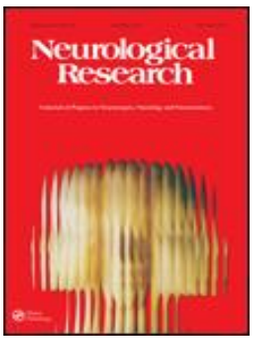

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# Relevance of functional neuroimaging in the progression of mild cognitive impairment

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# Relevance of functional neuroimaging in the progression of mild cognitive impairment

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***Aim:*** *To assess whether combining neuropsychological tests and cerebral blood flow markers improves progression accuracy from mild cognitive impairment (MCI) to Alzheimer's disease (AD) than each of them on its own.*

***Methods:*** *Forty-two patients were investigated prospectively, undergoing baseline and 3-year follow-up neuropsychological tests and neuroimaging with Tc-ECD–SPECT. Twenty-one patients had developed AD while 21 retained their initial diagnosis. The relative blood flow and cognitive differences were studied. Validity parameters, multivariant analysis and logistic regression model were calculated.*

***Results:*** *Patients who deteriorated showed lower scoring than stable subjects in some neuropsychological tests (p = 0.03–0.001) and in relative blood flow in selected regions (8–10%). Low cognitive test scoring and low relative blood flow in some regions showed sensibilities and specificities from 70% to 86% for the diagnosis of early Alzheimer's disease. The relative risk of progression to AD was up to 4.7 times higher for these patients (p = 0.0001).The left frontal relative blood flow, the CAMCOG and orientation scoring were the best data to predict the risk of progression to AD.*

***Conclusions:*** *The combination of functional imaging and neuropsychological tests can diagnose with high sensitivity and specificity if a patient is suffering cognitive impairment in its early stages, and may aid in predicting the risk of developing dementia.* [Neurol Res 2004; **26**: 496–501]

*Keywords: Mild cognitive impairment; SPECT; Alzheimer's disease; neuropsychological test; preclinical marker*

## INTRODUCTION

Mild cognitive impairment (MCI) is a syndrome described in DSM-IV (mild neurocognitive disorder)[1] and ICD-10 (mild cognitive impairment)[2], characterised by an acquired and chronic impairment of one or several cognitive domains, which does not correspond to a focal syndrome and does not fulfil enough severity criteria to be regarded as dementia[3].

The loss of cognitive function occurs as part of normal aging. Many elderly people complain of impaired memory and achieve low scores in neuropsychological screening tests, so that memory impairment would be a common finding in aging populations. Cross-sectional studies which have assessed loss of memory in the elderly have shown that it is heterogeneous among patients, including deficits in various skills and tasks, in the absence of a clinically defined dementia. Longitudinal studies have demonstrated a progressive deterioration in cognitive function over time, supporting the hypothesis that normal aging is associated with mental decline. However, differences in diagnostic criteria or confused definition of conditions, i.e. some individuals with depression or anxiety disorder may have been misdiagnosed as MCI[4], and arbitrary patient grouping may result in some individuals with early-stage dementia being included in the same study group as those subjects with age-related cognitive impairment.

Since MCI is a rather heterogeneous syndrome, a correct assessment of patients is required to achieve accurate outcomes. A review by DeCarli[5] shows how precise classification criteria are essential to ensure reliable and reproducible results. Conditions are divided into those that focus predominantly on memory impairment and those that include various degrees of impairment within all cognitive domains, including language, visuospatial awareness and attention[6,7]. Among the memory-dependent definitions, age-associated memory impairment[8] and MCI[3], the latter having been described as individuals with symptomatic and progressive memory impairment. This definition may be a potential tool for identifying individuals likely to have incipient AD and has implications for clinical trials aimed at secondary prevention. Cerebrovascular disease is also strongly associated with MCI[9]. Vascular cognitive impairment is the nosologic equivalent of MCI when considering vascular dementia. It's most frequent form is subcortical, with neuroimaging findings consistent with white matter damage and destruction of fronto-subcortical neuronal circuits, resulting in a clinical disconnection syndrome including apraxia, bradipsychia, attention and affective disorders, and motor or sensitive deficits[10].

