

Original Article

Atrophy and lower regional perfusion of temporo-parietal brain areas are correlated with impairment in memory performances and increase of EEG upper alpha power in prodromal Alzheimer's disease

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Received January 17, 2015; Accepted August 28, 2015; Epub September 10, 2015; Published September 15, 2015

Abstract: Background: Temporo-parietal cortex thinning is associated with mild cognitive impairment (MCI) due to Alzheimer's disease (AD). The increase of the EEG upper/low alpha power ratio has been associated with MCI due to AD subjects and to the atrophy of temporo-parietal brain areas. Moreover, subjects with a higher alpha3/alpha2 frequency power ratio showed lower brain perfusion than in the low alpha3/alpha2 group. The two groups have significantly different hippocampal volumes and correlation with the theta frequency activity. Methods: 74 adult subjects with MCI underwent clinical and neuropsychological evaluation, electroencephalogram (EEG) recording, and high resolution 3D magnetic resonance imaging (MRI). 27 of them underwent EEG recording and perfusion single-photon emission computed tomography (SPECT) evaluation. The alpha3/alpha2 power ratio as well as cortical thickness was computed for each subject. The difference in cortical thickness between the groups was estimated. Pearson's *r* was used to assess the correlation topography between cortical thinning as well as between brain perfusion and memory impairment. Results: In the higher upper/low alpha group, memory impairment was more pronounced both in the MRI group and the SPECT MCI group. Moreover, it was correlated with greater cortical atrophy and lower perfusional rate in temporo-parietal cortex. Conclusion: High EEG upper/low alpha power ratio was associated with cortical thinning lower perfusion in temporo-parietal. Moreover, atrophy and lower perfusional rate were both significantly correlated with memory impairment in MCI subjects. The increase of EEG upper/low alpha frequency power ratio could be useful for identifying individuals at risk for progression to AD dementia and may be of value in the clinical context.

Keywords: EEG, SPECT, MRI, memory, prodromal Alzheimer's disease

Introduction

The MCI commonly represents the at-risk state of developing dementia. There is, therefore, a need for developing early biomarkers which allow to identify subjects who could develop the disease, useful for early diagnosis and effective prevention therapies. The identification and validation of biomarkers for diagnosing, monitoring progression and predicting the onset of Alzheimer's disease (AD) has been the main focus of AD research in the past ten years. In line with recently published research criteria, it is becoming clear that the integration of different biomarkers is a milestone for a correct and early diagnosis of AD [1, 2]. To date, the most studied and validated biomarkers are

Abeta42 and tau protein in the cerebrospinal fluid (CSF), glucose hypometabolism on fluorodeoxyglucose positron emission tomography (18F-FDG-PET), atrophy of hippocampal volume (HV) on magnetic resonance (MR), and brain amyloid deposition on amyloid imaging with PET [3, 4]. Regardless, some controversies remain to debate. The latter biomarkers have a good sensibility in identifying subjects with neurodegenerative disorders at high risk of converting to dementia, but they lack a reliable specificity that allow a clear-cut diagnosis of the different subtypes of dementias. Of note is that, in neurodegenerative disorders, like AD or other dementias, the brain networks modify many years before clinical manifestations. Recent MRI studies have demonstrated that a large

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Table 1. Demographic and cognitive characteristics in the whole sample, disaggregated for increased levels of Alpha3/Alpha2. Numbers denote mean \pm standard deviation, number and [range]. P denotes significance on ANOVA

	Alpha3/Alpha2			p
	High	Middle	Low	
Demographic and clinical features				
Number of subjects	18	38	18	—
Age, years	70.4 \pm 6.7 [60-85]	68.4 \pm 8.2 [52-83]	70.4 \pm 7.4 [57-80]	.55
Sex, female	13 (%)	24 (%)	14 (%)	.51
Education, years	6.6 \pm 3.6 [4-18]	7.6 \pm 3.7 [3-17]	8.3 \pm 4.7 [3-18]	.42
Mini Mental State Exam	27 \pm 1.7 [23-29]	27.4 \pm 1.3 [24-30]	26.9 \pm 1.2 [23-30]	.46
WMHs (mm ³)	2.78 \pm 2.58	5.59 \pm 6.60	2.57 \pm 2.76	.09
Alpha3/alpha2	1.29 \pm 0.1 [1.17-1.52]	1.08 \pm 0.0 [1-1.16]	0.9 \pm 0.1 [0.77-0.98]	.000

