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Combined ^{99m}Tc-ECD SPECT and neuropsychological studies in MCI for the assessment of conversion to AD

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Abstract

Identifying pre-clinical Alzheimer's disease (AD) in subjects with mild cognitive impairment (MCI) is a major issue in clinical diagnosis. Establishing a combination of predictive markers from different fields of research might help in increasing the diagnostic accuracy. Aim of this study was to evaluate the potential role of ^{99m}Tc-ECD single photon emission computed tomography (SPECT) and memory scores in predicting conversion to AD in MCI subjects. Thirty-one MCI subjects underwent a clinical and neuropsychological examination, and a regional cerebral blood flow (rCBF) SPECT scan at baseline. Subjects had been followed periodically through 2 years in order to monitor the progression of cognitive symptoms. Canonical variate analysis of principal components was able to separate all subjects who converted to AD from those who remained stable, the former being characterized by a specific hypometabolic pattern, involving the parietal and temporal lobes, precuneus, and posterior cingulate cortex. Canonical correlation analysis of combined baseline memory deficits and rCBF SPECT images identified pre-clinical AD with a sensitivity and specificity of 77.8%.

The pattern of hypoperfusion ^{99m}Tc-ECD SPECT and the severity of memory deficits predict the risk of progression to probable AD dementia in MCI subjects.

Keywords: Mild cognitive impairment; Alzheimer's disease; ^{99m}Tc-ECD single photon emission computed tomography; Memory; Follow-up; Statistical parametric mapping; Principal component analysis; Canonical variate analysis; Canonical correlation analysis

1. Introduction

Mild cognitive impairment (MCI) is an operational diagnostic term used to describe subjects at risk to develop Alzheimer's disease (AD) or in the pre-clinical stage of the disease [18,19]. Nevertheless, it has been suggested that the proposed criteria for MCI may apply to an heterogeneous population in which memory complaints could be due to somatic diseases, drug-induced states, affective disorders, or other neurodegenerative diseases, rather than to an on-going AD-related process [21].

Identification of pre-clinical AD among MCI subjects is therefore mandatory for the timely detection of patients to whom currently available treatment options should be offered [4,15].

Neuropsychological assessment in MCI subjects shows that an impairment in memory tests, especially delayed recall, is a possible index of an incipient dementing process, and that severity of impairment on tests of episodic and semantic memory consistently predicts conversion to AD, thus supporting the role of cognitive testing in identifying early or pre-clinical AD [2,22]. However, neuropsychological mea-

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sures are only semi-objective, being confounded by such issue as participant motivation, and therefore are unlikely to achieve perfect discriminant value for individual subjects in this prodromal stage. At this point a purely objective marker would be useful to avoid misclassification.

Functional imaging studies demonstrated that hypoperfusion in parietal cortex as well as posterior cingulate cortex and precuneus might be an early functional marker of AD, suggesting its role in identifying the early stages of the disease [9,10,12]. In most studies, data analysis is based on regions of interest (ROIs) or voxel-based univariate methods, as the statistical parametric mapping (SPM). A new technique to perform principal component analysis (PCA) in ^{18}F-FDG positron emission tomography studies has been recently validated [23].

In the present follow-up study, we combined ^{99m}Tc-ECD SPECT scans and neuropsychological scores, with the following objectives:

(i) To identify the functional pattern which might predict the conversion to probable AD dementia.
(ii) To define the specificity and sensitivity of PCA method based on memory scores and SPECT measurements in differentiating MCI who converted to AD (MCI converters) and stable MCI (MCI non-converters).

2. Materials and methods

2.1. Subjects

Subjects were recruited from "Centre for Ageing Brain and Neurodegenerative Diseases", University of Brescia, Italy. The study was conducted in accordance with local clinical research regulations and an informed consent was required.

All subjects performed a somatic and neurological examination, and laboratory studies, and received a brain structural imaging study (computed tomography or magnetic resonance imaging).

