line (PC). We limited the volume of analysis in the lateral planes, superior and inferior planes of the brain. With this information, the Talairach technique rendered the brain volume into a normalized volume and allowed therefore, a voxel by voxel comparison of the HMPAO uptake in the brain cortex with a normal data-base of subjects, corrected also volumetrically, including normal adults aged 18-45 years and also for those over the age of 45 years [7]. The program we used allowed us to obtain for each patient volumetrical reconstructions of the qualitative analysis in which the cortical perfusion level was represented with a colorimetric continue scale (from orange to blue) (Fig 1-A) and volumetrical reconstructions of the semiquantitative analysis in which areas with perfusion values 2 or 3 standard deviations (SD) above the normal mean were colored in red and fuchsia respectively and areas with perfusion values 2 or 3 SD below normal mean in light blue and blue respectively (Fig 1-B).

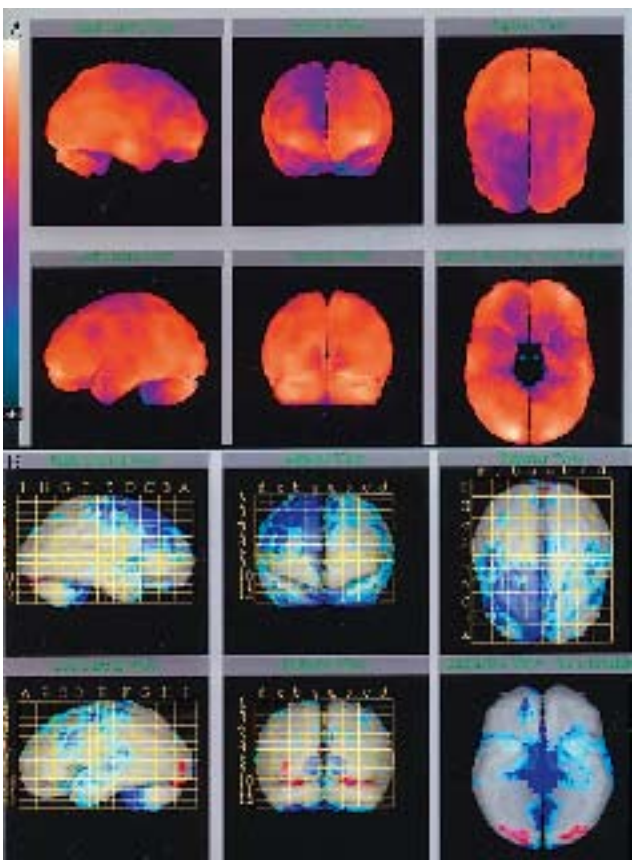

Figure 1. A: Qualitative analysis of a perfusion SPET of a FTD patient. Hypoperfusion of the frontal and the frontoparietal regions can be observed, being more evident on the right hemisphere. **B:** Volumetrical reconstruction of the semiquantitative analysis of the same patient. A significant hypoperfusion (<2-3 SD with respect to heathy subjects of the same age and gender) is shown in the frontal and frontoparietal regions, being more severe on the right side and also in the temporoparietal region bilaterally.

In order to define with high reproducibility the exact localization of areas of hypoperfusion we used for the semiquantitative analysis, a predefined Brodmann's area template. Perfusion SPET data of these 3D ROI were compared with those of

the data base of healthy subjects of the same age and gender, provided by manufacturers, expressing results as standard deviation difference with respect to normal subjects.

Statistical analysis

Mean values obtained in the ROI of Brodmann areas in the different groups of patients studied were evaluated by one-way ANOVA with Tukey's correction, considering P< 0.05 as the level of significance.

