Theta Frequency is Associated to Morpho-Strcutural and Perfusional Modifications in Subjects with Mild Cognitive Impairment

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Abstract: *Background*: In an attempt to find non-invasive biomarkers, researchers have investigated the feasibility of neuroimaging tools, such as MR, SPECT as well as neurophysiological measurements using EEG. The increase of theta frequency has been associated with mild cognitive impairment (MCI) and related to both grey matter (GM) changes of thalamus and basal ganglia and SPECT modifications. *Objective*: To study the association of prognostic theta frequency with specific GM and perfusional changes of thalamus and basal ganglia to detect biomarkers early predictive of mild cognitive impairment. *Methods*: 74 adult subjects with mild cognitive impairment underwent EEG recording and high resolution 3D magnetic resonance imaging (MRI). Moreover, 27 adult subjects with mild cognitive impairment underwent also perfusion single-photon emission computed tomography (SPECT) evaluation. The theta/gamma ratio was computed for each subject. Three groups were obtained according to increasing tertiles values of theta/gamma ratio. Grey matter density differences between groups were investigated using a Voxel Based Morphometry technique. *Results*: Subjects with higher theta/gamma ratio and increase of theta frequency showed minor atrophy in putamina nuclei bilaterally and a lower hippocampal perfusion in subjects with mild cognitive impairment. *Conclusion*: The integrated analysis of EEG and morpho-functional markers could be useful in the comprehension of anatomo-physiological underpinning of the MCI entity.

Keywords: EEG, theta rhythm, SPECT, mild cognitive impairment.

INTRODUCTION

EEG have been demonstrated a reliable diagnostic tool in dementia research [1-3].

MRI and SPECT-based studies, approaching the large scale neural connectivity issue found that the activation during a task was not altered between the MCI subjects and the healthy controls [4], suggesting that connectivity within a network is first altered due to the putative dementia neuropathology and then changes in activation occur in the brain. It may be that before recruitment of compensatory regions for a cognitive task, functional connectivity would be the first step leading to increased activation in a region that would activate as a compensatory mechanism.

The large neural network altered in dementia encompasses also thalamic structure [5-9]. In particular, atrophy of thalamus and basal ganglia have been demonstrated to be involved in non-AD dementia and in the symptomatic development [10, 11].

The relationship between the sources of different EEG rhythms and thalamus-basal ganglia structure have been widely studied and accepted. For instance, findings in human and animal studies suggest that coordinated simultaneous theta activity is observed in two networks linked, respectively to striatal nucleus [12] and to the frontal-anterior thalamic system [13-15]. As a consequence, the theta/gamma ratio is associated with fronto-basal ganglia networks and it could more associated with modifications in these structure. Accordingly, different EEG oscillations based on different anatomical networks has been suggested to have different functions. Specifically, synchrony of theta oscillations, impinging on fronto-striatal circuits play a crucial role in top-down modulated higher order visual processing [4, 16, 17]. As a consequence, modifications in theta/gamma ratio would like to reflect anatomopathological changes in those deep brain structure. Recent SPECT studies have demonstrated that a large neural network is altered in subjects with prodromal AD, including precuneus, medial temporal, parietal ad frontal cortices [18-21]. For instance, selective regional cerebral blood flow (rCBF) reductions in the left hippocampus and parahippocampal gyrus and in extended areas of cerebral association cortex were demonstrated in a two-year follow-up clinical study with rCBF-SPECT [22, 23]. Recent studies have separately demonstrated that in MCI patients the increase in theta frequency power is related to reduction of hippocampal volume, increase of volume in basal ganglia, and reduction of the cerebral regional blood flow in hippocampal complex [24-27].

In the present study the association of theta frequency with grey matter (GM) changes in thalamus and basal ganglia and SPECT modifications have been

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E-ISSN: 2313-1047/14 **© 2014 Savvy Science Publisher**

studied in subjects with MCI. The working hypothesis was that modifications of EEG marker could be underpinned by different deep brain structures and perfusion. Results show that subjects with higher theta frequency ratio showed minor atrophy in putamina nuclei bilaterally and lower brain perfusion.