Global cognitive function assessment was carried out according to standardized batteries, including *clinical dementia rating scale*, *mini-mental state examination*, *Alzheimer's disease assessment scale*. The neuropsychological assessment was accomplished by the following tests: Raven Colored Progressive Matrices, Controlled Oral Word Association Test, Category Fluency (animal names), Clock Drawing Test, Rey Complex Figure Copy and Recall, Story Recall Test, and Trail Making Test. Instrumental activities of daily living and activities of daily living were assessed as well. Behavioral and psychiatric disturbances were evaluated by Neuropsychiatric Inventory, Geriatric Depression Scale, and Hamilton Anxiety Rating Scale [17].

Petersen criteria for MCI were used for patients' inclusion: (1) *subjective memory complaint* as elicited by medical history; (2) *normal activities of daily living*; (3) *normal general cognitive function* defined as cognitive performance within the range of 1 standard deviation of normative data in an extensive neuropsychological test battery; (4) *abnormal memory for age* documented by performance of at least 1.5 standard deviation below mean normative data in the delayed recall condition of the used verbal or non-verbal memory task; (5) *not demented* according to DSM-IV criteria and excluded by fulfilling criteria 2 and 3 [19].

The following exclusion criteria were adopted: (a) major depressive disorder, bipolar disorder, schizophrenia, substance use disorder, or mental retardation according to criteria of the DSM-IV; (b) cerebrovascular disorders, hydrocephalus, and intra-cranial mass, documented by CT or MRI within the past 12 months; (c) abnormalities in serum folate and Vitamin B12, syphilis serology, or thyroid hormones' levels; (d) a history of traumatic brain injury or another neurologic disease (e.g. Parkinson disease, Huntington disease, seizure disorders); (e) significant medical problems (e.g. poorly controlled diabetes or hypertension; cancer within the past 5 years; clinically significant hepatic, renal, cardiac or pulmonary disorders).

2.2. Study design

This is a longitudinal, open study. At baseline, MCI subjects underwent a clinical and neuropsychological assessment and a ^{99m}Tc-ECD SPECT scan at baseline. Each subject was followed periodically through 2-year. At 2-year follow-up, each subject performed a SPECT scan as well. The final diagnosis at 2-year follow-up of MCI converter to AD based on the NINDS-ADRDA criteria [14] or MCI non-converter was carried out clinically by a rater (BV) blinded to neuroimaging findings.

For SPECT comparisons, a group of cognitive healthy controls was included ($n = 15$, mean age $\pm$ S.D. $= 56.3 \pm 15.4$).

2.3. ^{99m}Tc-ECD SPECT

Subjects were administered an intravenous injection of 1110 MBq ^{99m}Tc-ECD (ethylcysteinate dimer, Neurolite, Bristol-Myers Squibb Pharma) in a rest condition, lying supine in a quiet, dimly-lit room.

All subjects were imaged using a dual-head rotating γ camera (VG MILLENIUM GE) fitted with a low energy, high-resolution collimator, 30 min after intravenous injection of ^{99m}Tc-ECD.

A 128×128 pixel matrix was used for image acquisition with 120 views over a 360° orbit (in 3° step) with a pixel size and slice thickness of 1 mm, in 27 min or more if total counts were lower than 5×10^6.

Image reconstruction was performed by a ramp filtered-back projection and three-dimensionally smoothed with a Metz filter (order 3, enhancement 1.24, FWHM 6.7 mm, cut-off 0.61 cycles cm^{-1}). The reconstructed images were cor-

rected for γ ray attenuation using the Chang method (attenuation coefficient: 0.11 cm^{-1}).

2.4. Image pre-processing

We used SPM99 (Wellcome Department of Cognitive Neurology, University College, London), and Matlab 6.1 (Mathworks Inc., Sherborn, MA) for image pre-processing. Images were spatially normalized to a reference stereotactic template (Montreal Neurological Institute, MNI), and smoothed by a Gaussian kernel of 8 mm × 8 mm × 8 mm FWHM.