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Several clinical studies in the memory-impaired elderly have shown a rapid rate of conversion to AD, as high as 15% per year[3]. Therefore, MCI could be a transitional state between normal aging and AD. However, such a statement is not in agreement with the fact that not all individuals with MCI develop AD, especially if the general population is considered. Moreover, there are subjects with amnesic MCI, who may develop other kinds of dementia[11].

There are no clinical markers that predict progression to AD[12]. As new treatment options for patients suffering from dementia are being developed, detecting and recognising AD in the early stages, allows for treatment and care planning, giving families time to adjust to the diagnosis.

Age, sex, low score in neuropsychological memory tests[13], orientation[14] and gait[15] impairment, hippocampus or medial temporal lobe volume reduction[16–18] as well as reduced perfusion or metabolism of certain brain areas[4,19–22] have been described as risk factors for the development of dementia.

The aim of this study is to find if combining early neuropsychological and regional cerebral blood flow (rCBF) markers will improve accuracy on predicting the progression from MCI to AD than each of them on its own.

## MATERIALS AND METHODS

We performed a longitudinal prospective study on 42 patients who consecutively attended the Memory Unit within the Geriatrics and Neurology Departments. All of them fulfilled MCI diagnostic criteria as established by the International Psychogeriatric Association and the Alzheimer's Disease Cooperative Study, corresponding to stages 2 and 3 of the Reisberg Global Deterioration Scale (GDS).

The study was performed in accordance with both the international ethical recommendations regarding research and human clinical trials as set out in the Helsinki Declaration (1964) and the guidelines for good clinical research practice as laid down by the World Health Organisation (1995). The procedure of the research project was explained to the patients participating in the study. All subjects signed an informed consent form.

### Clinical assessment

A close relative of the patient underwent a clinical interview. Age, gender, educational level, social support and professional status of the patient were assessed. Appropriate classification of MCI was based on the Mini Mental State Examination (MMSE)[23] and GDS, supported by functional assessment and neuropsychological tests (*Table 1*). Exclusion criteria included dementia as defined by DSM-IV or ICD-10, functional or social disabilities, GDS score between 4 and 7, Hachinski Ischemia Scale score above 4, medical history of stroke, toxic abuse, metabolic, endocrine, inflammatory, infectious, psychiatric, renal, hepatic or current terminal diseases, and very low educational level. We performed additional investigations on every subject (Class II evidence level) as recommended by the American Neurology Association[24].

**Table 1:** Neuropsychological evaluations performed to the 42 subjects of the study

Cognitive domain:
- Mini Mental State Examination (MMSE)
- Cognitive subscale (CAMCOG) of the CAMDEX assessment schedule with the items:
  - Orientation
  - Language
  - Memory
  - Attention
  - Praxis
  - Calculus
  - Abstract thinking
  - Perception
- Rivermead Barrage Memory Test (RBMT)
- Benton visual memory test
- Wechsler Adult Intelligence Scale (WAIS) with the items:
  - Vocabulary
  - Digits
  - Number codes
  - Incomplete figures
  - Puzzles

Functional domain:
- Blessed Dementia scale
- Lawton and Brody activities scale

Affective domain:
- Yesavage Geriatric Depression scale

### Brain SPECT

All patients underwent brain single photon emission computed tomography (SPECT) on a dual-headed SOPHA VISION DST-XL gammacamera. 750 MBq $^{99m}$Tc ECD (Amersham Health) was administered intravenously in semi-darkness with reduced visual and auditory stimuli. The image acquisition and reconstruction protocol was as previously described[25].

### Clinical follow-up

All patients were followed-up for 1–3 years (IQR p25–p75 = 21–36 months) with symptomatic and cognitive assessment every 6 months. After this period, some patients developed AD while others retained the initial diagnosis of MCI. Then, patients were divided into two groups.