2. MATERIALS AND METHODS

2.1. Subjects

For the present study, 74 subjectes were selected from a prospective study on the natural history of cognitive impairment (the translational outpatient memory clinic—TOMC study) carried out in the outpatient facility of the National Institute for the Research and Care of Alzheimer's Disease (IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy). Patients with MCI underwent clinical and cognitive assessment, high-resolution MR, 18F-FDG PET, lumbar tap, and were seen at follow-up visits every 12 months until development of dementia. A detailed description has been provided elsewhere [8]. The data of same subjects were used in previously published works of our group [28]. The study protocol was approved by the local ethics committee and all participants signed an informed participation consent.

2.2. Diagnostic Criteria

MCI was defined as the presence of objective impairment in memory or other cognitive domains (performance lower than the fifth percentile on neuropsychological tests as detailed below) in the absence of functional impairment. History or neurological signs of major stroke were absent. Variables described below are those relevant to this study.

Clinical Assessment

We assessed global cognition with the Mini Mental State Examination (MMSE) [29], the Clinical Dementia Rating Scale (CDRS) [30], the Hachinski Ischemic Scale (HIS) [31], and the Instrumental and Basic Activities of Daily Living (IADL, BADL) [32]. All patients underwent: (i) semi-structured interview with the patient and - whenever possible - with another informant (usually, the patient's spouse or a child of the patient) by a geriatrician or neurologist; (ii) physical and neurological examinations; (iii) performance-based tests of physical function, gait and balance; (iv) neuropsychological battery assessing memory (Babcock Story Recall - Rey-Osterrieth Complex Figure, Recall - Auditory-Verbal Learning Test, immediate and delayed recall) [33], verbal and non-verbal memory, attention and executive functions (Trail Making Test B, A and B-A; Inverted Motor Learning-Clock Drawing Test) [33], abstract reasoning thinking (Raven Coloured Progressive Matrices) [33], frontal functions (Inverted Motor Learning); language (Phonological and Semantic fluency-Token test) [33], and apraxia and visuo-constructional abilities (Rey-Osterrieth Complex Figure, Rey figure copy, Clock Drawing Test) [33]; (v) assessment of depressive symptoms by means of the Center for Epidemiologic Studies Depression Scale (CES-D) [34]. As the aim of our study was to evaluate the relationship between GM loss and theta/ gamma ratios we did not consider the clinical subtype of MCI, i.e., amnesic, or non-amnesic, single or multiple domains. Hypertension, heart disease, diabetes mellitus, and hypercholesterolemia were investigated based on history, currently prescribed drugs, and historical charts: if treatment for one of this condition was assumed at the time of the investigation, then such condition was considered as present. Follow-up visits consisted of a cognitive, behavioural, and functional assessment, including administration of the MMSE, CES-D, and Lawton and Brody's scales. In particular, history of symptom progression was collected from a knowledgeable informant. We specifically focused on getting information about those symptoms useful in the differential diagnosis among the most frequent forms of dementia. The clinical diagnosis of dementia was made by the physician-in-charge (a neurologist or a geriatrician) according to the traditional clinical criteria [35-38].

2.3. 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). The ground electrode was placed in front of Fpz. The left and right mastoids served as reference for all electrodes (Figure **1**). The recordings were used off-line to re-reference the scalp recordings to the common average. Data were recorded with a band-pass filter of 0.3-70 Hz, and digitized at a sampling rate of 250 Hz (BrainAmp, BrainProducts, Germany). Electrodes-skin impedance was set below 5 kOhms. Horizontal and vertical eye movements were detected by recording the electrooculogram (EOG). The recording lasted 5 min, with subjects with closed eyes. Longer recordings would have reduced the