2.5. Statistical analysis

2.5.1. Univariate analysis

Global differences in the distribution of the tracer's uptake and age effect on it were covaried out for all voxels. Comparisons across the different groups were made using *t*-statistics with appropriate linear contrasts [6]. We considered any cluster above a statistical threshold set at $p < .001$, uncorrected. For completeness and according to an a priori hypothesis of involvement of posterior parietal and cingulate regions, the results were explored at $p < .01$ as well.

We performed the following groups comparisons: (1) MCI converters versus MCI non-converters to evaluate the specific perfusion pattern of MCI who converted to AD, (2) MCI converters versus controls, and MCI non-converters versus controls to obtain further information on differences in cerebral perfusion in the two clinical subgroups, (3) MCI converters at baseline versus MCI converters at follow-up, and MCI non-converters at baseline versus MCI non-converters at follow-up, in order to evaluate perfusion regional changes over time.

2.5.2. Multivariate analyses

The data were transformed by principal components analysis (PCA) to obtain new coordinates (PC-scores) of the observations in an orthogonal new coordinates system (PC-space) [22]. In order to maximize the separation between groups (MCI non-converters and MCI converters), the PC-scores were then used as features vector in a multivariate analysis of variance (CVA) to obtain the canonical variables which maximize the ratio $W^{-1}B$, where W is the within-groups sum of squares and cross-products matrix, and B the between-groups sum of squares and cross-products matrix. The eigenvectors of $W^{-1}B$ are the coefficients for the canonical variables CV, and they are scaled so the within-group variance of the canonical variables is 1.

The canonical variables (CVs) are linear combinations of the original variables (in our case the PC-scores of the data). Specifically, the first CV is the linear combination of the columns of the PC-scores that affords the best separation between groups. This means that among all possible linear combinations, it is the one with the most significant *F*-statistic in a one-way analysis of variance. The second CV has the maximum separation subject to it being orthogonal to the first CV, and so on. By the coefficients used in the calculation of the CVs, a linear combination of the images (PCs) is worked out to find the topographic pattern best separating the groups. Since CVs are based on an a priori definition of the groups, it cannot give information on a single subject diagnosis at follow-up. Consequently the CV result alone cannot be used for diagnostic purposes.

In order to provide a method helping to decide if a single subject belongs to one group or the other, we applied a canonical correlation analysis (CCA) on neuropsychological scores and PC-scores. This method does not imply an a priori division of the subjects into groups, and it calculates the linear combination among two sets of variables (in our case, neuropsychological scores and PC-scores) that gives the best correlation between the two sets. Thus, the evaluation of accuracy of each measure is not allowed by this analysis, two sets of variables being necessary.

In order to use for CCA only the most representative tests, we evaluated an independent sample of MCI, who performed the neuropsychological assessment at baseline, but no SPECT scans, and were followed for 2 years. In this sample, the test scores which better differentiated MCI converters ($n = 21$) and MCI non-converters ($n = 20$) were short story (6.4 ± 2.8 versus 9.0 ± 4.3, Spearman correlation analysis, $p = .01$), Rey figure recall (10.0 ± 5.8 versus 14.9 ± 7.2, $p = .02$), and Rey list delayed recall (5.1 ± 2.3 versus 7.0 ± 3.6, $p = .02$).

On the basis of these results, in the present sample we performed CCA including short story, Rey figure recall, Rey list delayed recall scores.

3. Results

Among the 31 MCI patients who performed the brain SPECT scan, 27 were considered for analysis and were subgrouped in MCI converters and MCI non-converters, according to the follow-up clinical diagnosis. Four subjects who progressed at the follow-up to non-Alzheimer type dementia (1 frontotemporal dementia, 2 Lewy Body dementia, 1 pseudodepressive dementia) were not considered for the analysis.

Demographic and clinical characteristics of patients are reported in Table 1.

