

# Electroencephalography reveals lower regional blood perfusion and atrophy of the temporoparietal network associated with memory deficits and hippocampal volume reduction in mild cognitive impairment due to Alzheimer's disease

Davide Vito Moretti

National Institute for the research and cure of Alzheimer's disease, S. John of God, Fatebenefratelli, Brescia, Italy

**Background:** An increased electroencephalographic (EEG) upper/lower alpha power ratio has been associated with less regional blood perfusion, atrophy of the temporoparietal region of the brain, and reduction of hippocampal volume in subjects affected by mild cognitive impairment due to Alzheimer's disease as compared with subjects who do not develop the disease. Moreover, EEG theta frequency activity is quite different in these groups. This study investigated the correlation between biomarkers and memory performance.

**Methods:** EEG  $\alpha3/\alpha2$  power ratio and cortical thickness were computed in 74 adult subjects with prodromal Alzheimer's disease. Twenty of these subjects also underwent assessment of blood perfusion by single-photon emission computed tomography (SPECT). Pearson's  $r$  was used to assess the correlation between cortical thinning, brain perfusion, and memory impairment.

**Results:** In the higher  $\alpha3/\alpha2$  frequency power ratio group, greater cortical atrophy and lower regional perfusion in the temporoparietal cortex was correlated with an increase in EEG theta frequency. Memory impairment was more pronounced in the magnetic resonance imaging group and SPECT groups.

**Conclusion:** A high EEG upper/low alpha power ratio was associated with cortical thinning and less perfusion in the temporoparietal area. Moreover, atrophy and less regional perfusion were significantly correlated with memory impairment in subjects with prodromal Alzheimer's disease. The EEG upper/lower alpha frequency power ratio could be useful for identifying individuals at risk for progression to Alzheimer's dementia and may be of value in the clinical context.

**Keywords:** electroencephalography, perfusion, atrophy, temporoparietal network, memory deficits, hippocampal volume, mild cognitive impairment, Alzheimer's disease

## Introduction

Mild cognitive impairment (MCI) commonly represents an "at-risk" state for developing dementia. Therefore, there is a need to develop early biomarkers allowing identification of subjects who could develop Alzheimer's disease (AD), early diagnosis, and potentially effective prevention therapies. The identification and validation of biomarkers for diagnosis, monitoring progression, and predicting the onset of AD have been a main focus of neurology research in the past 10 years. In line with recently published

Correspondence: Davide Vito Moretti  
National Institute for the Research and Care of Alzheimer's Disease, San Giovanni di Dio Fatebenefratelli, Brescia, Italy  
Tel +39 030 3501 597  
Fax +39 030 3533 513  
Email [davide.moretti@afar.it](mailto:davide.moretti@afar.it)

research criteria, it is becoming clear that integration of biomarkers is a cornerstone for correct and early diagnosis of AD.<sup>1,2</sup> To date, the most studied and validated biomarkers are Abeta42 and tau protein in the cerebrospinal fluid, glucose hypometabolism on fluorodeoxyglucose positron emission tomography, atrophy of hippocampal volume on magnetic resonance imaging (MRI), and brain amyloid deposition on imaging with positron emission tomography.<sup>3,4</sup> In the conceptual framework concerning integration of biomarkers for an early and highly predictive diagnosis, the electroencephalogram (EEG) could be a reliable tool.<sup>5–11</sup> Indeed, it is widely accepted that EEG rhythms reflect underlying brain network activity.<sup>12–16</sup> As a consequence, changes in EEG rhythms could be an early sign of AD. Recently, it has been demonstrated that an increase in high alpha power relative to low alpha power is a reliable EEG marker for atrophy of the hippocampus and amygdalohippocampal complex.<sup>17,18</sup> Further, the increase in  $\alpha3/\alpha2$  power ratio has been demonstrated to be predictive of conversion to AD in patients with MCI, but not in non-AD dementia.<sup>19</sup> The same increase in the  $\alpha3/\alpha2$  power ratio was found to be correlated with hippocampal atrophy in subjects with AD.<sup>20</sup> Finally, a recent study showed that MCI subjects with the highest  $\alpha3/\alpha2$  power ratio had a peculiar pattern of basal ganglia and thalamic atrophy detected by voxel-based morphometry when compared with MCI subjects with a middle or low  $\alpha3/\alpha2$  power ratio.<sup>21</sup> In contrast, subjects with a higher  $\alpha3/\alpha2$  frequency power ratio showed a consistent trend of lower perfusion than subjects with a low  $\alpha3/\alpha2$  frequency power ratio. The two groups were significantly different with regard to hippocampal volume and correlation with theta frequency activity.<sup>22</sup>

This study investigated the correlation between MRI and single-photon emission computed tomography (SPECT) values and memory impairment in subjects with MCI and a high  $\alpha3/\alpha2$  frequency power ratio. The results showed that memory impairment was more pronounced in MCI subjects with a higher upper/lower alpha frequency power ratio in both the MRI and SPECT groups. Memory impairment was also correlated with greater cortical atrophy and less perfusion in the temporoparietal cortex.