neural network is altered in subjects with prodromal AD [5-10]. In particular, subjects with cognitive decline have shown early atrophy and loss of grey matter in cortical specific brain areas [6-8], including precuneus, hippocampal, medial temporal, and parietal lobes. In the conceptual frame of the integration of biomarkers for early and highly predictive diagnosis, the EEG could be a reliable tool [11]. Indeed, it is widely accepted that the cerebral EEG rhythms reflect underlying brain network activity [12]. As a consequence, modifications in EEG rhythms could be an early sign of AD-. In particular, the study of alpha rhythm seems to be a very suitable tool for detecting a relationship between structural and functional brain networks [13-16]. Previous studies have convincingly demonstrated that there are thalamo-cortical and cortico-cortical components that interact in the generation of cortical alpha rhythms. Recently, it has been demonstrated that the increase of high alpha relative to low alpha power is a reliable EEG marker of hippocampal atrophy [17] and amigdal-hippocampal complex atrophy [18]. Furthermore, the increase in alpha3/alpha2 power ratio has been demonstrated predictive of conversion of patients with MCI in AD, but not in non-AD dementia [19]. The same increase of alpha3/alpha2 power ratio was found to be correlated with hippocampal atrophy in subjects with AD [20]. Finally, a recent study have shown that MCI subjects with highest alpha3/alpha2 power ratio present a peculiar pattern of basal ganglia and thalamic atro-

phy, detected with voxel-based-morphometry (VBM) technique as compared to MCI groups with middle and low alpha3/alpha2 power ratio [21-26]. On the other hand, subjects with higher alpha3/alpha2 frequency power ratio showed a constant trend to a lower perfusion than low alpha3/alpha2 group. The two groups were significantly different as about the hippocampal volume and correlation with the theta frequency activity [27]. In this study, the correlation between MRI and SPECT value and the memory impairment in the MCI group with higher alpha3/alpha2 frequency power ratio.

Results show that in higher upper/low alpha group memory impairment was more pronounced both in MRI group and the SPECT MCI group. Moreover, it was correlated with greater cortical atrophy and lower perfusional value in temporo-parietal cortex.

Materials and methods

Subjects

For the present study, 74 subjects with MCI were recruited from the memory Clinic of the Scientific Institute for Research and Care (IRCCS) of Alzheimer's and psychiatric diseases Fatebenefratelli in Brescia, Italy. All experimental protocols had been approved by the local ethics committee. Informed consent was obtained from all participants or their caregivers, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Diagnostic criteria

Patients were selected from a prospective study on the natural history of cognitive impairment carried out in the National Institute for the Research and Care of Alzheimer's Disease (IRCCS, Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy). Inclusion criteria of the study were described elsewhere [20-27]. Patients were rated with a series of standardized diagnostic and severity instruments, including the Mini-Mental State Examination (MMSE) [28], the Clinical Dementia Rating

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Scale (CDRS) [29], the Hachinski Ischemic Scale (HIS) [30] the Instrumental and Basic Activities of Daily Living (IADL, BADL) [31-33] and a complete neuropsychological assessment [34, 35]. Demographic and cognitive features of the subjects in the study are summarized in **Table 1**. There was no statistical difference in age, gender and education among the groups in the study.

EEG recordings

The EEG activity was recorded, continuously from 19 sites by using electrodes set in an elastic cap (Electro-Cap International, Inc.) and positioned according to the 10-20 international systems (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2). EEG procedure was described elsewhere [36-43].

Analysis of individual frequency bands

A digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed-ranging from 2 to 45 Hz-the power density of EEG rhythms with a 0.5 Hz frequency resolution. Two anchor frequencies were selected according to the literature guidelines [16, 19, 44-50]. The α_3/α_2 was calculated in all subjects, and three groups were obtained according to increasing tertiles values of α_3/α_2 : low ($\alpha_3/\alpha_2 < 1$), middle ($1 < \alpha_3/\alpha_2 < 1.16$) and high ($\alpha_3/\alpha_2 > 1.17$). The tertile division allows a balanced distribution of the study samples with the advantage to avoid the extreme value in the statistical analysis. The three groups of MCI have been demonstrated in previous studies to be different in nature. Moreover, this group subdivision has been chosen for a reason of homogeneity and comparability with the previous studies.

MRI scans

For each subject, a high-resolution sagittal T1 weighted volumetric MR scan was acquired at the Neuroradiology Unit of the Citta` di Brescia Hospital, Brescia, by using a 1.0 T Philips Gyroscan scanner, with a gradient echo 3D technique: TR = 20 ms, TE = 5 ms, flip angle = 30, field of view = 220 mm, acquisition matrix 256 256, slice thickness 1.3 mm.

Cortical thickness estimation steps

Cortical thickness measurements for 74 MCI patients were made using a fully automated

magnetic resonance imaging-based analysis technique: FreeSurfer v5.1.0, a set of software tools for the study of cortical and subcortical anatomy described elsewhere [50-59].

MRI statistical analysis

Differences between groups in sociodemographic and neuropsychological features were analyzed using SPSS version 13.0 (SPSS, Chicago, IL) performing an analysis of variance (ANOVA) for continuous variables and paired χ^2 for dichotomous variables. For continuous variables, post-hoc pairwise comparisons among groups were performed with the Games-Howell or Bonferroni tests depending on the homogeneity of variance tested with Levene's test.