Results

Different Brodmann areas were significantly impaired in the different categories of dementia subjects. Both areas 37 (temporal gyrus) and 39 (angular gyrus) of AD patients (mean±SD: 37L=–1.6±1.0; 37R=–1.5±1.1; 39L=–2.3±1.3; 39R=–1.9±1.2) showed significant hypoperfusion (P<0.05) versus MCI (37L=–0.9±0.7; 37R=–1.1±0.9; 39L= -1.4±1.1; 39R= -1.6±1.6.) and FTD (37L=–1.1±0.8; 37R=–1.0±0.9; 39L=–1.4±1.0; 39R=–1.2±1.2) subjects. AD patients showed significantly (P<0.01) decreased perfusion in area 40 (supramarginal gyrus) (40L=–2.6±1.0; 40R=–2.3±1.1) with respect to MCI patients (40L=–1.8±0.9; 40R=–1.7±1.2). Finally, FTD showed significant hypoperfusion (P<0.05) in both areas 47 (frontal association cortex) (47L=–1.8±0.8; 47R=–1.1±0.8) in comparison with MCI subjects (47L=–1.2±0.9; 47R=–0.9±0.9). These data are reported in Table 1.

Table 1. *Mean values (± standard deviation) of perfusion in the Brodmann Areas, which showed differences between groups. Perfusion values are expressed as standard deviation differences comparing healthy subjects of the same age and gender.*

AREA	AD	FTD	MCI
37 Right	-1.5 ± 1.1 SD*	-1.0 ± 0.9 SD	-1.1 ± 0.9 SD
37 Left	-1.6 ± 1.0 SD*	-1.1 ± 0.8 SD	-0.9 ± 0.7 SD
39 Right	-1.9 ± 1.2 SD*	-1.2 ± 1.2 SD	-1.6 ± 1.6 SD
39 Left	-2.3 ± 1.3 SD*	-1.4 ± 1.0 SD	-1.4 ± 1.1 SD
40 Right	-2.3 ± 1.1 SD°	-1.2 ± 1.3 SD	-1.7 ± 1.2 SD
40 Left	-2.6 ± 1.0 SD°	-2.1 ± 1.1 SD	-1.8 ± 0.9 SD
47 Right	-1.1 ± 1.2 SD	-1.1 ± 0.8 SD□	-0.9 ± 0.9 SD
47 Left	-1.6 ± 1.2 SD	-1.8 ± 0.8 SD□	-1.2 ± 0.9 SD

* P < 0.05 versus MCI e FTD, ° P < 0.01 versus MCI,
□ P < 0.05 versus MCI

Discussion

Our findings confirm that cerebral SPET with ^{99m}Tc-HMPAO with semiquantitative analysis is an useful tool in the differential diagnosis of different aging brain categories.

In our study, the semiquantitative analysis for each Brodmann area allowed us to identify hypoperfusion patterns typical and specific for AD and FTD. In particular hypoperfusion of areas 37, 39 and 40 represented a marker in our AD patients, while hypoperfusion of both areas 47 was observed in FTD patients. Brodmann area 37 is a subdivision of the temporal region of cerebral cortex located in the caudal portion of the fusiform gyrus and inferior temporal gyrus, bounded caudally by the peristriate Brodmann area 19, rostrally by the inferior temporal area 20 and middle area 21 and dorsally on the lateral aspect of the hemisphere by the angular area 39. Brodmann area 39 is a part of the temporo-parieto-occipital area, which includes Brodmann area 40, area 19 and area 37. This area corresponds to the angular gyrus surrounding the caudal tip of the superior temporal sulcus and dorsally bounded by the intraparietal sulcus and plays a role in semantic aphasia. Brodmann area 40 is a part of the parietal cortex and its inferior portion is in the area of supramarginal gyrus, which lies at the posterior end of the lateral fissure. It is bounded caudally by the angular area 39, rostrally and dorsally by the caudal postcentral area 2, and ventrally by the subcentral area 43 and the superior temporal area 22. Cytoarchitectonical subregions of the supramarginal gyrus are part of the mirror neuron system active, in humans, during imitation. Brodmann area 47 is part of the associative frontal cortex and it is bounded caudally by the triangular area 45, medially by the prefrontal area 11 and rostrally by the frontopolar area 10. Area 47 has been implicated in the processing of syntax in spoken and signed languages, and more recently in musical syntax.