## Materials and methods

### Subjects

Seventy-four subjects with MCI was recruited from the memory clinic at the Scientific Institute for Research and Care of Alzheimer's and Psychiatric Diseases in Brescia, Italy. All experimental protocols were approved by the local

ethics committee. Informed consent was obtained from all participants or their caregivers in accordance with the code of ethics laid down in the Declaration of Helsinki. Other data on the same subjects has been published previously by our group.

### Diagnostic criteria

Patients were selected from a prospective study on the natural history of cognitive impairment being carried out in the National Institute for the Research and Care of Alzheimer's Disease. Inclusion criteria for the study have been described elsewhere.<sup>23–33</sup> The demographic and cognitive characteristics of the study population are summarized in Table 1. There were no statistically significant differences between the study groups with regard to age, sex, or education.

### EEG recordings

EEG activity was recorded continuously from 19 sites using electrodes set in an elastic cap (Electro-Cap International Inc, Eaton, OH, USA) and positioned according to the 10–20 international system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). The EEG procedure used has been described elsewhere.<sup>34–43</sup>

### Analysis of individual frequency bands

Digital Fast Fourier Transform (FFT)-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) was used to compute (range 2–45 Hz) the power density of EEG rhythms with a 0.5 Hz frequency resolution. Two anchor frequencies were selected according to the

**Table 1** Demographic and cognitive characteristics in the total sample based on  $\alpha3/\alpha2$  frequency power ratio

	Alpha3/alpha2		P-value
	High	Low	
<b>Demographic and clinical features</b>			
Subjects (n)	18	56	–
Age, years	70.4±6.7 (60–85)	69.4±5.4 (52–83)	0.55
Sex, female	13 (%)	19 (%)	0.51
Education, years	6.6±3.6 (4–18)	8.1±2.6 (3–18)	0.42
Mini-Mental State Examination	27±1.7 (23–29)	27.2±1.5 (23–30)	0.46
WMH (mm <sup>3</sup> )	2.78±2.58	4.22±5.45	0.32
Alpha3/alpha2	1.29±0.1 (1.17–1.52)	1.01±0.3 (0.77–1.16)	0.000

**Notes:** Numbers denote mean ± standard deviation and range. P-value denotes significance on analysis of variance.

**Abbreviation:** WMH, white matter hyperintensity.

guidelines in the literature.<sup>16,19,44–50</sup> The  $\alpha3/\alpha2$  power ratio was computed in all subjects, and three groups were obtained according to increasing tertile values of  $\alpha3/\alpha2$ , ie, low ( $\alpha3/\alpha2 < 1$ ), middle ( $1 < \alpha3/\alpha2 < 1.16$ ), and high ( $\alpha3/\alpha2 > 1.17$ ). Division into tertiles allowed a balanced distribution of the study sample with the advantage of avoiding extreme values in the statistical analysis. The three groups of MCI have been demonstrated in previous studies to be different.<sup>19–22</sup>

## MRI scans

For each subject, a high-resolution sagittal T1-weighted volumetric MRI scan was acquired at the Neuroradiology Unit, Città di Brescia Hospital, Brescia, Italy, using a 1.0 T scanner (Gyrosan, Philips, Eindhoven, the Netherlands) with a gradient echo three-dimensional technique: repetition time 20 ms, echo time 5 ms, flip angle 30°, field of view 220 mm, acquisition matrix 256×256, and slice thickness 1.3 mm.