Concerning the neuroimaging analysis, the Qdec interface in Freesurfer software was used: a vertex-by-vertex analysis was carried out performing a general linear model to analyse whether any difference in mean cortical thickness existed between groups: low ($\alpha_3/\alpha_2 < 1$), middle ($1 < \alpha_3/\alpha_2 < 1.16$) and high ($\alpha_3/\alpha_2 > 1.17$). The tertile division allows a balanced distribution of the study samples with the advantage to avoid the extreme value in the statistical analysis). The following comparisons were carried out: High versus Low, High vs. Middle and Middle vs. Low. Age, sex, education, global cognitive level (MMSE score) and WMHs were introduced as covariates in the analysis to avoid confounding factors. We first tried to apply an appropriate Bonferroni multiple-comparison correction in our analysis (at $P < 0.05$ corrected). Unfortunately, no p -value survived after this correction. Thus, we choose to set more restrictive significance threshold (than $P < 0.05$ corrected) at $P < 0.001$ uncorrected for multiple comparisons. Moreover, we considered as significant only the clusters which also were broad equal or greater than 30 mm². Finally, the surface map was generated to display the results on an average brain. For illustrative purpose significance was set to a P -value of < 0.01 uncorrected for multiple comparisons.

As a control analysis, in order to exclude casual relationships between EEG markers and cortical volumes, a correlation between brain areas and memory performance has been studied. A correlation analysis was performed on the three samples separately (High α_3/α_2 , Low α_3/α_2 , Middle α_3/α_2) and on the entire sample

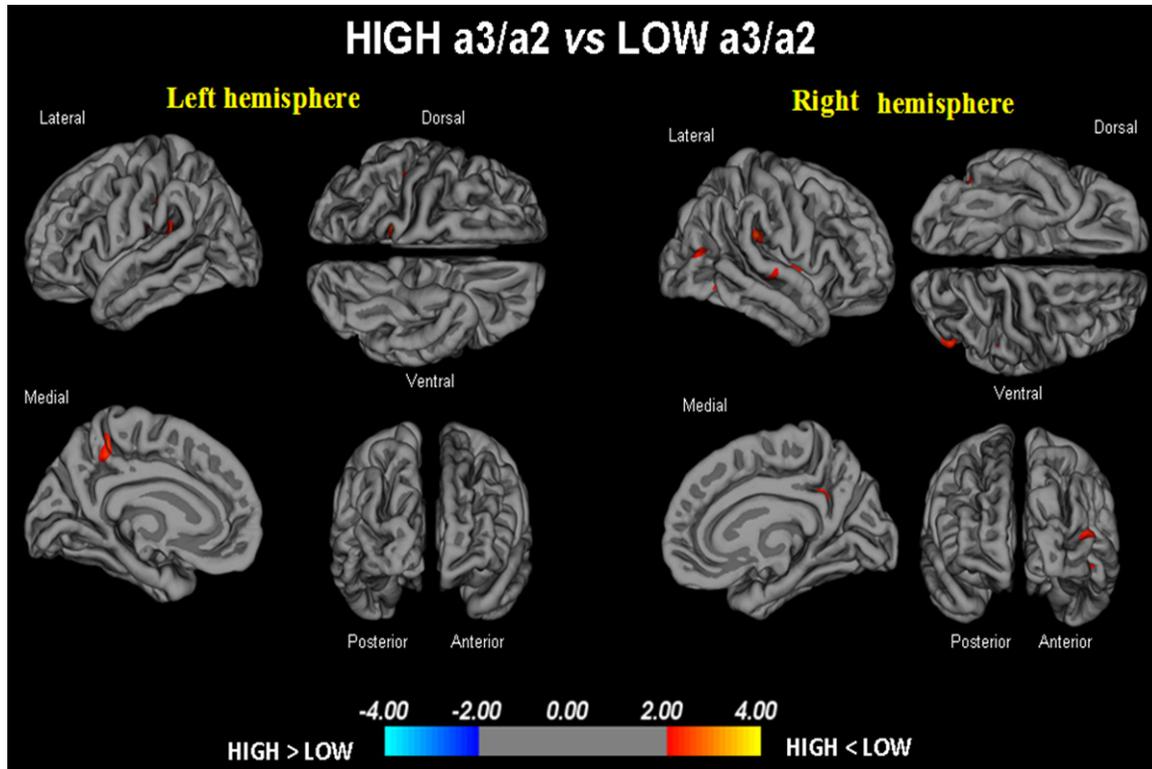


Figure 1. In red are represented the brain regions with higher regional cortical thickness in MCI with high a3/a2 ratio as compared to MCI with low a3/a2 ratio ($P < 0.01$ uncorrected). The colour-coding for p values is on a logarithmic scale. Results are presented on the pial cortical surface of brain: dark gray regions represent sulci and light gray regions represent gyri.