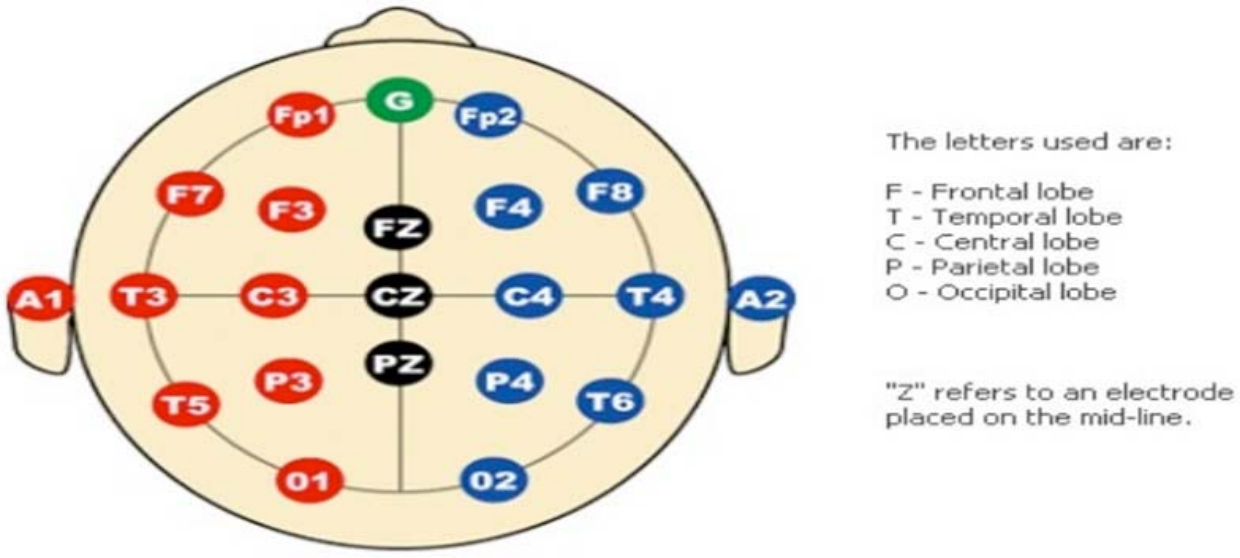

Figure 1: Electrodes placement on the scalp in 10-20 EEG international system.

variability of the data, but they would also have increased the possibility of slowing of EEG oscillations due to reduced vigilance and arousal. EEG data were then analyzed and fragmented off-line in consecutive epochs of 2 s, with a frequency resolution of 0.5 Hz. The average number of epochs analyzed was 140 ranging from 130 to 150. The EEG epochs with ocular, muscular and other types of artefacts were discarded [39].

2.4. Analysis of Individual Frequency Bands

All recordings were obtained in the morning with subjects resting comfortably. Vigilance was continuously monitored in order to avoid drowsiness. 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, that is, the theta/alpha transition frequency (TF) and the individual alpha frequency (IAF) peak [40, 41]. The TF marks the transition frequency between the theta and alpha bands, and represents an estimate of the frequency at which the theta and alpha spectra intersect. TF was computed as the minimum power in the alpha frequency range, since our EEG recordings were performed at rest. The IAF represents the frequency with the maximum power peak within the extended alpha range (5-14 Hz) [40, 41]. A detailed description has been provided elsewhere [24-28, 39, 42-60]. The mean frequency range computed in MCI subjects considered as a whole are: delta 2.9-4.9 Hz; theta 4.9-6.9 Hz; alpha1 6.9-8.9 Hz; alpha2 8.9-10.9 Hz; alpha3 10.9-12.9 Hz. Finally, in the frequency bands determined on an individual basis, we computed the relative power spectra for each subject. The relative power density for each frequency band was computed as the ratio between the absolute power and the mean power spectra from 2 to 45 Hz. The theta/gamma ratio was computed in all subjects. Three groups were obtained according to increasing tertiles values theta/gamma ratio: low (t/g<1.20) middle (1.21<t/g<1.56) and high (t/g>1.62). A tertile subdivision was chosen in which each tertile is statistical significantly different from others.