## Estimation of cortical thickness

Cortical thickness in the 74 MCI patients was measured using FreeSurfer version 5.1.0, a fully automated MRI-based analysis technique comprising a set of software tools for the study of cortical and subcortical anatomy, as described elsewhere.<sup>50–59</sup>

## Statistical analysis

Differences in sociodemographic and neuropsychological characteristics between the groups were tested for using Statistical Package for the Social Sciences version 13.0 software (SPSS Inc, Chicago, IL, USA). Analysis of variance was performed for continuous variables and the paired  $\chi^2$  test for dichotomous variables. For continuous variables, post hoc pairwise comparisons between groups were performed using the Games–Howell or Bonferroni tests depending on homogeneity of variance, estimated with Levene’s test. The correlation analysis was computed with Spearman’s correlation coefficients.

## SPECT scans

Twenty-seven patients and 17 controls underwent SPECT scanning in the nuclear medicine department at the Ospedali Riuniti Hospital, Bergamo, Italy, according a protocol described elsewhere.<sup>60</sup>

## Statistical analysis

We investigated the significance of differences in sociodemographic, clinical, and cognitive characteristics between the two groups (MCI subjects at low risk or high risk of

developing AD) using the  $\chi^2$  test for categorical variables (sex and apolipoprotein E carrier status) and the Student’s independent *t*-test for continuous variables (volumetrics, perfusion features, and EEG frequencies). In all cases, we set the threshold for statistical significance at  $P < 0.05$ . Spearman’s *r* correlations were assessed between the selected regions of interest for perfusion (in terms of age-corrected *W* scores) and the acquired EEG frequencies in both groups.

## Results

### MRI

Table 1 shows the sociodemographic and neuropsychological characteristics of the MCI subgroups defined according to  $\alpha3/\alpha2$  ratio. Analysis of variance showed no statistically significant differences between the groups, which were well matched for age, sex, white matter hyperintensity (WMH) burden, level of education, and global cognitive level. Age, sex, education, global cognitive level (Mini-Mental State Examination score) and WMH burden were introduced as covariates in the subsequent analysis to avoid confounding factors. The post hoc pairwise comparisons between groups were performed using the Games-Howell test.

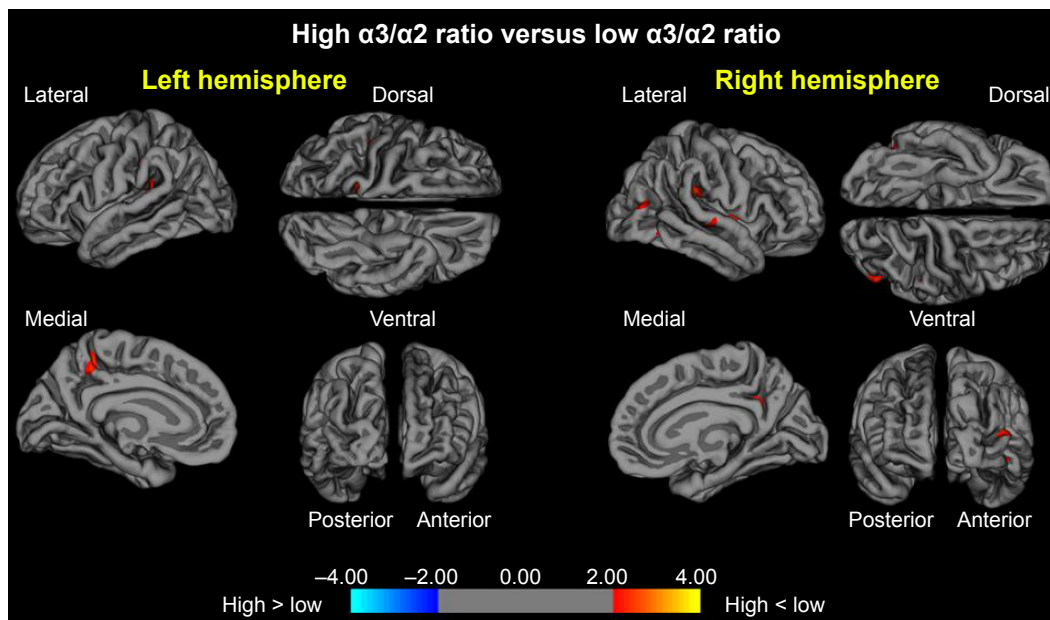
### Pattern of cortical thickness

When compared with subjects who had a low  $\alpha3/\alpha2$  ratio, patients with a high  $\alpha3/\alpha2$  ratio showed bilateral thinning in the superotemporal, supramarginal, and precuneus cortex, as well as in the right inferior parietal and insula areas (Figure 1).