(High and Low and Middle grouped together). An exploratory analysis of non-linear correlation does not fit purpose of testing our a priori hypothesis. Indeed we choose to apply a measure of linear dependence led by our a priori hypotheses for which the MCI group with the greater cortical thinning, and higher a3/a2 EEG level (showing an incipient AD) should show a clear relationship with the memory tests performance, in the sense that an increase in cortical thinning corresponds to a decrease in memory performance, and vice versa. Indeed, even if in the cognitive tests scores there are no significant differences, we hypothesised that the MCI group with the greater cortical thinning, and higher a3/a2 EEG level, indicating an incipient AD, should show a clear correlation with the memory tests performance. The correlation analysis on a vertex-by-vertex basis was performed individually for the following neuropsychological memory test results: Babcock Test, Rey auditory verbal learning test (AVLT) immediate recall, and Rey AVLT delayed recall. The analysis was thresholded at $P < 0.001$ uncor-

rected for multiple comparisons while results were mapped at P -value of < 0.005 uncorrected for illustrative purpose. Only the clusters which survived at the statistical threshold and wide equal or greater than 15 mm^2 were considered as significant.

SPECT scan

27 patients and 17 normal controls underwent SPECT scan in the nuclear medicine department of the Ospedali Riuniti hospital, Bergamo according a protocol described elsewhere [60].

SPECT statistical analysis

All statistical analyses were performed using SPSS software version 13.0. We investigated the significance of the difference between the 2 groups (MCI at low and at high risk to develop AD) in socio-demographic, clinical and cognitive features using χ^2 test for categorical variables (sex, and ApoE carriers) and Student's independent t test for continuous variables (volumetric,

