HBM 2004 Poster # WE377

Cortical GABA-A CBZR loss measured with ^{123}I-Iomazenil in Alzheimer' s disease: a SPECT study with Partial Volume Effect correction

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Introduction: Cortical synaptic/neuronal loss has been reported in neuropathological studies of patients with Alzheimer's disease and may contribute to GM density changes described recently in AD using VBM analysis of structural MRI images(1). PET/SPECT markers of GABA-A central benzodiazepine receptors (cBZR) have been proposed to detect in vivo early cortical synaptic/neuronal loss in AD. Only few studies have been reported with discordant results (2,3). Moreover these results may be in part affected by errors due to partial volume effects (PVE), an issue particularly important when atrophy is associated to the disease, as in the case of AD.

Aim of the study was to investigate whether cortical synaptic/neuronal loss may be detected in vivo in AD using SPECT with 123I-Iomazenil and to assess how the measurement of these receptor changes is affected by partial volume effect (PVE). For this we used a ROI-based method for PVE-correction which takes into account both WM and CSF (4,5).

Method: Five AD patients (NINDS-ADRDA criteria; mean age 70 ± 11 yrs, MMSE: 19±4) 8 patients with Mild Cognitive Impairment (MCI, mean age 74±6.5 yrs, MMSE: 27±2) and 3 healthy volunteers (Controls), mean age 60±5, MMSE: 30) underwent ^{123}I-Iomazenil-SPECT and volumetric MRI.
SPECT images were acquired during 20 minutes 180 min after the intravenous injection of the tracer using a brain-dedicated camera (Ceraspect; 64 transaxial slices; voxel size 1.67x1.67x1.67 mm) The reconstruction was performed using a Butterworth filter and the correction for attenuation using the Chang's algorithm (attenuation factor 0.120 cm-1)(6). These 'late images' were assumed to reflect essentially receptor binding.
MRI protocol (1.5T Intera, Philips Medical Systems) included conventional spin-echo sequences providing T1w (600/15) and PD/T2w (2400/15-90) 3mm-thick axial images (25cm FOV, 256x256 acquisition matrix), sampling the entire brain at 32 levels.
MRI triplets were segmented into GM, WM, and CSF with a fully automated procedure (7).
GM, WM and CSF maps were co-registered to SPECT studies. A set of Volume of interest (VOIs) including frontal, parietal, temporal, and occipital lobes, hippocampus and posterior cingulate cortex for each side, and a single region for cerebellum, was defined in the MNI space and adapted to each co-registered segmented GM using the SPM99 affine normalization matrix. For each VOI, uncorrected and PVE-corrected mean tracer concentrations were calculated and normalized by corresponding cerebellum values.
Comparisons between MCI, AD and C groups were performed by two tailed Student's T-test using data normalized to the cerebellum values. Significance level was set to P<0.05. Although the number of controls is obviously too small for statistical inference, we report the results of AD and MCI comparison with Controls because they are interesting for the general understanding of the results.

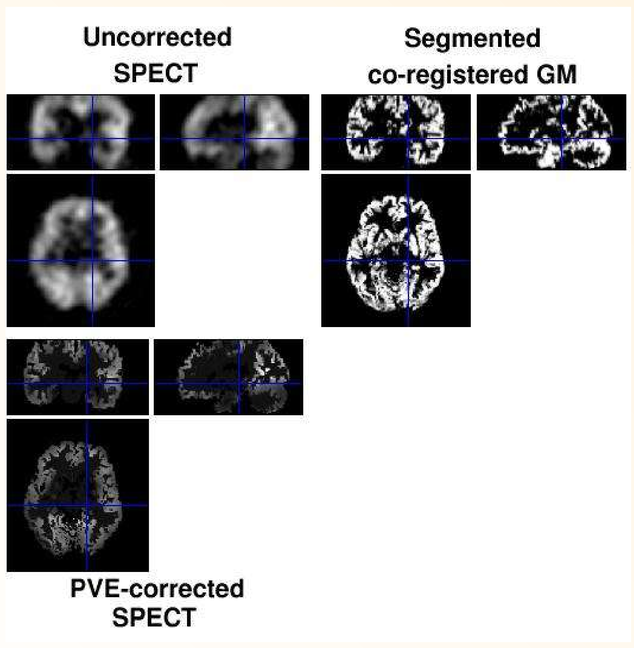

Figure 1: The segmented individual GM is coregistered to the uncorrected 123I-Iomazenil 'late images'.
Corresponding PVE-corrected images are also displayed