### Neuropsychological memory tests and cortical thickness

In the high  $\alpha3/\alpha2$  group, a significant positive correlation was found between logical memory performance on the Babcock test and thickness values in the left caudal middle frontal area (cluster size 36 mm<sup>2</sup>, stereotaxic coordinates x, y, z = –34, 22, 47, respectively;  $r=0.70$ ,  $P < 0.001$ ) and left inferior temporal area (15 mm<sup>2</sup>, –54, –28, –26;  $r=0.65$ ,  $P < 0.01$ ), right rostral middle frontal area (28 mm<sup>2</sup>; 2, 56, –13;  $r=0.69$ ,  $P < 0.005$ ). No significant correlation was found with the same regions nor in the other groups nor in the whole sample (Table 2).

In the high  $\alpha3/\alpha2$  group, immediate recall on the Auditory Verbal Learning Test (AVLT) was significantly correlated with cortical thickness in the bilateral precuneus area (left 47 mm<sup>2</sup>, stereotaxic coordinates x, y, z = –21, –61, 20, respectively;  $r=0.71$ ,  $P < 0.0001$ ; right 58 mm<sup>2</sup>, 20, –60, 25;  $r=0.70$ ,  $P=0.0008$ ), left fusiform area (40 mm<sup>2</sup>, –41, –25, –21;



**Figure 1** In red are represented the brain regions with higher regional cortical thickness in mild cognitive impairment with higher  $\alpha3/\alpha2$  ratio as compared with mild cognitive impairment with a lower  $\alpha3/\alpha2$  ratio ( $P < 0.01$ ). The color coding for  $P$ -values is on a logarithmic scale. Results are presented on the pial cortical surface of brain: dark gray regions represent sulci and light gray regions represent gyri.

**Table 2** Correlations between neuropsychological memory tests and cortical thickness in high  $\alpha3/\alpha2$  group and other groups

	Regions	High (n=18)	Middle (n=38)	Low (n=18)	All (n=74)
Babcock	Left caudal middle frontal	$r=0.70$ $P < 0.001^*$	$r=0.10$ $P=0.58$	$r=0.24$ $P=0.37$	$r=0.18$ $P=0.18$
	Right rostral middle frontal	$r=0.69$ $P < 0.005^*$	$r=0.08$ $P=0.69$	$r=0.37$ $P=0.16$	$r=0.16$ $P=0.21$
	Left inferior temporal	$r=0.65$ $P < 0.01^*$	$r=0.08$ $P=0.69$	$r=0.07$ $P=0.80$	$r=0.13$ $P=0.31$
AVLT immediate	Left precuneus	$r=0.71$ $P < 0.0001^*$	$r=0.25$ $P=0.18$	$r=-0.73$ $P=0.79$	$r=0.18$ $P=0.18$
	Left fusiform	$r=0.70$ $P < 0.0007^*$	$r=0.21$ $P=0.26$	$r=-0.08$ $P=0.76$	$r=0.16$ $P=0.22$
	Left inferior temporal	$r=0.66$ $P < 0.0008^*$	$r=0.29$ $P=0.12$	$r=-0.10$ $P=0.70$	$r=0.18$ $P=0.17$
	Left inferior parietal	$r=0.69$ $P < 0.005^*$	$r=0.28$ $P=0.14$	$r=0.12$ $P=0.67$	$r=0.21$ $P=0.09$
	Right precuneus	$r=0.70$ $P < 0.0008^*$	$r=0.18$ $P < 0.04^*$	$r=0.02$ $P=0.38$	$r=0.21$ $P=0.09$
Right banks of the superior temporal sulcus	$r=0.70$ $P < 0.00001^*$	$r=0.40$ $P < 0.03^*$	$r=0.04$ $P=0.38$	$r=0.12$ $P=0.09$	
AVLT delayed	Left inferior parietal	$r=0.80$ $P < 0.0001^*$	$r=0.25$ $P=0.18$	$r=-0.05$ $P=0.87$	$r=0.18$ $P=0.15$
	Left pericalcarine	$r=0.69$ $P < 0.001^*$	$r=0.15$ $P=0.42$	$r=0.69$ $P=0.80$	$r=0.17$ $P=0.17$
	Left banks of the superior temporal sulcus	$r=0.76$ $P < 0.0005^*$	$r=0.24$ $P=0.20$	$r=-0.15$ $P=0.58$	$r=0.12$ $P=0.34$
	Right inferior parietal	$r=0.71$ $P < 0.0007^*$	$r=0.19$ $P=0.31$	$r=0.03$ $P=0.92$	$r=0.16$ $P=0.21$
	Right superior temporal	$r=0.67$ $P < 0.01^*$	$r=0.20$ $P=0.30$	$r=0.16$ $P=0.56$	$r=0.21$ $P=0.09$