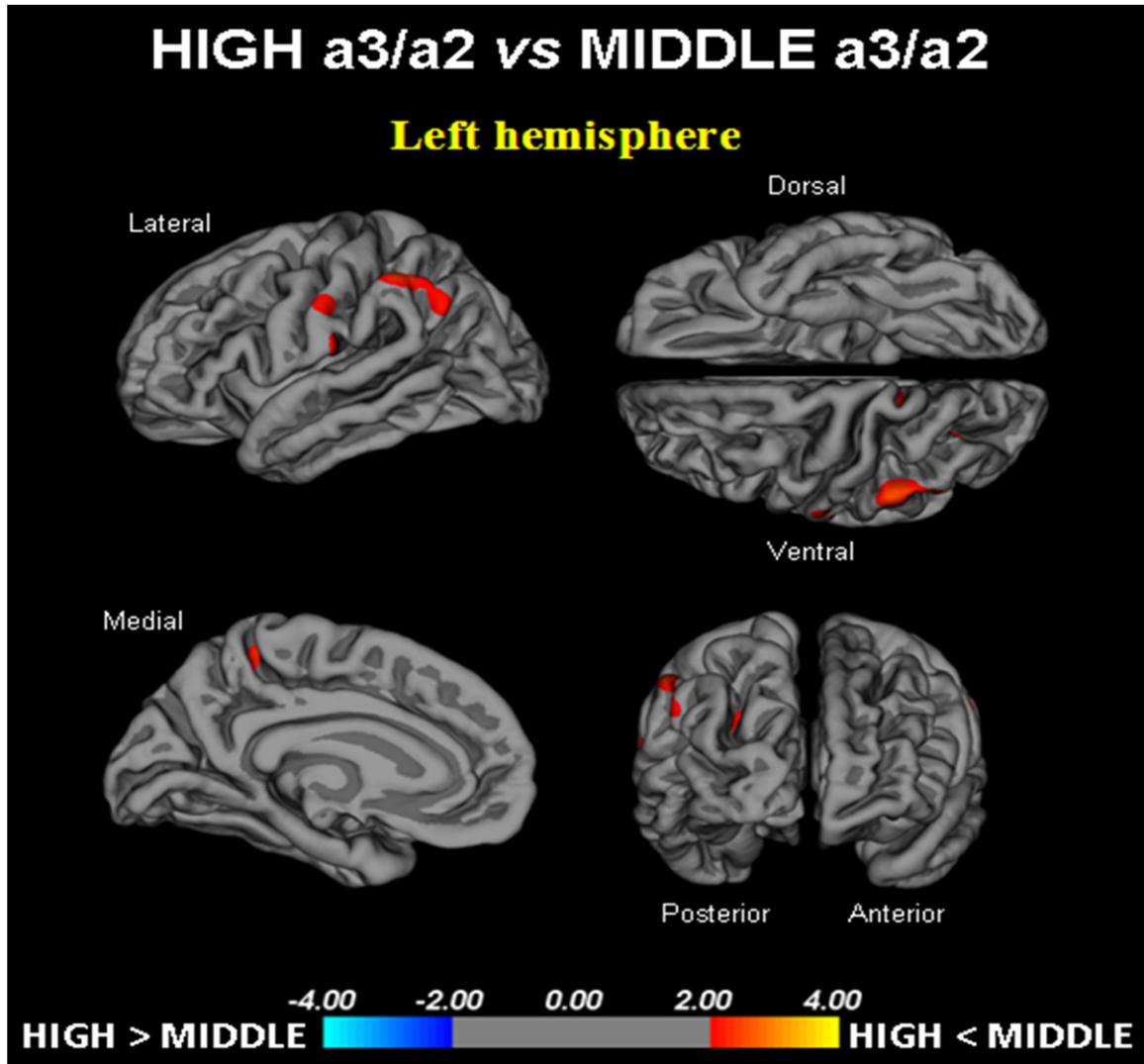


Figure 2. In red are represented the brain regions with higher regional cortical thickness in MCI with high $a3/a2$ ratio as compared to MCI with middle $a3/a2$ ratio ($P < 0.01$ uncorrected). The colour-coding for p values is on a logarithmic scale. Results are presented on the pial cortical surface of brain: dark gray regions represent sulci and light gray regions represent gyri.

perfusion features and EEG frequencies). In all cases, we set the significant threshold at $P < 0.05$. Since native SPECT scans were coregistered to their respective MR images, and the study-specific SPECT template was coregistered to the high-definition MR template, all the normalized SPECT and MR images used for the statistical analysis were coregistered to the SPM standard anatomical space. Moreover, Pearson's r correlations were assessed between the selected perfusion ROIs (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 MCI subgroups defined by the tertile values of $\alpha3/\alpha2$. The ANOVA analysis showed that there was not statistically significant differences between groups that resulted well paired for age, sex, white matter hyperintensities (WMHs) burden, education and global cognitive level. Regardless, age, sex, education, global cognitive level (MMSE score) and WMHs were intro-

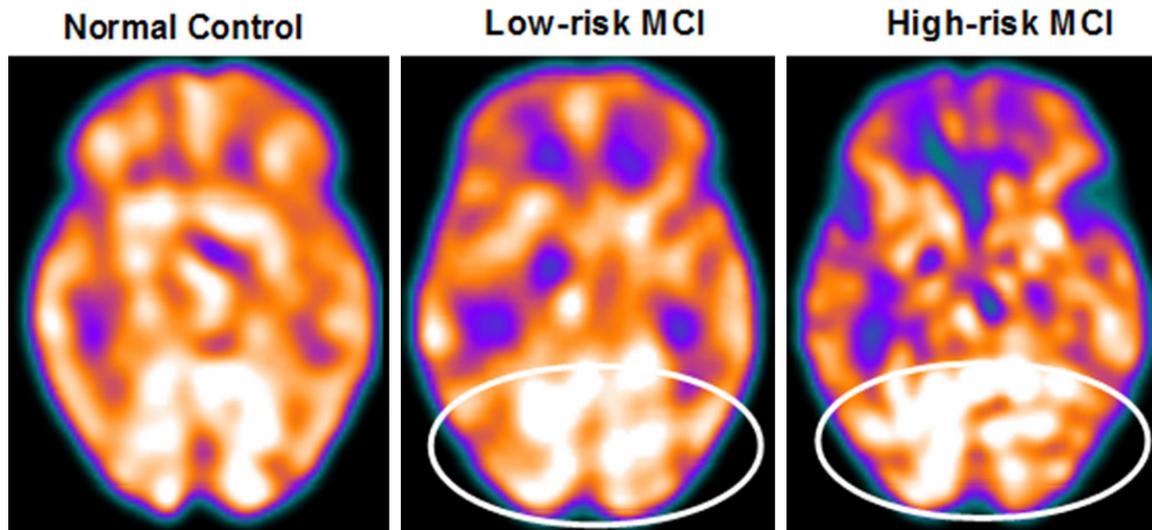


Figure 3. SPECT visual rating. The output shows a SPECT visual inspection of glucose uptake metabolism: the white square denotes an area of mild-to-moderate temporo-parietal hypometabolism in one of the 14 at low risk and in one of the 13 at high risk MCI patient respect to one of the 17 enrolled controls.

duced as covariates in the subsequent analysis to avoid confounding factors. Alpha3/alpha2 ratio levels were significant at Games-Howell post hoc comparisons ($P = 0.000$). The data of same subjects were partly used in previously published works of our group [41-43].

Pattern of cortical thickness between groups

High vs. Low: Patients with high a3/a2 ratio show thinning in the bilateral Superior Temporal, Supramarginal and Precuneus cortex, in the right Inferior Parietal and Insula when compared to subjects with low a3/a2 ratios. The total CGM reduction in High a3/a2 group than Low a3/a2 group was 471 mm² (**Figure 1**).

High vs. Middle: The same group showed a similar but less wide pattern of cortical thinning when compared to middle a3/a2 group: the areas of atrophy were located in the left Supramarginal gyrus left Precuneus and Post central cortex. The total CGM reduction in High a3/a2 group than Middle a3/a2 group was 160 mm² (**Figures 2, 3**). When High group was compared to Low group the total extension of cortical thinning (471 mm²) was 34% wider than the other comparison in which High group was compared to Middle group (160 mm²). No regions of greater cortical atrophy were found in groups with Middle or Low a3/a2 when compared to High a3/a2 power ratio group. No sig-

nificant cortical thickness differences were found between Middle and Low a3/a2 groups.