By SPM, the comparison of MCI converters versus controls showed significant hypoperfusion in superior (x, y, $z = -46$, -58, 52, $Z = 3.71$; 42, -58, 52, $Z = 3.70$), inferior parietal lobules (-54, -42, 40, $Z = 2.30$, $p < .01$; 46, -60, 44, $Z = 3.30$), precuneus (6, -68, 52, $Z = 2.60$, $p < .01$), (clusters size ranging from 15 to 90). MCI non-converters versus controls demonstrated bilateral hypoperfusion in the orbitofrontal cortex (10, 24, -24, $Z = 4.11$) and superior frontal gyrus (14, 42, 32, $Z = 3.34$) (clusters size 80–200).

The direct comparison between MCI converters and MCI non-converters showed a pattern similar to the one described above for MCI converters versus controls, involving also inferior right temporal gyrus (36, -10, -32, $Z = 2.78$ at $p < .01$,

cluster size 25). The degree of statistical significance is represented by the color bar shown in Fig. 1 ($T > 2.5$, $p < .01$). Statistical threshold was set at $p < .001$ unless indicated; according to an a priori hypothesis of involvement of posterior parietal and cingulate regions in Alzheimer's disease, the results were explored at $p < .01$ as well.

The pattern which better separates MCI converters and MCI non-converters was found by CVA performed on the first 22 principal components (PCs, 96% of the total variance), and was able to separate all the MCI converters from MCI non-converters (Fig. 2). The results shows that MCI converters, compared to MCI non-converters, are bilaterally hypoperfused in the inferior parietal lobule (−40, −54, 52; −40, −52, 44), precuneus (−2, −46, 44), cingulate gyrus (−2, −26, 32), lingual gyrus (−16, −92, −12), inferior frontal gyrus (−54, −62, −12), inferior temporal gyrus (−56, −54, −20; 60, −36, −24; see Fig. 3).

Furthermore, the CCA, considering the neuropsychological tests' scores (short story, Rey figure recall and Rey list delay recall, see Section 2 and Table 1), and the PCs obtained from the PCA of the SPECT images, gives a distribution of the subjects in a coordinate system with 14 MCI convert-