SPECT Scan

27 patients and 17 normal controls underwent SPECT scan in the nuclear medicine department of the Ospedali Riuniti hospital, Bergamo. Each subject received an intravenous injection of 925 MBq of technetium- 99m ethyl cysteinate dimer (^{99m}Tc-ECD) in resting conditions, lying supine with eyes closed in a quiet, dimly lit room. Forty to sixty minutes after injection, brain SPECT was performed using a dual-head rotating gamma camera (GE Elscint Helix) equipped with low energy-high resolution, parallel hole collimators. A 128 x 128 pixel matrix, zoom=1.5, was used for image acquisition with 120 views over a 360° orbit (in 3° steps) with a pixel size and slice thickness of 2.94 mm. Butterworth filtered-back projection (order=7, cutoff= 0.45 cycles/cm) was used for image reconstruction, and attenuation correction was performed using Chang's method (attenuation

coefficient = 0.11/cm). Images were exported in DICOM format.

SPECT Processing Protocol

To achieve a precise normalization, we generated a study-specific SPECT template using both SPECT and MR scans of all patients and normal controls under study, following a procedure described in detail elsewhere [61]. Briefly, we created a customized high-definition MR template, we converted SPECT scans to Analyze format using MRIcro [62], and we coregistered them to their respective MR scans with SPM2 (SPM, Statistical Parametric Mapping, version 2 (2002)). London: Functional Imaging Laboratory. We normalized each MR to the customized MR template through a nonlinear transformation (cutoff 25mm), and we applied the normalization parameters to the coregistered SPECT. We obtained the customized SPECT template as the mean of all the latter normalized SPECT images. The creation of a study-specific template allows for better normalization, since low uptake in ventricular structures and cortical hypoperfusion effects frequently present in elderly patients are accounted for. For each coregistered SPECT scan, we set origin to the anterior commissure, using the respective MR image as a reference, and we processed all scans with SPM2 according to an optimized processing protocol described in detail elsewhere [61]. Brain perfusion correlates of medial temporal lobe atrophy and white matter hyperintensities in mild cognitive impairment): (I) we smoothed each scan with a 10mm full width at half maximum (FWHM) Gaussian, and spatially normalized it with an affine deformation to the customized SPECT template. We applied the same deformation to the unsmoothed images; (II) we masked the unsmoothed normalized images from I to remove scalp activity using SPM2's "brainmask". We smoothed with a 10mm FWHM Gaussian, and warped them to the customized template with a nonlinear transformation (cutoff 25mm).We applied the same transformation to the unsmoothed masked images; (III) we smoothed the normalized unsmoothed images from II with a 12mm FWHM Gaussian. The following Region of Interest (ROI) were chosen for perfusion analyses in each hemisphere from the Pick atlas by a sub-routine implemented on SPM2: frontal, parietal and temporal lobes, the thalamus and the hippocampal-amygdalar complex [63].

2.5. MRI Scans

For each subject, a high-resolution sagittal T1 weighted volumetric MR scan was acquired by using a 1.0 T Philips Gyroscan scanner, with a gradient echo 3D technique: TR = 20 ms, TE = 5 ms, flip angle = 30^{o}, field of view = 220 mm, acquisition matrix 256 · 256, slice thickness 1.3 mm.

The pattern of grey matter atrophy was studied using the Voxel Based Morphometry technique [63].

2.6. Voxel-Based Morphometry

3D images were processed through SPM5 software package (Statistical Parametric Mapping, Version 5; Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm), running on Matlab 7.0.1 (Math-Works, Natick, MA, USA). DICOM files were converted in ANALYZE format image, the extra-cranial voxels were removed and the anterior commissure (AC) was manually set for all images as the origin of the spatial coordinates for an anatomical normalization algorithm implemented in SPM. Converted files were then segmented into gray and white matter and normalized to the GM population templates, generated from the complete image set, using the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) registration method [64]. This non-linear warping technique minimizes between-subject structural variations.

Spatially normalized images were modulated by the Jacobian determinants derived from the spatial normalization, to ensure that the overall amount of each tissue class was not altered by the spatial normalization procedure. The final voxel resolution after DARTEL was 1.5X1.5X1.5 mm. Finally each modulated, warped GM image was transformed to MNI space and smoothed with a 8-mm full-width at half-maximum (FWHM) Gaussian kernel filter. The experimenter performing the MRN computations was blinded to the results of previous EEG works, so that there were not biases in the analysis.