Correlations between neuropsychological memory tests and cortical thickness in High a3/a2 group and other groups

Babcock test: A significant positive correlation was found in High alpha3/alpha2 group between logical memory performance at Babcock test and thickness values in the left Caudal Middle Frontal (cluster size = 36 mm²; stereotaxic coordinate x, y, z = -34 22 47; $r = 0.80$; $P = 0.0001$) and left Inferior Temporal (15 mm²; -54 -28 -26; $r = 0.72$; $P = 0.001$), right Rostral Middle Frontal (28 mm²; 23 56 -13; $r = 0.74$; $P = 0.0007$) (**Figure 3**). No significant correlation was found with the same regions nor in the other groups nor in the whole sample.

AVLT immediate recall: In High alpha3/alpha2 group memory performance were significant related with the cortical thickness values in the bilateral Precuneus (left: 47 mm²; -21 -61 20; $r = 0.78$; $P < 0.0000$; right: 58 mm²; 20 -60 25; $r = 0.72$; $P = 0.0007$), left Fusiform (40 mm²; -41 -25 -21; $r = 0.76$; $P = 0.0005$), Inferior Parietal (43 mm²; -46 -60 11; $r = 0.74$; $P = 0.0001$), Inferior Temporal (35 mm²; -53 -34 -21; $r = 0.71$; $P = 0.0008$), and right Banks of the Superior Temporal Sulcus (44 mm²; 48 -48 9; $r = 0.81$; $P < 0.000$). Memory performance was

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Table 2. Demographic and cognitive characteristics in the whole sample, disaggregated for increased levels of Alpha3/Alpha2 Numbers denote mean \pm standard deviation, number and [range]. P denotes significance on ANOVA

	At low-risk MCI	At high-risk MCI	p
N	14	13	
Age (years)	69.1 \pm 7.6	70.6 \pm 5.5	0.555
[Range]	[57÷83]	[62÷78]	
Gender (females)	6 (43%)	9 (69%)	0.168
Education (years)	8.2 \pm 4.3	7.9 \pm 4.5	0.865
[Range]	[4÷18]	[3÷18]	
MMSE score	27.9 \pm 1.6	27.2 \pm 1.9	0.309
[Range]	[25÷30]	[24÷29]	
ApoE ϵ 4 genotype (carriers)	2 (29%)	5 (39%)	0.152
Left Hippocampal Volume (mm ³)	2,606 \pm 353	2,073 \pm 412	0.001
[Range]	[1,923÷3,017]	[1,234÷2,641]	
Right Hippocampal Volume (mm ³)	2,581 \pm 473	2,296 \pm 501	0.141
[Range]	[1,549÷3,150]	[1,589÷3,086]	
Wahlund total score*	3.58 \pm 3.29	3.78 \pm 2.63	0.886
[Range]	[0.0÷10.0]	[0.0÷7.0]	

correlated in the Middle group with both the right Precuneus also ($r = 0.19$ and $P = 0.03$), and the right Banks of the Superior Temporal Sulcus ($r = 0.44$, $P = 0.02$). No significant associations were found in the Low group nor in the entire sample.

AVLT delayed recall: In High alpha3/alpha2 group memory function correlate significantly with cortical thickness in the bilateral Inferior Parietal (left: 95; -44 -58 12; $r = 0.86$; $P < 0.0000$; right: 49; 50 -50 9; $r = 0.74$; $P = 0.0005$), left Pericalcarine cortex (54; -7 -8 11; $r = 0.76$; $P < 0.0000$) and Banks of the Superior Temporal Sulcus (31; -51 -41 -5; $r = 0.81$; $P = 0.0002$); in the right Superior Temporal (22; 56 -34 13; $r = 0.73$; $P = 0.001$). No significant correlation was found with the same regions nor in the other groups nor in the whole sample.

SPECT

27 MCI patients were enrolled for the present study, and they were classified as at high risk (when the a3/a2 EEG rhythm median was above 1.17) or at low risk (when the a3/a2 EEG rhythm median was under 1.17) to develop AD. The two groups (AD high risk, $N=13$, AD low risk, $N=14$) were similar for age ($P = 0.56$), education in years ($P = 0.87$), gender ($P = 0.17$), ApoE genotype ($P = 0.15$), MMSE scores ($P =$

0.31) and white matter lesions load ($P = 0.88$; **Table 2**). **Figure 3** shows the visual rating scale of the SPECT scans representative of normal control, MCI with low and MCI with high risk to convert in AD, respectively. ANOVA results show that the selected cut-off was useful in detecting two different groups: patients with high risk to develop AD show significantly higher alpha3/alpha2 power ratio than patients with low risk ($P = 0.0001$). Moreover, a control analysis was performed on the individual frequencies. The results show that the increase of

alpha3/alpha2 frequency power ratio was due to both increase of alpha3 ($P = 0.001$) and decrease of alpha 2 ($P = 0.0001$) and not to the modification of a single frequency. This control analysis was performed because the change of only one frequency could be due to the chance. However, it was not the case.