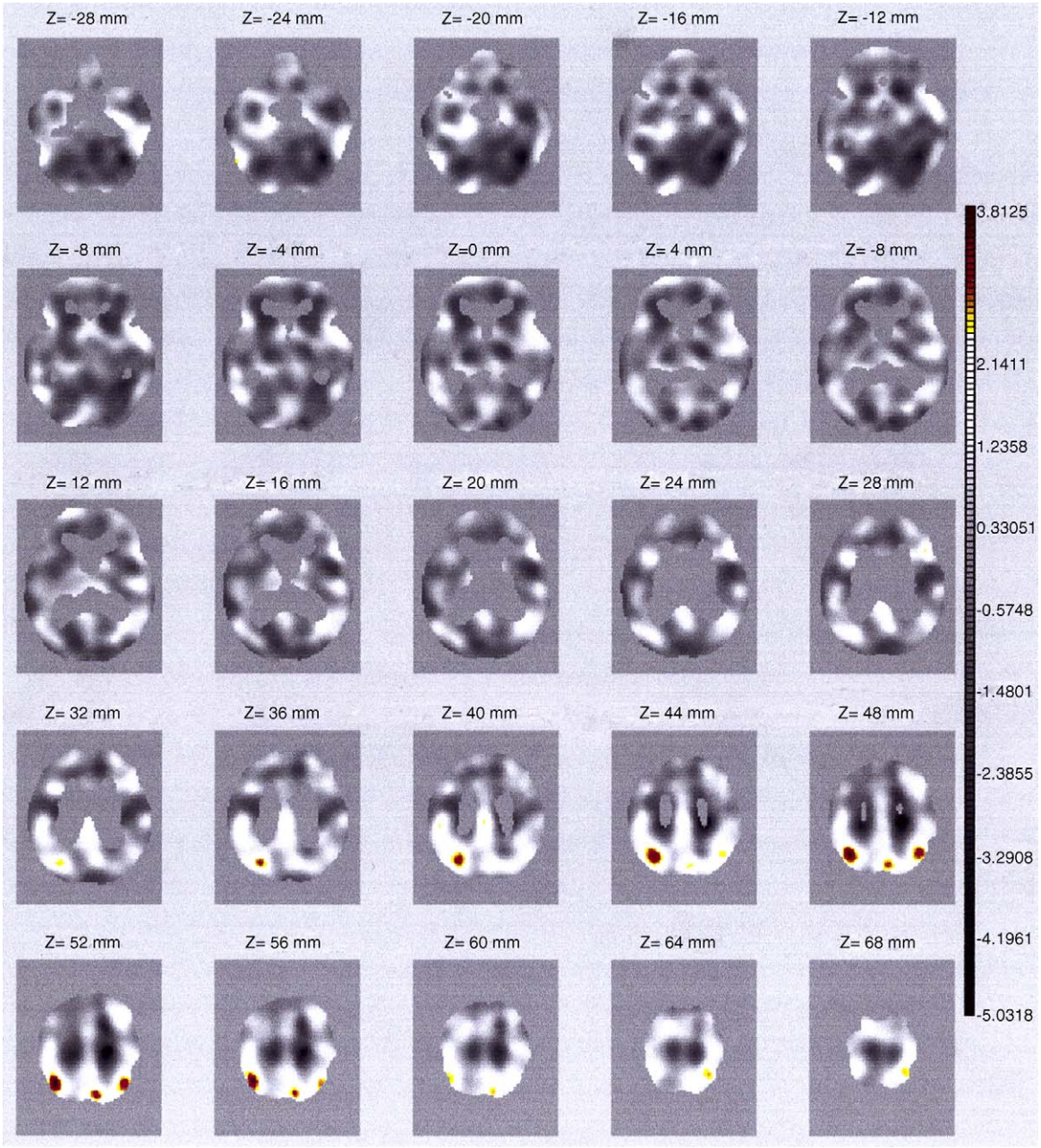

Fig. 1. Pattern of hypoperfusion in MCI converters compared to MCI non-converters by statistical parametric mapping.

Table 1
Demographic, clinical and neuropsychological characteristics of MCI subjects

Variable	MCI converters	MCI non-converters	p[a]
Number	18	9	–
Gender, F/M	15/3	6/3	.32[b]
Age (years)	68.8 ± 7.3	70.6 ± 7.0	.33
CDR, baseline	0.5 ± 0.0	0.5 ± 0.0	–
CDR, follow-up	0.9 ± 0.4	0.5 ± 0.0	.05
MMSE, baseline	27.3 ± 2.1	28.0 ± 1.4	.21
MMSE, follow-up	22.8 ± 3.7	27.9 ± 1.6	.01
IADL (lost), baseline	0	0	–
IADL (lost), follow-up	1.7 ± 0.8	0	.0001
Short story, baseline	5.8 ± 2.3	9.4 ± 3.4	.001
Rey figure recall, baseline	10.7 ± 3.7	15.3 ± 4.3	.001
Rey list delay recall, baseline	4.7 ± 1.8	7.4 ± 2.5	.001

Results are expressed as mean ± standard deviation. MCI converters: MCI who developed AD within 2 years; MCI non-converters: MCI who maintained stable cognitive functions at follow-up; CDR: clinical dementia rating; MMSE: mini-mental state examination; instrumental activities of daily living; F: female; M: male.
[a] Student's t-test.
[b] Pearson's χ^2-test.

ers out of 18 laying in the inferior left quadrant (sensitivity: 77.8%), and that 7 MCI non-converters out of 9 laying in the superior right quadrant (specificity: 77.8%) (Fig. 4).