2.7. MRI/EEG Statistical Analysis

VBM results were assessed at an uncorrected threshold of $p \leq 0.05$. This threshold has an important limit in that it allows the tipe I statistical error. Anyway, a more permissive threshold could be more adequate to this explorative study, it in order to avoid the beta (or type II) statistic error, with the risk to neglect interesting results. Anyway, the power of the study was allowed by size of the sample, and by the robust results of the subsequent analyses. The same sample was disaggregated according to the increasing values of theta/gamma ratio into the following groups: low-t/g

(t/g<1.20), middle-t/g (1.21<t/g<1.56), high-t/g (t/g>1.62).

Voxel-based analyses were carried out comparing the three groups with increasing values of the theta/gamma ratio (high-t/g; middle-t/g; low-t/g).

For the EEG marker studied (theta/gamma), between-group regional differences in GM volumes were assessed by using a full-factorial ANOVA design, entering group as three values variable (high, middle, low), and age, gender, education, MMSE scores as covariates. Moreover, the total intracranial volume was introduced in the statistical analysis as a covariate, to avoid the confounding item of the global cortical atrophy. The total intracranial volume (TIV) was computed by manually tracing the entire intracranial cavity on 7-mm thick coronal slices, by the use of the software DISPLAY 1.3 tools. Correlation or regression analyses were not performed. The reason is that the EEG marker represents different patients population (MCI who will convert and MCI who will not), as previously demonstrated [28]. As a consequence, it is not correct to use the regression analysis because significant results should have masked. It would be possible only within each of the three groups individuated by the tertile subdivisions, but the size of each group dose not allow a powerful regression analysis.

All the analyses were restricted to the thalamus and basal ganglia as regions of interest in order to focus the relationship between their brain areas and EEG markers. It should be possible to perform a computation encompassing other brain areas, but this was beyond the scope of the present work. Moreover, the relationship of EEG markers with hippocampus and amygdala was faced in previous papers [48]. To this purpose, a mask including Caudate Nucleus, Putamen, Globus Pallidus, Accumbens Nucleus and Thalamus, was entered into the models as explicit mask. It was manually traced, through the software MRIcroN, on the previous template generated from the complete image set.

The detection of the anatomical regions was based on the localization of the thalamic nuclei and basal ganglia in histological sections from a human atlas [65].

SPECT Statistical Analysis

All statistical analyses were performed using SPSS software ver. 13.0. We investigated 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, 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

Table **1** and **2** show socio-demographic characteristics of the study sample

Table 1: Demographic and cognitive characteristics in the whole sample, disaggregated for increased levels of Theta/gamma ratios. Numbers denote mean ± standard deviation, number and [range]. p denotes significance on t- and chi-square tests. p denotes significance on ANOVA and chi-square test.

	ALL	Theta/Gamma			
		High	Middle	*Low*	*p*
Number of subjects	74	18	39	17	
Age, years	69.4 ± 7.6 [52-85]	72.2 ± 4.2 [63-79]	68.9 ± 8.4 [52-85]	67.3 ± 8.3 [54-80]	0.15
Sex, female	51 (%)	10 (%)	31 (%)	10 (%)	0.11
Education, years	7.6 ± 3.9 [3-18]	5.3 ± 2.4 [3-13]	7.8 ± 4.4 [3-18]	9.3 ± 3 [5-13]	0.008
Mini mental state exam	27.2 ± 1.7 [23-30]	26.3 ± 1.7 [23-28]	27.3 ± 1.5 [23-30]	27.9 ± 1.6 [25-30]	0.009
Theta/gamma	1.5 ± 0.39 [0.78-2.86]	2 ± 0.3 [1.63-2.86]	1.4 ± 0.1 [1.21-1.56]	1.04 ± 0.1 [0.78-1.20]	0.000

3.1. EEG Theta/Gamma Ratio

Middle-t/g group: When contrasted to patient with high theta/gamma ratios, subjects with middle theta/gamma ratio showed GM loss in the Putamen bilaterally, but smaller in the left brain hemisphere where the spot was restricted to the dorsal part (see Figure **2**).

Table 2: Socio-demographic, clinical and volumetric features in MCI patients by risk to develop AD. Values are mean ± standard deviations for continuous variables or frequency (percentage) for gender and ApoE carriers.