**Note:** \*indicates significance.

**Abbreviation:** AVLT, Auditory Verbal Learning Test.

$r=0.70$ ,  $P<0.0007$ ), left inferior parietal area (43 mm<sup>2</sup>, -46, -60, 11;  $r=0.69$ ,  $P<0.005$ ), left inferior temporal area (35 mm<sup>2</sup>, -53, -34, -21;  $r=0.66$ ,  $P<0.0009$ ), and right bank of the superior temporal sulcus (44 mm<sup>2</sup>, 48, -48, 9;  $r=0.79$ ,  $P<0.0001$ ). Memory performance was also correlated in the middle group with both the right precuneus area ( $r=0.18$ ,  $P<0.04$ ), and the right bank of the superior temporal sulcus ( $r=0.40$ ,  $P=0.03$ ). No significant associations was found either in the low group or in the entire sample.

In the high  $\alpha3/\alpha2$  group, delayed recall on the AVLT was significantly correlated with cortical thickness in the bilateral inferior parietal area (left 95 mm<sup>2</sup>, stereotaxic coordinates x, y, z = -44, -58, 12, respectively;  $r=0.80$ ,  $P<0.0001$ ; right 49 mm<sup>2</sup>, 50, -50, 9;  $r=0.71$ ,  $P<0.0007$ ), left pericalcarine cortex (54 mm<sup>2</sup>, -7, -8, 11;  $r=0.69$ ,  $P<0.001$ ), left bank of the superior temporal sulcus (31 mm<sup>2</sup>, -51, -41, -5;  $r=0.76$ ,  $P<0.0005$ ), and in the right superior temporal area (22 mm<sup>2</sup>, 56, -34, 13;  $r=0.67$ ,  $P<0.01$ ). No significant correlation was found with the same regions nor in the other groups nor in the whole sample.

## SPECT

Twenty-seven MCI patients were enrolled in this study and were classified as at high risk (when the  $\alpha3/\alpha2$  EEG rhythm median was above 1.17) or at low risk (when the median  $\alpha3/\alpha2$  EEG rhythm was under 1.17) for developing AD. The two groups (high risk of AD, n=13; low risk of AD, n=14) were similar for age ( $P=0.56$ ), years of education ( $P=0.87$ ), sex ( $P=0.17$ ), apolipoprotein E genotype ( $P=0.15$ ), Mini-Mental State Examination scores ( $P=0.31$ ), and white matter lesion load ( $P=0.88$ ; Table 3). Figure 2 shows the visual rating scale of the SPECT scans representative of normal controls, subjects with MCI and a low risk of conversion to AD, and MCI subjects with a high risk of conversion to AD. Analysis of variance showed that the selected cutoff was effective in detecting the two different groups, ie, patients at high risk

of developing AD had a significantly higher  $\alpha3/\alpha2$  power ratio than patients at low risk ( $P=0.0001$ ).

## Pattern of cortical perfusion differences between groups

Although mean perfusion in all the selected regions of interest was similar between the groups (all  $P>0.38$ ), the group with a high  $\alpha3/\alpha2$  frequency ratio showed a consistent trend of lower perfusion. Moreover, left hippocampal volumes were lower in subjects at high risk of AD when compared with those at low risk ( $P=0.001$ ).

In patients at low risk of developing AD, a significant Pearson's  $r$  negative correlation was found between the perfusion in the region of interest, the hippocampal complex volume and the theta rhythm ( $r=-0.544$ ,  $P=0.044$ ). In patients at high risk of developing AD, more and dissimilar correlations were found: a positive correlation, inverted respect to patients at low risk, between the perfusion in the region of interest, the hippocampal complex volume and the theta rhythm ( $r=0.729$ ,  $P=0.005$ ).

## Neuropsychological memory tests and regional brain perfusion

In the high  $\alpha3/\alpha2$  group, a significant positive correlation was found between logical memory performance on the Babcock test and lower perfusion values in the bilateral precuneus (left,  $r=0.63$ ,  $P<0.03$ ; right,  $r=0.70$ ,  $P<0.001$ ) and superior temporal sulcus ( $r=0.72$ ,  $P<0.006$ ). Moreover, a positive correlation was found with hippocampal atrophy ( $r=0.75$ ,  $P=0.001$ ).