Finally, the evaluation of SPECT functional progression from pre-clinical stage to AD, performed by SPM comparisons between baseline and follow-up SPECT scans, showed a further worsening of the hypoperfusion with more extended pattern in the same areas. No difference in brain SPECT scans between baseline and follow-up was found in MCI subjects who maintained stable cognitive functions.

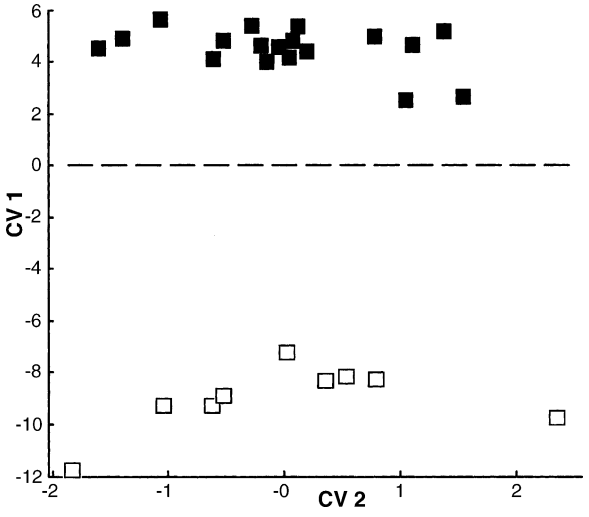

Fig. 2. Canonical variate analysis performed on the first 22 PCs is able to separate all the MCI converters from MCI non-converters. CV1: first canonical variable; CV2: second canonical variable; MCI converters in black; MCI non-converters in white.

4. Discussion

In the present study, we confirmed that MCI is a heterogeneous clinical condition and a major risk factor for dementia [13,19,22].

As in most hospital-based studies, inclusion of patients was carried out by a multidisciplinary diagnostic work-up to limit the enrolment of individuals affected by other concomitant somatic or neurological diseases, thus minimising the inclusion of false negatives. The stringent criteria are the likely explanation for the higher rate of conversion to AD noted in this study (33% per year) as compared to studies in out-patient clinic and community populations.

We corroborated that the brain functional pattern usually occurring in the early symptomatic phase of AD, is already present 2 years before the clinical onset of symptoms. Moreover, combining routinely performed techniques, such as SPECT imaging and neuropsychological scores, we were able to detect patients at risk to progress to AD with high sensitivity and specificity values.

Over the past 3 years, functional neuroimaging studies have provided evidence for brain changes in the very early phase of dementia [10–12]. The severity of memory impairment, specifically in the domain of long-term memory, such as the delayed recall, may prove useful for detection of progressive MCI [2,8].

However, the neuroimaging and neuropsychological assessments have been always addressed separately, with the exception of a recent work identifying different subgroups of MCI combining SPECT investigation and cognitive performances by univariate methods [10]. Noteworthy, the authors demonstrated that although the conversion to AD could be predicted with high accuracy evaluating separately either cerebral blood flow changes in selected parietal regions or neuropsychological scores such as MMSE, block design and word recognition, their combination might result advantageous to achieve diagnostic certainty. In fact, both SPECT and neuropsychologic performance are limited by intrinsic and extrinsic factors which affect the predictive power of these markers, in isolation. In particular, though there is evidence that severity of impairment on tests of memory, attentional processing and mental speed consistently predict conversion to AD, a unavoidable problem with neuropsychological measures, in addition to the confounding effect of affective and motivational variables, is the lack of good normative data for the oldest old, diverse cultural groups, those with low educational attainment and those with premorbid cognitive disabilities. To support diagnostic accuracy and predictivity of cognitive testing, a purely objective marker would be therefore useful.