	At low-risk MCI	At high-risk MCI	p-value
N	14	13	
Age (years) [Range]	69.1±7.6 [57÷83]	70.6±5.5 [62÷78]	0.555
Gender (females)	6 (43%)	9 (69%)	0.168
Education (years) [Range]	8.2±4.3 [4÷18]	7.9±4.5 [3÷18]	0.865
MMSE score [Range]	27.9±1.6 [25÷30]	27.2±1.9 [24÷29]	0.309
ApoE ε4 genotype (carriers)	2 (29%)	5 (39%)	0.152
Left Hippocampal Volume (mm3) [Range]	2,606±353 [1,923÷3,017]	2,073±412 [1,234÷2,641]	0.001
Right Hippocampal Volume (mm3) [Range]	2,581±473 [1,549÷3,150]	2,296±501 [1,589÷3,086]	141
Wahlund total score* [Range]	3.58±3.29 [0.0÷10.0]	3.78±2.63 [0.0÷7.0]	0.886

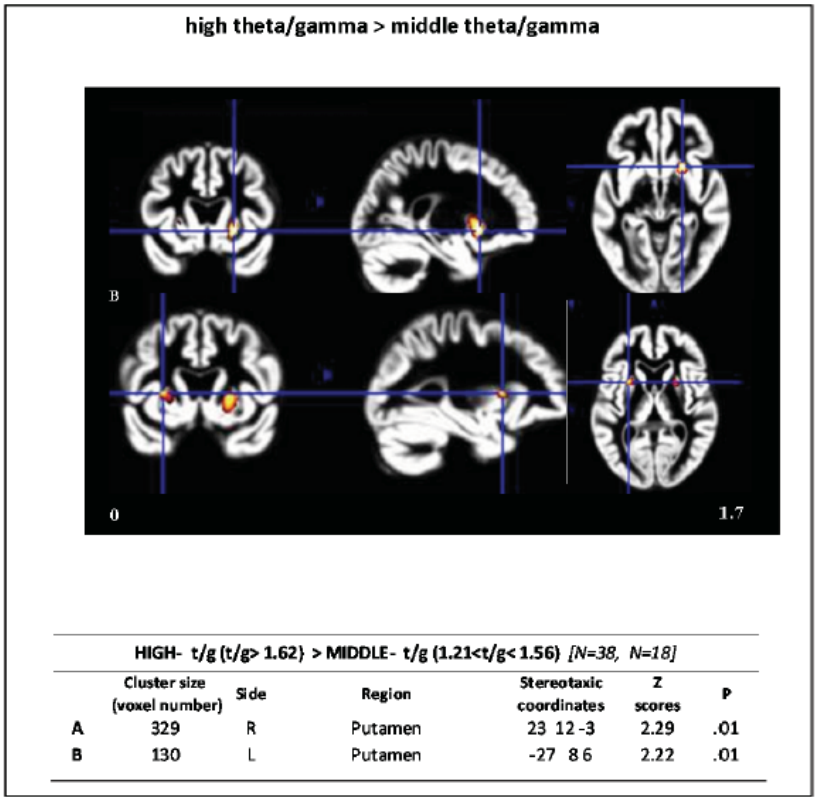

Figure 2: Regions of major regional gray matter density in patients with high theta/gamma ratio contrasted to patients with middle values of theta/gamma ratio ($p \leq 0.05$ uncorrected, the symbol '**>**' denotes '**major grey matter density then'**, see also table).

No regions of significant GM tissue loss were found in other comparisons in this group.