Group I: 21 cases were diagnosed with probable AD according to the DSM-IV criteria supported by neuropsychological tests. These patients are defined as having progressive mild cognitive impairment (PMCI). The appropriate classification of dementia as AD was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria, a score in the Hachinski Ischemia Scale lower than 5, with no evidence of cerebral cortical infarcts and no more than a subcortical lacunar infarct lower than 1.5 cm on computed tomography (CT) or magnetic resonance imaging (MRI). AD patients were in stages 4–7 of the GDS.

Group II: 21 subjects who did not develop dementia and retained the initial diagnosis of MCI. These patients are defined as having stable mild cognitive impairment (SMCI). MCI individuals were in stages 2 or 3 of the GDS.

**Table 2:** Neuropsychological data of the 42 study subjects

| | Group I (AD) ($n=21$) | Group II (MCI) ($n=21$) | $p$ |
|---|---|---|---|
| MMSE | 22.2 (20.5–23.9) | 25.3 (23.93–26.69) | 0.005 |
| Rivermead test | 5.55 (3.81–7.28) | 7.81 (6.27–9.36) | 0.048 |
| Blessed scale | 4.33 (3.30–5.37) | 2.33 (1.72–2.95) | 0.001 |
| CAMCOG global score | 72.29 (68.23–76.25) | 84.57 (79.84–89.31) | <0.001 |
| Orientation* | 7.57 (6.97–8.17) | 8.95 (8.51–9.40) | <0.001 |
| Language* | 23.24 (22.04–24.43) | 25.33 (24.33–26.33) | 0.008 |
| Memory* | 13.57 (12.44–14.70) | 18.38 (16.21–20.55) | <0.001 |
| Calculus* | 1.52 (1.25–1.80) | 1.86 (1.69–2.02) | 0.035 |
| Perception* | 6.52 (5.87–7.18) | 8.24 (7.76–8.71) | <0.001 |

Data shown are mean and 95% CI.
MCI, mild cognitive impairment; AD, Alzheimer's Disease; MMSE, Mini Mental State Examination; CAMCOG, global cognitive subscale of the Cambridge mental disorders in the elderly examination assessment schedule.
*CAMCOG subtest.

Finally, rCBF and cognitive differences between the two groups were studied.

### Statistical analysis

Data were analysed with SPSS 10.0 for Windows® and Epidat 2.01. Qualitative variables are shown with their frequency distribution and their 95% confidence interval (CI). Quantitative variables are represented by their mean and standard deviation. Their association was assessed by means of the chi-squared or $t$-test. Relative blood flow (RBF) was defined as the mean of the ratio of counts in selected regions of interest (ROIs) normalized to cerebellar activity and expressed as a percentage. The effect size was estimated by absolute differences between the study groups and their 95% confidence interval (CI). To establish the predictive values of RBF and cognitive scores in the progression to AD, receiver operating characteristic (ROC) curves were calculated. Areas under the ROC curve and cut-off points with the highest predictive values (maximum sensitivity and specificity) were estimated. The significance of the area below the curve was established by the fact that 0.5 was not included within the 95% CI. RBF and neuropsychological validity parameters were calculated: sensitivity (Se), specificity (Sp), positive and negative predictive values and positive and negative likelihood ratios. In all cases 95% CI were calculated. Relative Risk (RR) with 95% CI was also estimated to compare the probability of developing AD in patients who showed blood flow reduction or worse neuropsychological scores at the beginning of the study to those who had higher blood flow or neuropsychological scores than that established by the calculated cut-off points. To evaluate the predictive independent variables for cognitive decline, we adjusted a logistic regression model. In all hypothesis contrasts, the null hypothesis was rejected with a type 1 or $\alpha$ error of $<0.05$.