We used a multivariate method, the PCA, to measure the predictive values in the progression of MCI to AD. In contrast to univariate methods, in which the inference is made on just a subset of voxels, a multivariate method allows to assess the effects of all brain voxels at the same time, account-

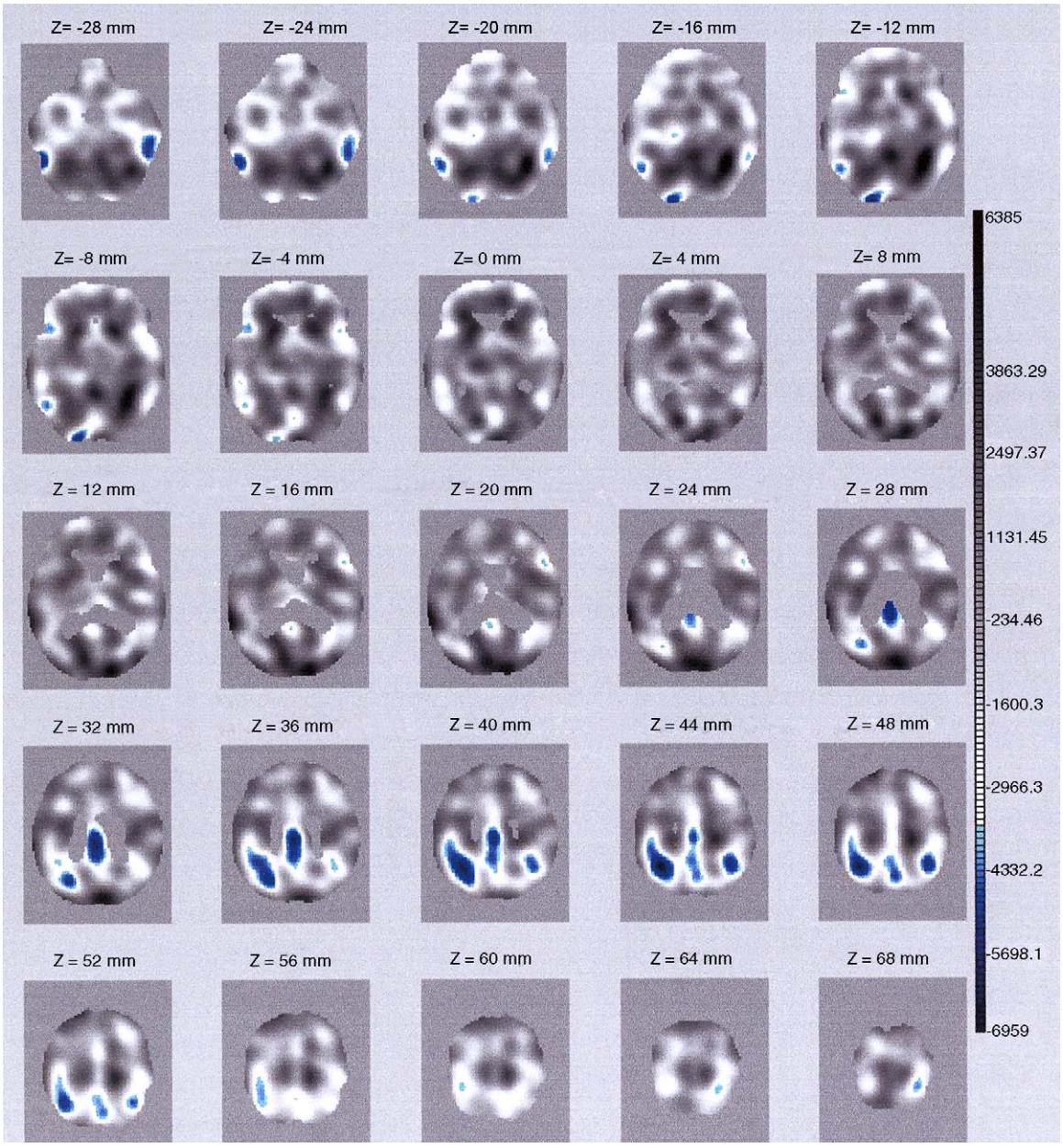

Fig. 3. Pattern of hypoperfusion in MCI converters compared to MCI non-converters resulting from the linear combination of the first 22 PCs, which better separates the two subgroups (canonical variate analysis).