In the high  $\alpha3/\alpha2$  group, immediate recall on the AVLT was significantly correlated with lower perfusion values in the caudal bank of the right inferior temporal sulcus ( $r=0.71$ ,  $P<0.001$ ) and middle frontal gyrus ( $r=0.73$ ,  $P<0.003$ ). Further, memory function on the AVLT was significantly correlated with lower perfusion values in the left inferior parietal lobule, particularly in the supramarginal gyrus ( $r=0.80$ ,  $P<0.0001$ , Table 4).

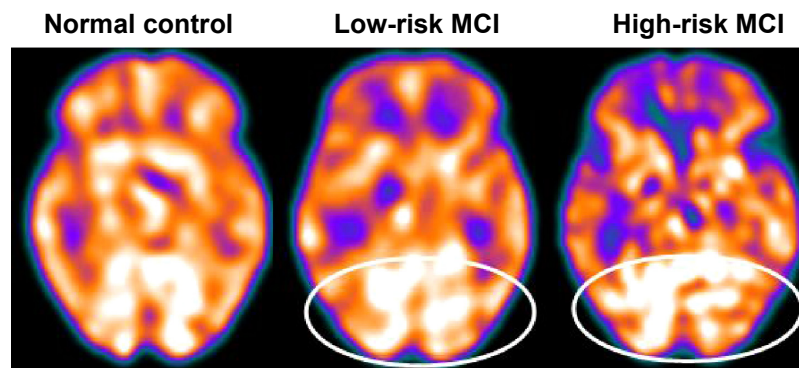
**Table 3** Demographic and cognitive characteristics in the total sample, based on  $\alpha3/\alpha2$  frequency power ratio

	MCI at low risk	MCI at high-risk	P-value
Subjects (n)	14	13	
Age (years)	69.1±7.6 (57–83)	70.6±5.5 (62–78)	0.555
Sex (females)	6 (43%)	9 (69%)	0.168
Education (years)	8.2±4.3 (4–18)	7.9±4.5 (3–18)	0.865
Mini-Mental State Examination score	27.9±1.6 (25–30)	27.2±1.9 (24–29)	0.309
Apolipoprotein E ε4 genotype (carriers)	2 (29%)	5 (39%)	0.152
Left hippocampal volume (mm <sup>3</sup> )	2,606±353 (1,923–3,017)	2,073±412 (1,234–2,641)	0.001
Right hippocampal volume (mm <sup>3</sup> )	2,581±473 (1,549–3,150)	2,296±501 (1,589–3,086)	0.141
Wahlund total score	3.58±3.29 (0.0–10.0)	3.78±2.63 (0.0–7.0)	0.886

**Notes:** Numbers denote mean ± standard deviation and range. P-value denotes significance on analysis of variance.

**Abbreviation:** MCI, mild cognitive impairment.





**Figure 2** SPECT visual rating. The output shows a SPECT visual inspection of glucose uptake metabolism. The white oval denotes an area of mild-to-moderate temporoparietal hypometabolism in one of the 14 MCI patients at low risk and in one of the 13 MCI patients at high risk versus a control subject.

**Abbreviations:** MCI, mild cognitive impairment; SPECT, single-photon emission computed tomography.

## Discussion

The present study provides an overview of the correlation between structural and neurodegeneration biomarkers and brain rhythms associated with MCI due to AD.

### Association between EEG markers and changes in gray matter

This study investigated the relationship between an EEG marker (the  $\alpha3/\alpha2$  power ratio) and cortical thickness in subjects with MCI. The  $\alpha3/\alpha2$  power ratio was chosen because previous work has demonstrated that MCI subjects with a higher  $\alpha3/\alpha2$  ratio are at increased risk of developing AD.<sup>19–22</sup> In the present study, the MCI group with a higher  $\alpha3/\alpha2$  ratio had more global cortical atrophy than the other subgroups, thus confirming a large body of literature.<sup>6,19</sup> Further, the greater extent of atrophy was significant in two specific brain areas, ie, the precuneus and the supramarginal gyrus (located in the inferior parietal lobule), in both the left

and right hemispheres. These results were largely expected, considering previous studies. Indeed, structural and functional abnormalities of the precuneus were observed in subjects with MCI as well as in those with AD, so atrophy of the precuneus has been considered as pathognomonic of early AD.<sup>61–66</sup> Recent studies suggest that specific regions, namely the precuneus and posterior cingulate gyrus, together with the medial temporal lobe, are particularly vulnerable to early amyloid deposition in AD pathology.<sup>67,68</sup>