Of note, no differences were found for beta 1, beta 2, gamma, theta EEG power and theta/gamma frequency power ratio (all $P > 0.11$). Although the mean perfusion in all the selected ROIs was similar between groups (all $P > 0.38$), in a group with high alpha3/alpha2 frequency ratio there is a constant trend to a lower perfusion. Moreover, left hippocampal volumes were lower for AD-high risk patients respect to low-risk ones ($P = 0.001$).

In patients at low risk to develop AD, significant Pearson's R negative correlation was found between perfusion in the hippocampal complex ROI and theta rhythm ($r = -0.544$, $P = 0.044$).

In patients at high risk to develop AD otherwise, more and dissimilar correlations were found: a positive correlation, inverted respect to patients at low risk, between the perfusion in the hippocampal complex ROI and theta rhythm ($r = 0.729$, $P = 0.005$), while temporal ROI correlated positively with theta/gamma ratio rhythms ($r = 0.736$, $P = 0.004$). No other signifi-

cant correlations were found in both groups between perfusion ROIs and other EEG rhythms or hippocampal volumes. Moreover, no significant correlations were found between hippocampal complex ROI and theta rhythm pooling low and high-risk patients together ($r = 0.086$, $P = 0.671$).

Correlations between neuropsychological memory tests and regional brain perfusion in High α_3/α_2 group and other groups

Babcock test: A significant positive correlation was found in High α_3/α_2 group between logical memory performance at Babcock test and lower perfusion values in bilateral precuneus (0.63 $P = 0.03$) and superior temporal sulcus ($r = 0.74$, $P = 0.005$). Moreover a positive correlation was found also with hippocampal atrophy ($r = 0.75$, $P = 0.001$).

AVLT immediate recall: In High α_3/α_2 group memory performance were significant related with lower perfusion values in caudal bank of right inferior temporal sulcus and middle frontal gyrus ($r = 0.75$, $P = 0.003$).

AVLT delayed recall: In High α_3/α_2 group, memory function correlates significantly with lower perfusion values inferior parietal lobule, in particular in the submarginal gyrus ($r = 0.009$, $P = 0.05$).

Discussion

EEG markers and GM changes

Our results show that the MCI group with higher α_3/α_2 ratio has a greater global cortical atrophy than the other subgroups, thus confirming a large body of literature [6, 19]. Furthermore, the greater atrophy is significant in two separate brain areas: precuneus and supramarginal gyrus (a brain area belonging to the inferior parietal lobule), both in left and right hemisphere. These results were mostly expected considering previous studies. Recent studies suggest that different regions, namely the precuneus and posterior cingulate, together with the medial temporal lobe, are selectively vulnerable to early amyloid deposition in AD pathology [61-68].

EEG markers and perfusional changes

These results confirm previous studies which have shown that patients with high risk of

developing AD have and reduced SPECT perfusion in temporo-parietal carrefour and inferior parietal lobule [55, 56]. Moreover, our results also confirm a well-known association with hippocampal atrophy [55]. The present study shows a correlation between cerebral perfusion and theta rhythm. Anyway, the correlation emerges only when considering the different groups individuated on the α_3/α_2 frequency power ratio. This result is confirmed by the finding that when the groups are merged, no correlation can be found. The patients at lower risk to develop AD (i.e., those who have a constant trend towards a higher brain regional blood perfusion) maintain low levels of hippocampal theta power, while patients at higher risk (i.e., those with lower cerebral blood perfusion) tend to have a higher theta rhythm. This increase could be due to the synchronized depolarization of hippocampal neurons arising field potentials with a main frequency of 3-7 Hz and, i.e. the hippocampal theta rhythm [47, 48]. This permanent state of overdepolarization could be explained by the glutamatergic hypothesis of AD, in which septal cholinergic neurons are affected by a glutamatergic overstimulation, leading to hyperexcitability and, perhaps, excitotoxicity of hippocampus.