The hypoperfusion of these different Brodmann areas is related to a specific impairment of topographically different brain areas, causing different characteristic symptoms of cognitive decline. These neurological symptoms are typically present in the different types of dementia that we have studied, thus suggesting that the hypoperfusion of these Brodmann areas might represent a marker of disease.

In AD a functional impairment of the temporo-parieto-occipital area, a multisensory associative area involved in cognitive functions such as attention language, is widely known [10]. In our study we observed that specific Brodamnn areas, included in the larger temporo-parietal area, were particularly involved in AD.

Similarly, in FTD the most relevantly impaired area among those of the frontal cortex, is Brodmann area 47, implicated in the construction of sentences in spoken and signed language.

We did not identify any typical perfusion deficit in MCI patients, as can be easily explained by the intrinsic characteristic of this nosological entity, a heterogeneous borderline phase that can remain stable or evolve to dementia.

More targeted studies to assess functional impairment in the different subcategories of MCI could contribute to the differential diagnosis and to the prediction of the possible evolution of patients to dementia. Actually the most widely used software for semiquantitative analysis of SPET data is statistical parametric mapping (SPM), www.fil.ion.ucl.ac.uk/spm/, a program developed for research purposes, first applied for positron emission tomography (PET) and magnetic resonance imaging (MRI) data analysis. SPM is used for group comparative studies and employs a robust statistical analysis with a strong theoretical basis. Althought this is a certain ad-

vantage in its application in research field, it could be a limit in the routinary clinical practice.

In the last few years, interesting studies have been performed to validate SPM technique in activation SPET studies [10-13]. The authors simulated specific situations of increased rCBF, in which the activity distribution of the source was known and all parameters were controlled. Only a recent work, assessed the performance of SPM in detecting changes of rCBF by simulating on phantom patterns of both hypo and hyperperfusion [14]. The authors demonstrated a dependence of the SPM capability to detect a given foci from the sample size, with an increase of the necessary size when the activation factor and/or the focus volume is decreased.

The first work that studied the possibility of using SPM for the comparison of SPET data of single patients affected by AD or Lewy Body Dementia (LBD), with a normal subjects database, is that by Kemp et al. [3] published in 2005. In this study, SPM demonstrated the capability to reliably detect abnormalities in most of the patients with either mild AD or LBD and appeared to be most useful in preventing "over-calling" of images and false positive with respect to visual analysis. However, the authors concluded that before incorporate SPM into clinical practice, logistical implications would need to be considered. In fact, to routinely prepare statistical parametric maps requires an additional time of about 30min and the need of a representative normal database results in the necessary introduction of a covariate for age into the mathematical modelling. Moreover, it has to be considered the need of strictly defining at the outset rigid criteria for the identification of abnormalities on statistical parametric maps and ^{99m}Tc-HMPAO images, because it can result in a bad responsiveness of the model with the reality of the clinical situation.

In our study, SPET images were elaborated by NeuroGam program (Segami Corp. Columbia, MD, USA). This is a simple program, easier than SPM, and the database of healthy subjects divided for age and gender, volumetrically corrected, is provided by manufacturers. The database is constructed from SPET data with ^{99m}Tc-HMPAO. This is the reason why we used ^{99m}Tc-HMPAO as radiopharmaceutical. Both ^{99m}Tc-HMPAO and ^{99m}Tc-ethylene-cisteinat-dimer (ECD) are widely used for cerebral SPET studies, although they have been shown to distribute differently at the cortical level both in physiological [15] and in pathological [16] conditions.

A recent study demonstrated that the results of the comparison between patients and controls vary depending on the template used to normalize images, a customized radiopharmaceutical-matched SPET template or a not matched template [17]. Thus, the correspondence of radiopharmaceutical used for SPET studies of patients and of healthy subjects is important for a better reliability of results.