### Relationship between EEG markers and changes in perfusion

These results confirm previous studies showing that patients at high risk of developing AD have reduced perfusion on SPECT in the temporoparietal intersection and inferior parietal lobule,<sup>55,56</sup> and also confirm the well-known correlation between reduced regional perfusion and hippocampal atrophy.<sup>55</sup> The present study shows a correlation between cerebral

**Table 4** Correlations between neuropsychological memory tests and regional brain perfusion in higher  $\alpha3/\alpha2$  frequency power group

	Regions	High risk (n=14)	Low risk (n=13)
Babcock	Left precuneus	$r=0.63$ $P<0.03^*$	$r=0.24$ $P=0.37$
	Right precuneus	$r=0.70$ $P=0.001^*$	$r=0.37$ $P=0.16$
	Superior temporal sulcus	$r=0.72$ $P\leq 0.006^*$	$r=0.17$ $P=0.80$
AVLT immediate	Right banks of the Inferior temporal sulcus	$r=0.71$ $P<0.0001^*$	$r=-0.23$ $P=0.79$
	Right middle frontal gyrus	$r=0.73$ $P<0.003^*$	$r=-0.25$ $P=0.13$
AVLT delayed	Left supramarginal gyrus	$r=0.80$ $P<0.0001^*$	$r=-0.25$ $P=0.2$

**Note:** \*indicates significance.

**Abbreviation:** AVLT, Auditory Verbal Learning Test.

perfusion and theta rhythm, which emerges only when the different groups individuated by the  $\alpha3/\alpha2$  frequency power ratio. This is confirmed by the lack of a correlation when the groups are merged. This result represents the principal issue of the study and the main novelty of this research.

The subjects at lower risk of developing AD, in whom there was a steady trend toward higher regional blood perfusion in the brain, maintained low levels of hippocampal theta power, while subjects at higher risk, with a basically lower cerebral blood perfusion, tended to show a higher theta rhythm. Theta rhythms are usually not appreciated in a normal awakening EEG. However, an increase in theta power is observed over the frontal and temporal areas during learning and memory tasks. Theta rhythms recorded during these tasks are thought to be produced by activation of the septal-hippocampal system. The hippocampus has cholinergic innervation originating from the basal forebrain, medial septum, and vertical limb of the diagonal band of Broca. Populations of GABAergic and glutamatergic neurons have also been described in several basal forebrain structures. The synchronized depolarization of hippocampal neurons produces field potentials that have a main frequency of 3–12 Hz and is usually known as hippocampal theta rhythm.<sup>47,48</sup> A cholinergic-glutamatergic hypothesis of AD has been advanced, whereby most symptoms may be explained by cholinergic-glutamatergic deficits. Neuronal injury/loss may include an excitotoxic component that possibly contributes to the early cholinergic deficit. This excitotoxic component may occur, at least in part, at the septal level where somas of cholinergic neurons are found. This insult may modify septal networks and contribute to the abnormal information processing observed in the AD brain, including its hyperexcitability states.

## Neurophysiological and clinical implications

Recent studies have demonstrated that, during successful encoding of new items, there is a desynchronization in the temporoparietal memory-related networks whereas a synchronization prevents a successful semantic encoding.<sup>66,69</sup> The deleterious role of synchronization has recently been demonstrated by an interesting study addressing the intriguing relationship between functional and structural degeneration in AD.<sup>67</sup> The authors detected some hub (heteromodal associative) regions that are selectively vulnerable in AD pathology, caused by damage to inhibitory interneurons, providing a loss of inhibition at the cellular level.<sup>70–75</sup> According to the authors, this disinhibition provokes an increasing amount of neural activity at the network level, ultimately resulting in a hypersynchronization of brain areas. Of