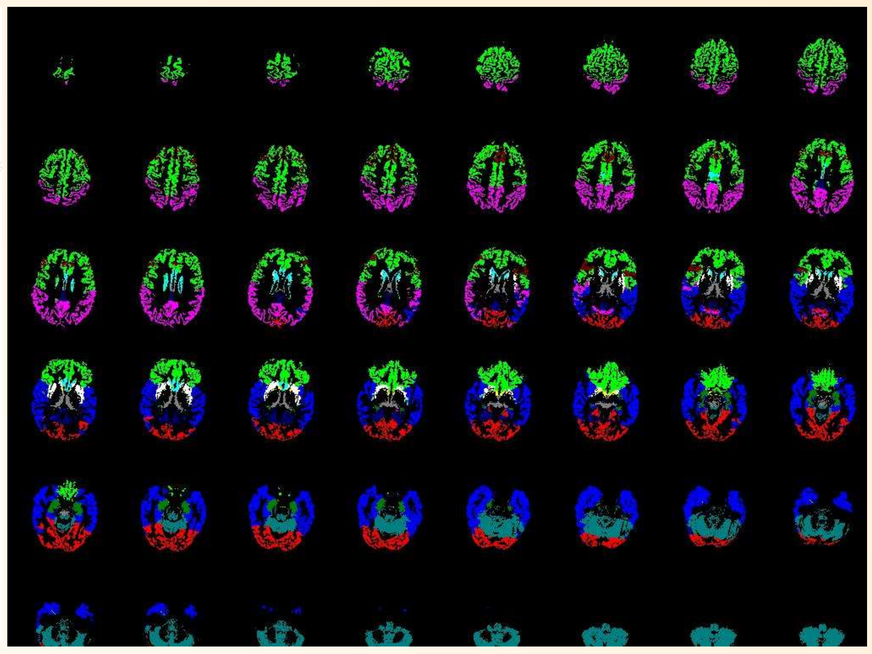

Figure 2: **VOIs definition**. Labeling of segmented GM voxels is obtained by warping the MNI space onto the patient's SPET space. Warping coefficients are derived using the normaliza-tion matrix calculated by SPM (affine components only). For the present analysis the deep GM structures were not used.

Preliminary results: Before PVE-correction (fig 3), as compared to C the AD revealed a significant 123I-Iomazenil reduction bilaterally in all cortical regions except the occipital and right frontal cortices and left hippocampus while the MCI showed a significant reduction in the left posterior cingulate and a trend in the right posterior cingulate. The direct comparison of AD to MCI revealed a significant reduction of 123I-Iomazenil bilaterally in the parietal, temporal cortices and posterior cingulate and in the right hippocampus.

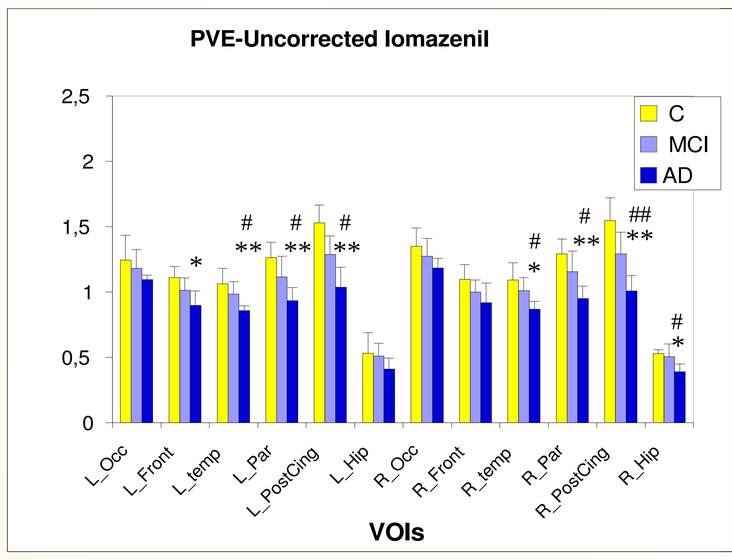

Figure 3: 123-Iomazenil before PVE correction in all VOIs in AD, MCI and Controls (C) . Significant reduction in AD vs Controls= * p<0.05: ** p<0.01. Significant reduction in AD vs MCI s= # p<0.05; ## p<0.01.

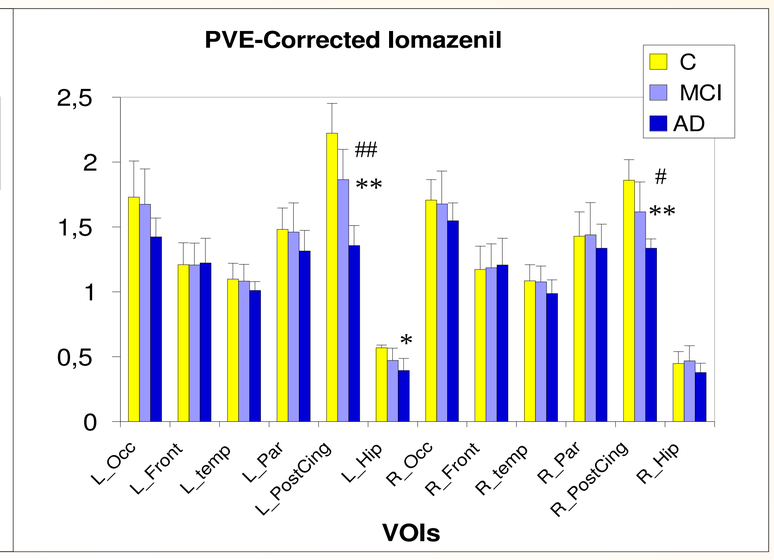

Figure 4: 123-Iomazenil after PVE correction in all VOIs in AD, MCI and Controls (C) . Significant reductionin AD vs Controls= * p<0.05: ** p<0.01. Significant reduction in AD vs MCI = # p<0.05; ## p<0.01.

After PVE-correction (Fig 4) this decrease remained significant in both left and right posterior cingulate and in the right hippocampus when AD were compared to Controls and in the left and right posterior cingulate when AD were compared to MCI.

Conclusions: These preliminary results provide two interesting observations: 1) In AD patients the GABA-A-cBZD receptors are significantly reduced as compared to Controls and MCI in the hippocampus, and other associative cortical areas. 2) This reduction survives the PVE-correction in some cortical areas particularly vulnerable in AD (posterior cingulate cortex and, to a lesser extent, the hippocampus).
Overall these findings suggest that GABA-A-cBZR alterations in AD parallel but also exceed structural changes as measured by MRI segmentation. Further data are required to confirm these findings in larger groups of subjects.

Supported also by QRLT-2000-00502-NCI-MCI, and from the Italian Ministry of Health (Progetto Alzheimer, Attività di ricerca finalizzata D. Lgs. 502/92 e D. Lgs. 229/99, n. ICS150.1/RA00-47) is acknowledged.

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Acknowledgment:
EU fifth framework program QLG3-CT2000-00594 has funded the project.