Neurophysiological and clinical implications

Recent studies have shown that during the successful encoding of new items there is a desynchronization in the temporo-parietal memory-related networks whereas a synchronization prevent a successful semantic encoding [66, 69]. The deleterious role of synchronization has been recently demonstrated by an interesting study facing the intriguing relationship between functional and structural degeneration in AD [67]. The authors identified some hub regions (eteromodal associative regions) selectively vulnerable in AD pathology, due to the damage of inhibitory interneurons providing a loss of inhibition at cellular level. According to the authors, the disinhibition provokes an increasing amount of neural activity at system level, giving as a final result an hypersynchronization of brain areas. Of note, this overactivity is excitotoxic and determines cellular apoptosis and brain atrophy. The role of the inhibitory interneuron dysfunction, leading to hypersynchronization was emphasized by other authors [70-73]. A possible integrative view of all the results could be as follows: 1). The higher neuronal activity in the hub areas starts from a dysfunc-

tion of cellular inhibition; 2). The consequent disinhibition drives neural network to an over synchronization; 3). This over synchronization is peculiar of the hub regions with higher amyloid burden; 4). These overactivated regions are prone to degeneration and atrophy; 5). A possible neurophysiologic sign of this over synchronization is the increase of the alpha3/alpha2 power ratio we have found in typical hub regions [74-77]. It is of great interest that there is an overlapping between the brain regions associated with an increase of EEG alpha3/alpha2 frequency power ratio (or hypersynchronization of upper alpha) in our study and the areas associated to higher amyloid burden related to memory processes [70, 71]. Moreover, in the present study, there is a very interesting result. The atrophy of precuneus is coupled with the atrophy in supramarginal gyrus and, at lesser extent, with an inferior parietal, insula and superior temporal gyrus. This atrophy pattern is clearly expressed in the group of MCI subjects with higher alpha3/alpha2 power ratio. In a recent resting state fMRI study [78], the authors found that there is a preferential pathway of connectivity of the dorsal precuneus with supramarginal gyrus, parietal cortex, superior temporal gyrus and insula. As a consequence, the atrophy we detected in the MCI group with higher alpha3/alpha2 ratio power could be hypothesized as the loss of GM in an entire anatomic-functional network more than the atrophy of isolated brain areas [79]. In subjects with low or middle alpha3/alpha2 power ratio the cognitive impairment is possibly due to the cerebrovascular impairment or non-AD degenerative process. Although the rigid selection criteria adopted to include patients with primary cognitive deficits in the study, in clinical practice it is not infrequent to have MCI subjects not due to AD.

Memory performance

In order to exclude a random relationship between EEG markers and cortical atrophy, the correlation between brain areas and the performance to memory tests was investigated in all MCI subgroups. The memory tests were chosen because of their well known greater impairment in MCI subjects who will convert to AD [1, 9]. Our results show no significant memory difference among the groups. This could be a paradoxical outcome. Anyway, it could not be con-

sidered a so surprising result, taking in mind the globally mild and early impairment of the whole group of subjects. In other words, when considering the memory performance strictly, the groups are not different. This is probably due to the early and generally mild cognitive impairment. Anyway, despite having no significant difference in the memory test scores, when focusing on the relationship between the memory performance and a reliable structural marker, such as the the cortical thickness, the MCI group with the higher alpha3/alpha2 power ratio has shown a (negative) correlation between memory tests performance and the cortical thickness, as expected in patients with probable prodromal AD. This result confirms the peculiar nature of this MCI group, showing a clear specificity about both the cortical atrophy and the correlated memory performance. Moreover, no other socio-demographical or structural differences were observed in the MCI groups that could explain the correlation analysis results. The cortical areas associated with cortical thinning and those correlated with memory tests performance 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 more susceptible to convert to AD could show impairment also in other cognitive domains like as visuospatial attention or in execution and preparation of spatially guided behaviour [80-83]. Of note, the cortical network encompassing the precuneus and inferior parietal cortex is deeply involved in visuospatial abilities left hippocampal atrophy [78]. As a speculative interpretation, we could hypothesize that the memory deficits could be due to an impaired network underlying the semantic coding of the spatial features of the 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. In any event, the discussion of memory-related brain networks was beyond the scope of the present study. Only a weak negative correlation was found in the middle alpha3/alpha2 EEG power ratio, suggesting a possible degenerative nature of the memory impairment in this group. No significant associations were found in low alpha3/alpha2 power ratio group and the whole sample. Taken together, these results strengthen the position of the higher alpha3/alpha2

ratio MCI group as at major risk to developing Alzheimer's disease.

Implications at system level

Klimesch and coworkers have convincingly demonstrated that the upper alpha band (10-13 Hz) specifically reflects encoding memory processes [84]. Recent EEG and magnetoencephalography (MEG) studies have confirmed that the correct functioning of memory, both in encoding and retrieval, requires the high alpha rhythm desynchronization (or power decrease) [24, 84-91]. About cognitive impairment due to AD, the typical synaptic loss could prevent the physiological flexibility of brain neural assemblies, impeding the desynchronizing downstream modulation of the brain activity. As a consequence, it could be hypothesized that the disruption of the cortical network due to degenerative disease, inducing cortical atrophy, could determine an over synchronization of the brain oscillatory activity. The synchronization state of the high alpha power associated to the decreased cerebral blood flow activity, could prevent the creation of a semantic sensory code and, consequently, of the episodic memory trace [92-117].

Conclusion

The of EEG upper/low alpha frequency power ratio could be useful for early diagnosis of subjects at significant risk to developing AD dementia and may be helpful in the clinical and research context.

Disclosure of conflict of interest

None.

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