SPECT

In patients at high risk to develop AD otherwise, more and dissimilar correlations were found: a positive correlation, inverted respect to at low risk patients, 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 significant correlations were found in both groups between

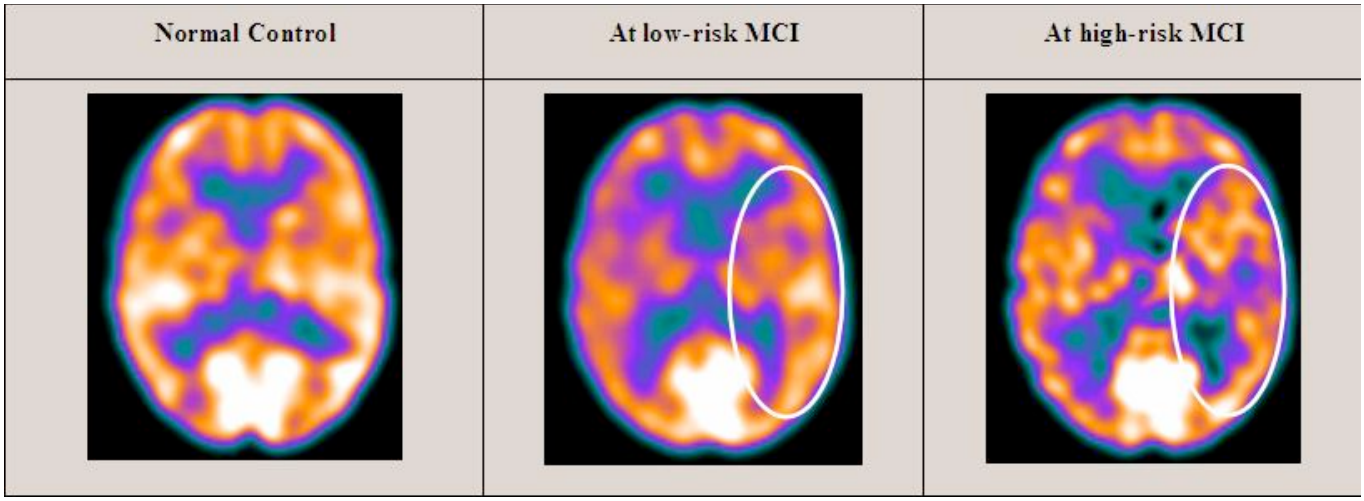

Figure 3: SPECT visual rating. The output shows a SPECT visual inspection of glucose uptake metabolism: the white square denotes an area of mild-to-moderate temporo-parietal hypometabolism in one of the 14 at low risk and in one of the 13 at high risk MCI patient respect to one of the 17 enrolled controls.

perfusion ROIs and other EEG rhythms or hippocampal volumes. Moreover, no significant correlations were found between hippocampal complex ROI and theta rhythm pooling at low and high-risk patients together (r=0.086, p=0.671; Figure **3**).

DISCUSSION

Theta and Neuroanatomy

The theta frequency was first thought to be determined by the intensity of relatively undifferentiated tonic activity ascending from the reticular formation, reflecting the state of 'arousal'. From animal lesion and stimulation studies it was subsequently shown that the medial septal region was a pacemaker for theta [66]. The medial septal pacemaker generated theta recorded in all subfields of the hippocampus and parahippocampal regions, and acted as an intensity/frequency transducer for afferent stimulation from the reticular nucleus. Importantly they demonstrated that theta-rhythmic supramammillary nucleus cell activity occurred independently of hippocampal theta, and that transduction of the intensity of reticular activation to the frequency of the theta oscillation arises in the supramammillary nucleus, not the medial septal region. Frequency coded information from the supramammillary nucleus is fed into at least two recurrent memory networks: a hippocampal-anterior thalamic axis for encoding and recall of episodic and spatial memory; an anterior thalamus-perirhinal cortex network for recognition and familiarity judgments

In summary, theta is involved in two types of functional network: one is the classical mescencephalic-cortical arousal system governing the ascending modulation of the mean EEG spectral frequency. Another relates to recurrent limbic networks which relate to both cognition and arousal/ emotion/ motivation. Hence the theta circuitry disclosed allows for the underpinning of both the cognitive and emotional correlates of theta, and for their coordination [66].

Association between EEG Markers and GM Changes

Results show that the EEG index is associated with different patterns of gray matter changes in a wide MCI population. The increase of theta/gamma ratio is mostly associated with minor atrophy of putamina bilaterally. These results confirm previous studies on demented patients, showing both basal ganglia and thalamic involvement [67-75].