## RESULTS

On the follow-up assessment, 21 patients met clinical criteria for dementia from an initial population of 42 subjects. Therefore, the rate of progression to dementia in our population was 50%. No significant differences were noted between the groups regarding age, sex distribution or duration of disease evolution. No relevant differences were noted with respect to the following population characteristics: years of schooling, professional status and social support[25].

### Neuropsychological study

Compared with Group II (SMCI), Group I (PMCI) showed significantly lower scoring on basal MMSE, Blessed dementia scale, Rivermead Barrage memory test, global cognitive subscale (CAMCOG) of the Cambridge mental disorders in the elderly examination (CAMDEX) assessment schedule, and its subtests orientation, language, memory, calculus and perception (*Table 2*).

We performed Se and Sp study with the data that had been significantly different between the diagnostic groups, against the clinical diagnosis on evolution. The best data for differentiating both groups (Se and Sp $>70\%$, and areas under the ROC curve close to 80%) are the following CAMCOG items: global score, perception, orientation and memory subtests.

The probability and RR study with the data that had the best Se and Sp results is shown on *Table 3*. Subjects with a CAMCOG score of $<79.5$ have 4.5 times higher risk of progression to AD. Subjects with an orientation score of $<8.5$ have 3.5 times higher risk of progression to AD. Subjects with a memory score of $<15.5$ have 2.9

**Table 3:** Probability and Relative Risk of progression to AD from 42 MCI subjects by the neuropsychological data

| Test | Score | Probability of progression to AD ($n$) | $p$ | RR (CI 95%) |
|---|---|---|---|---|
| CAMCOG | <79.5 | 75% (24) | <0.0001 | 4.5 (1.6–13) |
| Global score | ≥79.5 | 16.7% (18) | | |
| Orientation* | <8.5 | 73.9% (23) | 0.001 | 3.5 (1.4–8.7) |
| | ≥8.5 | 21.1% (19) | | |
| Memory* | <15.5 | 72.7% (22) | 0.002 | 2.9 (1.3–6.5) |
| | ≥15.5 | 25% (20) | | |
| Perception* | <7.5 | 77.3% (22) | <0.001 | 3.9 (1.6–9.6) |
| | ≥7.5 | 20% (20) | | |

AD, Alzheimer's disease; MCI, mild cognitive impairment; RR, Relative Risk; CAMCOG, global cognitive subscale of the Cambridge mental disorders in the elderly examination assessment schedule; CI 95%, 95% confidence interval.
*CAMCOG subtest.