note, this overactivity is excitotoxic and determines cellular apoptosis and brain atrophy. Palop and Mucke emphasize the role of dysfunctional inhibitory interneurons in hypersynchronization.<sup>54</sup> Our results are in line with these previous influential studies. A possible integrative view of all the results could be as follows: the higher neuronal activity in the hub regions starts from dysfunctional cellular inhibition; the consequent disinhibition drives the neural network toward oversynchronization; this oversynchronization is specific to hub regions with a higher amyloid burden; these overactivated regions are prone to degeneration and atrophy; a possible neurophysiological sign of this oversynchronization is the higher  $\alpha3/\alpha2$  power ratio we have found in typical hub regions.<sup>70–75</sup> It is of great interest that there is overlap between the brain regions associated with an increased EEG  $\alpha3/\alpha2$  power ratio (hypersynchronization of upper alpha) in our study and the regions associated with higher amyloid burden related to memory processes.<sup>70,71</sup> Moreover, in the present study, there is a very interesting result. Atrophy of the precuneus is coupled with atrophy in the supramarginal gyrus and, to a lesser extent, with the inferior parietal lobule, insula, and superior temporal gyrus. This pattern of atrophy was clearly expressed in the MCI subjects with a higher  $\alpha3/\alpha2$  power ratio. This finding fits well with the results of a recent study that investigated the functional connectivity of the human precuneus by resting state functional MRI.<sup>75</sup> The authors of that study found that there is a preferential pathway for connectivity between the dorsal precuneus and the supramarginal gyrus, parietal cortex, superior temporal gyrus, and insula. As a consequence, the atrophy detected in the MCI group with a higher  $\alpha3/\alpha2$  power ratio could be hypothesized to reflect loss of gray matter in an entire anatomofunctional network rather than atrophy of isolated brain areas. Of note, it is widely accepted that AD is the result of cortical network impairment more than atrophy of single cortical areas.<sup>75</sup> In subjects with a low or middle  $\alpha3/\alpha2$  power ratio, the cognitive impairment is possibly due to cerebrovascular impairment or a non-AD degenerative process. Although the rigid selection criteria adopted to include in the study patients with primary cognitive deficits, in the clinical practice is not infrequent to have MCI subjects not due to AD.

## Memory performance

In order to exclude a random relationship between the EEG marker and cortical atrophy, the correlation between brain areas and performance on memory tests was investigated in all MCI subgroups. The memory tests were chosen because of their well-known greater impairment in MCI subjects who convert to AD.<sup>1,9</sup> Our results showed no significant

difference in memory performance between the groups. This could be a paradoxical outcome, but should not be considered too surprising, bearing in mind the globally mild and early impairment of the whole group of subjects. In other words, the groups are not different when considering memory performance alone. This is probably due to early and general MCI. Despite the lack of a significant difference in the memory test scores, when focusing on the relationship between memory performance and a reliable structural marker, such as cortical thickness, the MCI group with the higher  $\alpha3/\alpha2$  power ratio showed a (negative) correlation between performance on memory tests and cortical thickness, as expected in patients likely to have prodromal AD. This result confirms the peculiar nature of this MCI group, and shows a clear specificity as regard to both cortical atrophy and the correlated memory performance. Moreover, no other sociodemographic or structural differences were observed in the MCI groups that could explain the results of the correlation analysis. Cortical areas associated with cortical thinning and those correlated with performance on memory tests are only partly overlapping. This could be due to the particular nature of the memory domain, underpinning a large number of brain areas. On the other hand, MCI subjects at higher risk of converting to AD may show impairment in other cognitive domains, such as visuospatial attention or in execution and preparation of spatially guided behavior.<sup>75</sup> Of note, the cortical network encompassing the precuneus and inferior parietal cortex is deeply involved in visuospatial abilities.<sup>75</sup> As a speculative interpretation, we could hypothesize that the memory deficits may be due to an impaired network underlying the semantic coding of the spatial features of episodic memory traces. In this view, the atrophy of a specific brain network (more than global volume measures) is more reliable in detecting MCI subjects with prodromal AD. However, discussion of memory-related brain networks is beyond the scope of the present study. Only a weak negative correlation was found in the group with a middle  $\alpha3/\alpha2$  EEG power ratio, suggesting a possible degenerative type of memory impairment in this group. No significant associations were found in the low  $\alpha3/\alpha2$  power ratio group or in the whole sample. Taken together, these results strengthen the view that MCI patients with a higher  $\alpha3/\alpha2$  ratio are at increased risk for developing AD.<sup>75</sup>

## Conclusion

In this study, a higher EEG upper/low alpha power ratio was associated with cortical thinning and decreased perfusion in the temporo-parietal brain areas. This atrophy and

decreased perfusion were both significantly correlated with memory impairment in MCI subjects. The EEG upper/low alpha frequency power ratio could be useful for identifying MCI individuals at risk for progression to AD dementia and may be of value in the clinical context.

## Disclosure

The author reports no conflicts of interest in this work.

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