Anatomo-Physiological Relationship between EEG Markers and GM Changes

Our results show the presence of different patterns of GM changes associated with an EEG marker. This could suggest the existence of a specific neural network underlying peculiar degenerative disease. We suggest an interesting, although speculative, hypothesis that could explain the novelty emerging from our results. As regards the putamina nuclei, the specific involvement of the putamen in non-AD

dementia, in particular in fronto-temporal spectrum of dementias, has been recently demonstrated [76]. A possible explanation of the increase of the theta/gamma ratio suggests the dysfunction of fronto-subcortical circuit probably due to hyperactivity of amigdalo-hippocampal theta due to excitation by putaminal input or by lack of inhibition by the pre-frontal cortex. This could explain the behavioural disturbances as well as the cognitive dysfunction found in non-AD dementia [77]. Moreover, the decrease of gamma rhythm could be associated with the impairment of the working memory/planning functions of the dorsal prefrontal-cortex. Indeed, the "bounding function" typical of the working memory, is carried out by the gamma frequency [78].

The lack of results in the comparison between both high and low and middle and low theta/gamma frequency is counterintuitive and puzzling to be interpreted. The most plausible reason is that the neurophysiologic phenomena become evident when the atrophy of deep grey matter nuclei reaches a threshold level, highlighting the strength of the EEG markers-guided analysis in a prognostic view. Indeed, in the other groups could present MCI subjects that will remain stable or with depression or with prevalent cerebrovascular disease.

Anatomo-Phyisiological Implications at Network Level

Putamina nuclei are connected, in a parallel segregated loop, with ventro-medial prefrontal cortex and is more related with executive, language, and behavioural function. The two systems do not work in isolation but they interact each other, resulting in a powerful mediation of cognitive function and motor planning. The impairment of the information transfer could underlie the onset of different clinical syndromes.

Recent studies, facing the neural network connectivity issue, using functional magnetic resonance imaging, positron emission tomography as well as electroencephalography demonstrate that connectivity of brain activity is altered in demented patients and correlates with cognitive deficits [79]. An hyperactivation of memory networks was found in subjects with MCI with clinical cognitive impairment [4, 71]. Our present results could offer a possible comprehensive explanation. As a speculative hypothesis it could be possible that, in MCI subjects at risk to develop non-AD dementia, discrete networks prevails on long-range networks (disconnection theory). In the same time, the survive of hyperactive, although short-range network, permits the maintenance of a normal performance (compensation theory), at least in the early phases of disease.

SPECT and EEG Theta Frequency

The original contribution from the present study is provided by the correlation between cerebral perfusion and theta rhythmin patients at higher risk, with a basically lower cerebral blood perfusion, theta rhythm tends to be higher. This latter finding is also confirmed by the increased ratio of theta / gamma frequency power ratio in the temporal region, adjacent to the hippocampus. Theta rhythms are usually not appreciated in normal awakening EEG. However, a theta power increase is observed over the frontal and temporal areas during learning and memory tasks. The theta rhythms that are recorded during these tasks are thought to be produced by the activation of septal-hippocampal system. Hippocampus has a cholinergic innervation originating from basal forebrain, the medial septum, and the 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 are usually known as hippocampal theta rhythm [80]. The increased theta production in AD would derive from hyperexcitability of the septal-hippocampal system [81].

CONCLUSION

The integrated analysis of EEG and morpho-structural markers could be useful in the comprehension of anatomo-physiological underpinning of the MCI entity.

DISCLOSURE STATEMENT

Moretti D V: I state that I have no actual or potential conflicts of interest.

Paternicò D: I state that I have no actual or potential conflicts of interest.

Prestia A: I state that I have no actual or potential conflicts of interest.

Binetti G: I state that I have no actual or potential conflicts of interest.

Zanetti O: I state that I have no actual or potential conflicts of interest.

Frisoni G B: I state that I have no actual or potential conflicts of interest.

Moretti DV: on the behalf of all coauthors I declare that appropriate approval and procedures were used concerning human subjects.

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Received on 15-02-2014 Accepted on 03-04-2014 Published on 10-06-2014

DOI: http://dx.doi.org/10.12974/2313-1047.2014.01.01.1

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