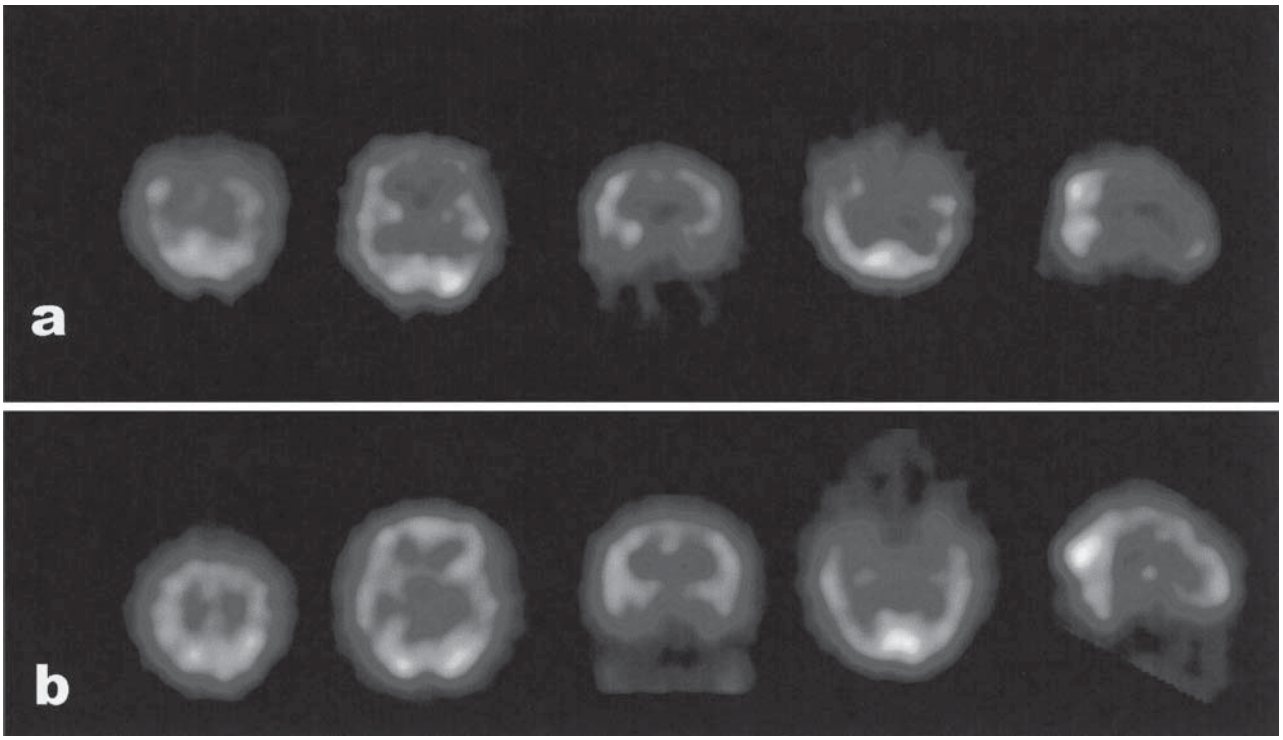


**Figure 1:** Brain SPECT of patients with MCI. (a) Patient who deteriorated to PMCI (hypoperfusion in the prefrontal, parietal and temporal lobes). (b) Patient who remained with SMCI (hypoperfusion in the temporal lobe)

times higher risk of progression to AD. And subjects with a perception score of $<7.5$ have 3.9 times higher risk of progression to AD.

### Regional cerebral blood flow study

Compared with patients in group II (SMCI), patients from group I (PMCI) showed a statistically significant reduction in relative blood flow (RBF) ranging from 7 to 10% in the following ROIs: right (RPF) and left (LPF) prefrontal, right (RFR) and left (LFR) frontal, right (RPA) and left (LPA) parietal, right (RT) and left (LT) temporal, right (RFPT) and left (LFPT) frontoparietotemporal and left posterior lateral temporal (LPLT) (*Figure 1*). ROC curves were designed and Se, Sp, positive and negative predictive values and positive and negative likelihood ratios were calculated. ROIs showing Se and Sp $>75\%$ and areas under the ROC curve close to 80% were, in diminishing order: LPF, LPA and LFR[25].

The probability and RR of progression of MCI to AD according to selected ROIs with a higher diagnostic yield are shown in *Table 4*. An RBF of $<83$–87% in RPF, LPF, RFR, LFR and LPA increase significantly ($p=0.007$–$0.0001$) the RR (2.4–3.7) of progression to AD.

### Multivariant study

We performed a multivariant analysis to find associations between the diagnostic groups, the clinical data and the RBF that had good Se, Sp and RR results. For LPF, an RBF of $<86\%$ with a CAMCOG score of $<79.5$ showed a probability of progression to AD of 86.7% ($p=0.04$), with an RR of 2.2, and with an orientation score of $<8.5$ showed a probability of progression to AD of 92.3% ($p=0.03$), with an RR of 2.1. For RFR, an RBF of $<85\%$ with a CAMCOG score of $<79.5$ showed a probability of progression to AD of 87.5% ($p=0.005$), with an RR of 4.4. For LFR, an RBF of $<83\%$ with a CAMCOG score of $<79.5$ showed a probability of progression to AD of 100% ($p<0.0001$), with an RR of 3.5, and with a memory score of $<15.5$ a probability of progression to AD of 100% ($p=0.001$), with an RR of 2.2. For LPA, an RBF of $<85\%$ with a CAMCOG score of $<79.5$ showed a probability of progression to AD of 93.8% ($p=0.001$), with an RR of 4.7. For LFR, an RBF of