ing for dependencies among them [1], and it is specifically helpful in identifying a characteristic pattern of brain hypoperfusion, comparable to the AD pattern, and its correlation with the severity of neuropsychological impairment. Thus, CVA provides insight into the perfusion pattern which better discriminates the groups, based on an a priori definition of subjects according to follow-up diagnosis, while CCA is able to identify the clinical outcome correlating neuropsychological performances and PCs. Indeed, CVA may result in an over-fitting of the findings to the data, and it has been used as an exploratory procedure to find whether it is possible to separate MCI converters and MCI non-converters by SPECT images and whether the pattern, which better separates the two groups, makes sense from a functional perspective. On the contrary, the CCA uses the eigenvectors only to find out the correlation between SPECT data and neuropsychological tests, thus the discrimination cannot be biased. In fact, the follow-up diagnosis is not introduced to compute the analysis, but only to classify the subjects once the analysis was performed.

A possible application of the CCA in clinical practice is the estimation of the risk of AD development in a single MCI subject. This can be achieved analysing subject's SPECT image and memory scores within subgroups of already defined MCI converter and MCI non-converter subgroups, and fitting the diagnostic subgroup he/she belongs to.

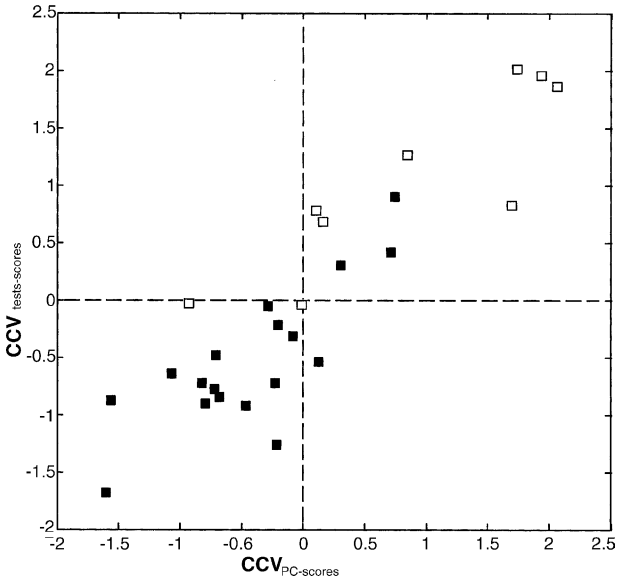

Fig. 4. Canonical correlation analysis of combined baseline SPECT images and neuropsychological findings. $CCV_{PC\text{-}scores}$: canonical correlation variables, principal components; $CCV_{tests\text{-}scores}$; MCI converters in black; MCI non-converters in white.

The consistency of our results with those of a widely used method such as SPM, suggests that the application of PCA method onto SPECT data is reliable in cases of neurodegenerative disorders even in the earliest, pre-symptomatic stages.

We thus suggest a new approach in analyzing combinations of data obtained from different sources, in order to obtain high diagnostic accuracy by the contribution of statistical and mathematical methods not yet used in research on neurodegenerative disorders.

The principal components identified in this study should be validated by applying them to a second group of subjects for a more rigorous assessment and application in similar correlative analysis.

In conclusion, our results suggest that functional neuroimaging, such as SPECT perfusion method, and correlative analysis between perfusion and the degree of memory impairment, may represent an additional tool for pre-clinical diagnosis of dementia, although clinical decision-making requires additional sensitivity and validation.

Further studies, based on the interplay of neuropsychological, biological (CSF Aβ and τ, platelet APPr) [3,16,20] or neuroimaging [5,7] markers might establish with greater accuracy the risk of dementia in MCI subjects and might determine the predictive power of different measures to be used in clinical setting.

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