The program we used is capable to provide, with a unique elaboration process, the visualization by slices or by a 3D reconstruction of qualitatives data, the 3D reconstruction of the distribution of differences (expressed as standard deviation) in rCBF between the patient and an age and gender matched healthy subject, and allows a semiquantitative analysis for each lobe or for each Brodmann area (the operator can also design different ROI by himself). Some authors utilized Neurogam in activation studies [18-20]. A very interesting study on functional cerebral modifications after auditory monaural stimulation with pure tones, used Neurogam for the semiquantitative analysis of SPET findings for each Brodmann area [20]. This allowed them to highlight not only the activation (significative hyperperfusion), during auditory stimulation, of areas 39-40 (auditory center), 9,10 (frontal executive cortex) 21, 22 (Wernicke's area) and thalamus, but also the simultaneous inhibition (hypoperfusion) of area 38 and caudate nucleus. With the help of semiquantitative analysis authors could, hence, demonstrate the presence of a complex functional substrate, involved in the answer to auditory stimuli, made of activations and deactivations in different cortical and subcortical areas.

Others employed Neurogam for the semiquantitative analysis of SPET data of subjects with diagnosis of affective bipolar disorders [4]. Furthermore, in this case Neurogam processing demonstrated in these patients, the significative hyperperfusion of areas 8, 9, 10 (executive area), of area 7 (posterior parietal lobe) and of thalamus, caudate and lentiform nucleus and the significant hypoperfusion of areas 24, 32 (internal frontal lobe), 25 (affective area), 21, 22 and 38 (temporal lobe), indicating the involvement, in the affective modulation, of a complex circuit of neo-cortical and sub-cortico-limbic structures.

Only one study has recently reported the results obtained after applying Neurogam for the diagnosis of dementia, particularly of AD [21]. The authors studied 152 individuals, 93 with the diagnosis of AD, 28 with depression and 31 normal volunteers. Each patient underwent a brain SPET study analysed using both SPM and Neurogam software. SPET data were reviewed by 4 experts and 4 non-experts observers in 3 successive sessions. In the first only the data in the standard horizontal, sagittal and coronal cuts were available. In the second session, the results of the SPM analysis were also provided and in the third session the results of the Neurogam program were given, despite the SPM ones. The measurements under the ROC curve demonstrated that none of the two added a definitive diagnostic improvement to the experts. To note however, that for the non-experts the contribution of SPM resulted to be lower than that of Neurogam, the first improving the performance of only one of them and the second contributing to the diagnosis of three of the 4 non-experts. To our knowledge however, studies on the performance of this software in the differential diagnosis of different degenerative diseases of CNS are still missing. The semiquantitative analysis for each Brodmann area performed by Neurogam allowed us to identify hypoperfusion patterns typical and specific for AD and FTD.

Further studies are necessary to contribute to the comparison between SPM and Neurogam performance. In fact, even if Neurogam has the advantage of a greater simplicity (in its use and in the interpretation of results) and seems to be more suitable than SPM for clinical use, being made for the

evaluation of the differences between the single cases and normal subjects, its use in the comparison between mean values of deviations from the norm of different groups of patients, could show a minor statistical reliability with respect to SPM. On the other hand, the statistical rigor of that made it less manageable and adjustable according to the different situations studied.

Brain SPET is confirmed to be a very useful methodology for the diagnosis of pathological aging brain, being able to identify perfusion/functional impairment due to the degeneration process. The semiquantitative analysis of SPET data can improve the diagnostic performance allowing to investigate the significance of rCBF changes and, thanks to the reorientation process, to associate them to precise anatomic/functional territories.

In conclusion our results suggest that semiquantitative analysis of single Brodmann areas identify frontal area hypoperfusion in FTD patients, and also parietal and temporal impairment in AD patients. In MCI patients, no hypoperfusion pattern is identified.

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