**Table 4:** Probability and Relative Risk of progression of MCI to AD according to selected Relative Flow Ratio ROIs with higher diagnostic yield

| ROIs | RBF | Probability of progression to AD (*n*) | *p* | RR (95% CI) |
|---|---|---|---|---|
| RPF | $<87$ | 70% (20) | 0.007 | 2.4 (1.2–5.1) |
| | $\geq 87$ | 28.6% (21) | | |
| LPF | $<86$ | 75% (20) | <0.0001 | 3.7 (1.5–9.3) |
| | $\geq 86$ | 20% (20) | | |
| RFR | $<85$ | 71.4% (21) | 0.002 | 2.9 (1.3–6.4) |
| | $\geq 85$ | 25% (20) | | |
| LFR | $<83$ | 75% (20) | 0.001 | 3.1 (1.4–7) |
| | $\geq 83$ | 23.8% (21) | | |
| LPA | $<85$ | 76.2% (21) | <0.0001 | 3.2 (1.4–7.1) |
| | $\geq 85$ | 23.8% (21) | | |

MCI, Mild cognitive impairment; AD, Alzheimer's disease; ROIs, regions of interest; RPF, right prefrontal; LPF, left prefrontal; RFR, right frontal; LFR, left frontal; LPA, left parietal; RBF, relative blood flow (%); RR, Relative Risk; 95% CI, 95% confidence interval.

**Table 5:** Logistic regression model to evaluate the predictive independent variables for cognitive decline

| Data | Se and Sp of the model | *p* | RR (95% CI) |
|---|---|---|---|
| CAMCOG Global score | Se: 82.4S Sp: 85.7 | 0.04 | 12.6 (1.1–147.5) |
| Orientation* | | 0.09 | 8.1 (0.7–95.4) |
| LFR† | | 0.01 | 24.4 (1.9–315.3) |

Se, Sensibility; Sp, specificity; RR, Relative Risk; 95% CI, 95% confidence interval; CAMCOG, global cognitive subscale of the Cambridge mental disorders in the elderly examination assessment schedule.
*CAMCOG subtest; †relative blood flow on left frontal region.

>83% with a perception score of >7.5 showed a probability of progression to AD of 7.1% ($p=0.01$), with an RR of 8.0. For RPF, an RBF of >87% with a CAMCOG score of >79.5 showed a probability of progression to AD of 7.7% ($p=0.006$), with an RR of 8.1, with a memory score of >15.5 showed a probability of progression to AD of 14.3% ($p=0.04$), with an RR of 4.0, and with a perception score of >7.5 a probability of progression to AD of 7.1% ($p=0.002$), with an RR of 10.0. And for LPA, an RBF of >85% with a memory score of >15.5 showed a probability of progression to AD of 8.3% ($p=0.05$), with an RR of 5.3.

### Logistic regression model

As shown in *Table 5*, the global CAMCOG and orientation scoring and the RBF on the LFR ROI were the best data to predict the risk to progress from MCI to AD. These variables classify the 82% of the patients that will progress to AD and the 86% that will not, with an RR between 8 and 24, and statistical significance between 0.01 and 0.09.

## DISCUSSION

MCI is associated with an increased risk of developing dementia. The rate of conversion reported in a recent review[26] ranged from 23% to 47% over a period of 2.6 years. We have found a rate of progression to dementia in our population of 50%[25], in accordance with previously reported conversion rates[27]. Petersen[3,28] summarizes the previous data reporting a rate of conversion from 6% to 25% per year, and found that by 6 years ~80% of the MCI individuals had developed AD. These wide variations among studies may be due to different follow-up times and heterogeneous classification, definition or inclusion criteria. Recently, many clinical studies have been aimed at identifying those subjects complaining of memory symptoms, who would progress to dementia[29–33]. We found that the perception, memory and the orientation subtests and the global score on the CAMCOG, had high Se, Sp and RR predicting those patients who developed AD on an average of 3 years.

Hippocampus volume estimation with MRI and entorrhinal glucose metabolism measured by positron emission tomography–fluorodeoxyglucose (PET–FDG) are good neuroimaging markers for distinguishing between the healthy elderly and all those with MCI. The temporal neocortex can differentiate between MCI and AD[34]. However, markers on cross-sectional studies have prognostic limitations since they do not assess the natural history of the disease and thus may not be regarded as predictive. Some longitudinal studies have been developed to assess prognosis. The best predictive markers would be those which could be detected on healthy subjects, even before clinical symptoms are evident.

Reduction of both metabolism and volume of the entorrhinal cortex may predict deterioration towards MCI in the healthy elderly[20]. Combined temporoparietal metabolism quantification and visuospatial assessment may have prognostic value in detecting progression of subjects with MCI[11].

The natural history of MCI reveals a group of patients who remain stable (SMCI) and of those who progress to dementia (PMCI)[35]. PET–FDG studies in PMCI showed reduced glucose uptake in the right temporoparietal cortex compared with SMCI[36]. Moreover, Chételat studied the morphological and functional substrates for encoding and retrieval with PET–FDG and MRI in 21 patients diagnosed of amnesic MCI and 30 controls[37]. Encoding and retrieval defects correlated with grey matter density reduction in the hippocampus in MCI patients against the control group, and with glucose metabolism reduction in the hippocampus and posterior cyngulus, respectively.

Another PET longitudinal study[38], found additional temporoparietal deficit in PMCI against controls. After 1 year follow-up, there was bilateral prefrontal reduction in PMCI, with additional deterioration in temporoparietal and posterior cyngulus. Most areas where there was reduced metabolism are similar to those with predicitve value described in our study. However, the medial temporal areas are not valid as predictors of progression, in accordance with findings reported by other authors[27], since hypoperfusion was detected both in PMCI and SMCI. This discrepancy may be due to the fact that Drzezga *et al.*[38] performed a different anatomic ROI selection, using a mixed lobe region (temporoparietal).

Our findings have shown RBF reduction mainly in the LPF, LFR and LPA ROIs, which have high value as predictors of progression to AD. Se and Sp of these ROIs are larger than 75%, with areas below the ROC curve close to 80%, and an RR of patient progression between 3.1 and 3.7.

Regarding the multivariant analysis, the highest RR of developing AD in an individual suffering from MCI reaches up to 4.7 times according to the RBF in LPA and the scoring on CAMCOG global score. In the logistic regression model, two cognitive variables (CAMCOG global score and orientation subtest) and the RBF in LFR predict the risk of progressing from MCI to AD with high Se and Sp. They classify most of the patients correctly as to whether or not they will deteriorate.

These findings are in accordance with a longitudinal prospective study[11], which showed poorer episodic memory, visuospatial and general cognitive functions in PMCI against SMCI. Moreover, PMCI had lower biparietal rCBF than SMCI and controls. No significant differences were found between SMCI and controls.

They concluded that SPECT and neuropsychological tests showed moderate discrimination between PMCI and SMCI at baseline with the area under the ROC curve at 75–77%. The combination of both methods improved the diagnostic accuracy with the area under the ROC curve at 82–84%.

Our study has assessed the natural progression of disease not just clinically, but with brain SPECT, so that we have been able to identify clinical and neuroimaging markers which are relevant to the prognosis.

## CONCLUSION

The combination of neuropsychological tests with functional neuroimaging can differentiate and predict with high Se and Sp if a concrete patient is suffering a cognitive impairment in its early stages, and may aid in predicting the risk of developing dementia.

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